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Anticonvulsant Activity of MK-801 and Nimodipine Alone and in Combination Against Pentylenetetrazole and Strychnine

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O'NEILL, S. K. AND G. T. BOLGER. *Anticonvulsant activity of MK-801 and nimodipine alone and in combination against pentylenetetrazol and strychnine.* PHARMACOL BIOCHEM BEHAV **32**(3) 595–600, 1989.—The effects of the N-methyl-D-aspartate receptor antagonist MK-801 and the dihydropyridine calcium channel antagonist nimodipine were assessed for their anticonvulsant activity alone and in combination against clonic convulsions to pentylenetetrazole (PTZ) and strychnine (STR) in mice. Nimodipine (2–20 mg/kg) and MK-801 (0.1 and 0.5 mg/kg) did not affect the number of mice displaying clonic convulsions to PTZ. However, nimodipine in a dose-dependent manner increased (100%) the latency to clonic convulsions and lethality (mortality from tonic extension convulsions and respiratory failure) following PTZ. In contrast, MK-801 did not increase the latency to PTZ convulsions, but prevented the lethal effects of PTZ. When combined, MK-801 and nimodipine produced a significant reduction in the number of animals (40–60%) displaying PTZ convulsions and a greater increase in the latency to PTZ convulsions than did nimodipine alone. In contrast, MK-801 decreased the onset time, and increased the severity of STR convulsions. A combination of MK-801 and nimodipine which afforded significant protection against PTZ convulsions did not affect STR convulsions. These findings suggest that MK-801 and nimodipine, while possessing significant anticonvulsant activity on their own, produce a potent anticonvulsant synergism against PTZ but not STR.

Anticonvulsant Nimodipine Calcium antagonist MK-801 NMDA receptor antagonist

ANTAGONISTS of the N-methyl-D-aspartate (NMDA) receptor subclass of excitatory amino acid receptors have been widely investigated for their activity as anticonvulsants, since the activation of the NMDA receptor and the cation channel associated with it have been implicated in mediating seizure activity in the central nervous system (CNS) (7). Although an exact mechanism remains to be determined, NMDA receptor activation likely mediates seizure activity by increasing neuronal calcium conductance (7–9); calcium playing a pivotal role in seizure etiology (22–24). NMDA receptor antagonists investigated for their anticonvulsant activity include the competitive inhibitors D-amino-5-phosphonovaleric acid, 2-amino-2-phosphonoheptanoic acid and its corresponding rigid analogue, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) and the noncompetitive antagonists MK-801, phencyclidine and phencyclidine-like drugs (6–9, 19, 20, 30, 32, 35). While competitive NMDA receptor antagonists act directly to block the access of aspartate and/or glutamate to the NMDA receptor (6–8, 19, 20, 30, 32), the noncompetitive antagonists act by binding to the NMDA receptor gated calcium channel (7, 13, 35). When administered intracerebroventricularly, the competitive NMDA antagonists prevented NMDA-induced convulsions (9), threshold pentylenetetrazole (PTZ) convulsions in SWR mice (13), audiogenic convulsions in DBA/2 mice (6,13) and barbital withdrawal-induced convulsions in rats (29). Either intracerebroventricular or parentral administration of the noncompetitive NMDA receptor antagonists MK-801 and phencyclidine has been shown to provide protection against convulsions (7, 13, 36). Furthermore, selective anticonvulsant effects have been observed. Phencyclidine protected against tonic but not clonic convulsions to PTZ and was only slightly effective in suppression of STR-induced convulsions (13).

Dihydropyridine calcium channel antagonists have also been found to possess anticonvulsant activity. The majority of these studies have focused on nimodipine, in light of its greater ability to cross the blood-brain barrier in comparison to other dihydropyridines (2, 3, 16). Nimodipine, while ineffective against electroshock (14), afforded substantial protection against seizures mediated by PTZ, bicuculline, ischaemia, picrotoxin and sound

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(DBA/2 mice) (15, 22–24). Furthermore, dihydropyridine calcium antagonists protected against convulsions following cocaine administration (31), phencyclidine intoxication (4), and withdrawal from morphine in opiate-dependent animals (3). Although it is clear that nimodipine has anticonvulsant properties, the doses at which it is effective in this regard range from 40–60 mg/kg when administered intraperitoneally or subcutaneously (10, 14, 15).

Several studies have indicated that high affinity dihydropyridine binding sites in the CNS (which may mediate the anticonvulsant effects of nimodipine) are not altered following chemical and electrically-evoked convulsions (2,34). Because of their ability to block calcium channels and the apparent inability of dihydropyridine binding sites to be affected by the convulsive state of the CNS, it has been theorized that drugs active at these sites or a site that they modulate may potentially be useful anticonvulsants (22–24). Recently, it was observed that within the nucleus tractus solitari complex of the rat, NMDA receptor-mediated deglutative responses were blocked by dihydropyridine calcium channel antagonists (12). This observation suggested that dihydropyridine calcium channel antagonists may modulate the NMDA receptor-activated calcium channel. Thus, we have explored the possibility that NMDA receptor blockers and nimodipine might be synergistic in their anticonvulsant activity. In light of their ability to cross the blood-brain barrier (3, 7, 28), we chose to study the anticonvulsant effects of MK-801 and nimodipine alone and in combination against PTZ- and STR-induced convulsions.

METHOD

Animals

For all experiments, male mice (CD-1, weighing 25–33 grams, Canadian Breeding Farms, St. Constant, Quebec) were used. They were housed four per cage under a 12/12 hr light/dark cycle and allowed free access to food and water.

Observation of Convulsions

For studying the convulsant actions of either PTZ or STR, five mice were placed in individual cages (clear acrylic plastic, 29 × 18 × 12 cm) and allowed to acclimate to their surroundings. They were then administered saline or drug(s) (at the times and doses described in the table and figure legends) for a 30-min period. Subsequently, they were administered either PTZ or STR and scored for the appearance of convulsions. The onset time (sec) for convulsions represents the time between injection of convulsant to the development of clonic convulsions severe enough to result in posture loss. For PTZ the monitoring time for convulsions was set at 10 min, while for STR the monitoring time for convulsions was 15 min. Mortality represents death following full tonic-extension convulsions and respiratory failure. The severity and duration of clonic convulsions was scored objectively. All drugs were injected intraperitoneally in a total volume not exceeding 0.2 ml. For more than one drug injection, the drugs were injected on opposite sides of the abdomen.

Drugs

Pentylenetetrazole and strychnine were obtained from the Sigma Chemical Co., St. Louis, MO; nimodipine was provided by Dr. A. Scriabine, Miles Laboratories, West Haven, CT; verapamil was obtained from Knoll AG, West Germany; diltiazem was obtained from Marion Laboratories, Kansas City, MO. MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,dcyclohepten-5,10 imine maleate] was provided by Drs. P. S. Anderson and W. L. Heckler, Merck Sharp and Dohme, Rahway, NJ. STR, PTZ and MK-801 were dissolved in isotonic saline. Nimodipine was first dissolved in one volume of diluted Emulphor and subsequently nine volumes of saline. Diluted Emulphor is 50% Emulphor (EL 620, GAF Corporation, Mississauga, Ontario), 50% ethanol (w/w). Drug solutions were prepared fresh daily and protected from light.

TABLE 1

CONVULSANT EFFECTS OF PTZ IN DRUG-TREATED MICE

Drug(s)	Onset Time (sec) for Clonic Convulsions	%-Convulsing	%-Mortality	N
PTZ 85 mg/kg	71 ± 3	88	23	60
The following drugs were injected 30 min prior to PTZ 85 mg/kg.				
MK-801 0.1 mg/kg	77 ± 5	73	13	15
MK-801 0.5 mg/kg	89 ± 16	100	0‡	15
Nimodipine 2 mg/kg	66 ± 8	100	N.D.	15
Nimodipine 6 mg/kg	78 ± 4	87	53‡	15
Nimodipine 10 mg/kg	139 ± 22*	83	N.D.	30
Nimodipine 20 mg/kg	125 ± 15*	71	43‡	35
Verapamil 10 mg/kg	77 ± 16	87	13	15
Diltiazem 10 mg/kg	57 ± 8	80	27	15
MK-801 0.1 mg/kg + nimodipine 6 mg/kg	150 ± 25*†	63‡	0‡	19
MK-801 0.1 mg/kg + nimodipine 10 mg/kg	120 ± 15*	53‡	0‡	15
MK-801 0.5 mg/kg + nimodipine 2 mg/kg	156 ± 58*†	40‡	0‡	15
MK-801 0.5 mg/kg + nimodipine 6 mg/kg	143 ± 38*†	40‡	0‡	15
MK-801 0.5 mg/kg + nimodipine 10 mg/kg	222 ± 47*	60‡	0‡	25
MK-801 0.5 mg/kg + nimodipine 20 mg/kg	176 ± 31*	47‡	0‡	15

The animals were scored for the appearance of clonic convulsions that were severe enough to result in posture loss over 10 min. The data for onset time are presented as the mean ± S.E.M. of (N) animals. %-Convulsing and %-mortality represent the fraction of animals (N) displaying clonic convulsions and dying (see the Method section) respectively. Significantly different: *from PTZ alone, $p<0.05$, Student's t-test; †from the corresponding dose of nimodipine, $p<0.005$, Student's t-test; ‡from PTZ alone, $p<0.05$, chi-squared test with 1 degree of freedom. N.D. means not determined.

Statistics

The significance of differences between groups of data were analyzed using either a Student's t-test or a chi-squared test with one degree of freedom.

RESULTS

Effects of Drugs on PTZ Convulsions

Consistent with previous observations (6), PTZ at a dose of 85 mg/kg produced severe clonic convulsions in 88% of the mice injected, with a mean onset time of 77 ± 3 sec and 23% mortality (Table 1, Fig. 1). Clonic convulsive activity lasted 9 ± 1 sec (n = 8) and was followed by a postictal period of decreased motor activity and subsequently, further convulsive activity. In some

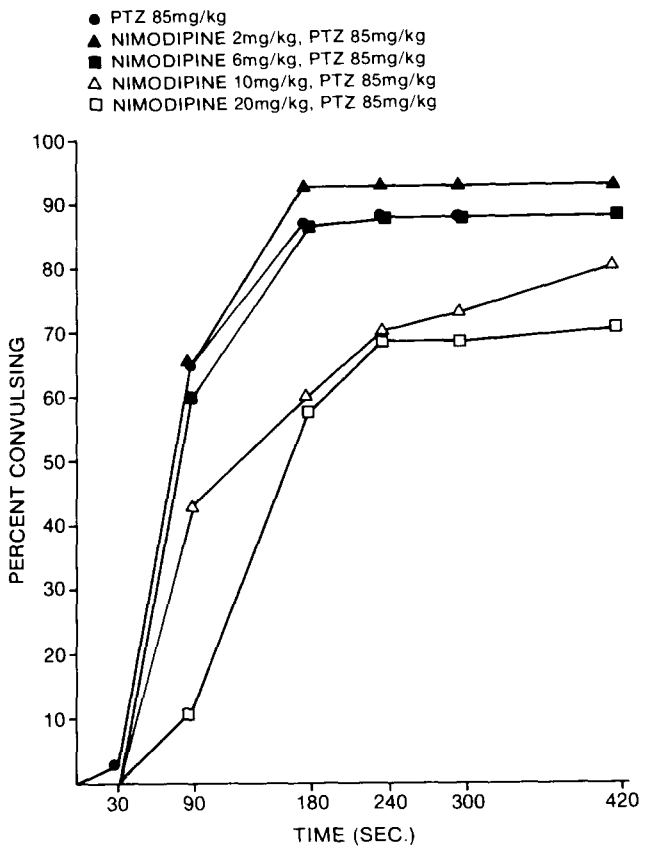

FIG. 1. Effects of nimodipine on the development of clonic convulsions to PTZ. Nimodipine at doses of 2, 6, 10, and 20 mg/kg was administered 30 min prior to the administration of PTZ, 85 mg/kg. Each data point represents the fraction of animals having clonic convulsions severe enough to result in posture loss at the times indicated. The total measurement period was 10 min. Table 1 contains the number of mice tested at each dose.

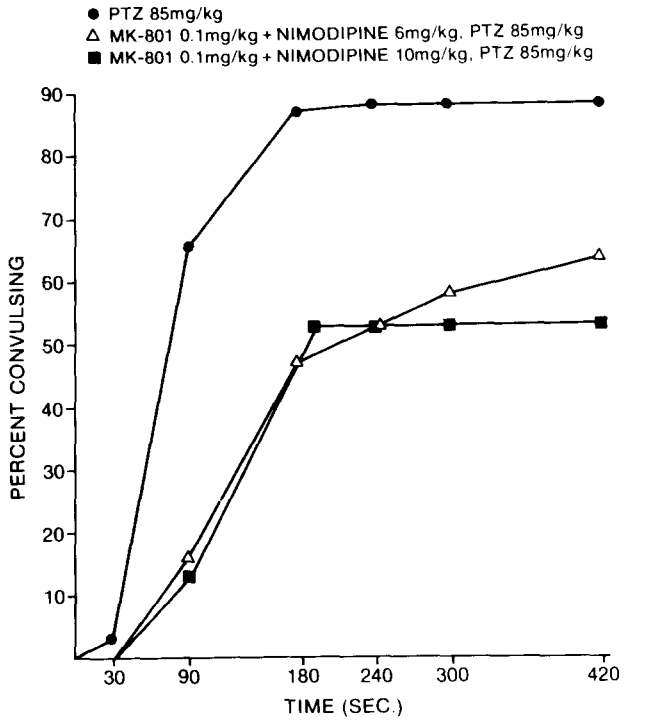

FIG. 2. Effects of MK-801 in combination with nimodipine on the development of clonic convulsions to PTZ. MK-801 at a dose of 0.1 mg/kg was combined with nimodipine at doses of 6 and 10 mg/kg. Doses of drugs were administered on opposite sides of the abdomen 30 min prior to PTZ 85 mg/kg. The data are presented as described in the legend of Fig. 1.

cases this further convulsive activity led to full extension tonic convulsions resulting in death. However, in other cases, clonic convulsions were quickly followed by tonic extension convulsions and death. MK-801 at doses of 0.1 and 0.5 mg/kg did not significantly affect the onset time and number of mice displaying clonic convulsions to PTZ (Table 1). The highest dose of MK-801 chosen for these studies was 0.5 mg/kg, since higher doses resulted in spontaneous convulsive behavior consisting of running fits and "popcorn"-like verticle motor activity (27). MK-801 (0.5 mg/kg) produced a small increase in motor activity, ataxia and hyperreactivity which was not seen at 0.1 mg/kg (27). The severity and duration of the convulsive episode following PTZ were not affected by the doses of MK-801 tested. However, MK-801 (0.5 mg/kg) did protect against mortality due to PTZ (Table 1).

The effects of nimodipine on PTZ clonic convulsions were investigated in the dose range of 2–20 mg/kg, since it was of interest to establish whether doses of nimodipine which inhibit neurotransmitter release (2,21) were anticonvulsant. At doses of 10 and 20 mg/kg, nimodipine significantly increased the onset time to PTZ convulsions (Fig. 1, Table 1); all doses of nimodipine investigated neither affecting the number of mice displaying convulsions to PTZ nor their duration and severity. At 6 and 20 mg/kg nimodipine, doses that were scored for the lethal effects of PTZ convulsions, nimodipine significantly increased the percent mortality to PTZ (Table 1). The nondihydropyridine calcium channel antagonists verapamil and diltiazem did not affect PTZ convulsions (Table 1).

Several dose combinations of MK-801 and nimodipine were investigated for their anticonvulsant effects against PTZ (Table 1). Throughout the dose combinations investigated, there was a significant increase in the onset time to PTZ convulsions, a significant reduction in the number of mice displaying convulsive activity (Figs. 2 and 3) and a complete protection against the lethal effects of PTZ. Dose combinations of MK-801 (0.1 and 0.5 mg/kg) and nimodipine (2 and 6 mg/kg) produced a significant increase in onset time over that produced in the presence of nimodipine alone (Table 1). All dose combinations of MK-801 and nimodipine reduced the severity but not the duration of clonic convulsions to PTZ and increased postictal mobility. Furthermore, nimodipine (2–20 mg/kg) reduced the increased motor activity and hyperreactivity observed with MK-801 0.5 mg/kg (27).

The effects of MK-801, nimodipine, and a combination of both drugs, were also evaluated on STR-induced convulsions. Consistent with previous observations (33), STR produced clonic convulsive activity in 85% of the animals with an onset of 276 ± 20 sec and 54% mortality (Table 2). MK-801 (0.5 mg/kg) produced a significant decrease in the onset time to STR convulsions and an increase in the percent mortality which did not attain significance ($p > 0.05$) (Table 2). Nimodipine (10 mg/kg) did not affect STR convulsions. Combinations of MK-801 and nimodipine, at doses which produced a significant protection against PTZ convulsions, did not affect the convulsive profile of STR. However, nimodipine did prevent the MK-801-mediated decrease in the onset time of STR convulsions (Table 2).

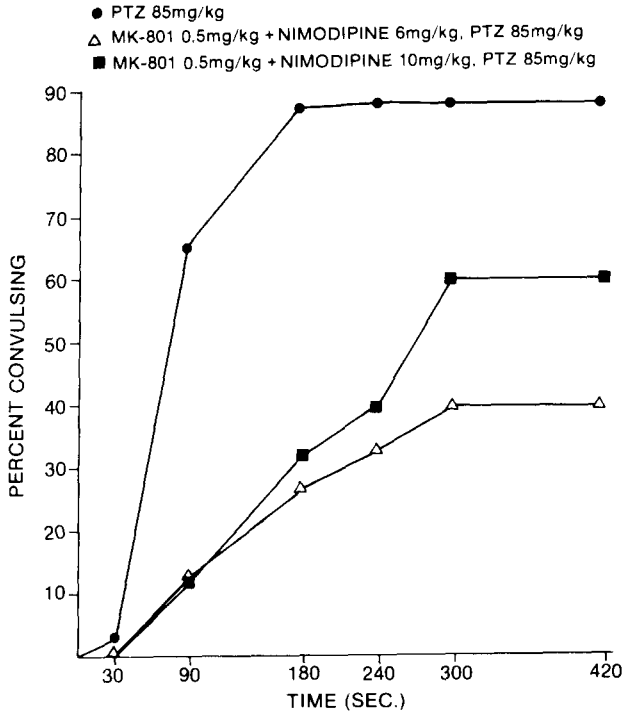

FIG. 3. Effects of MK-801 in combination with nimodipine on the development of clonic convulsions to PTZ. MK-801 at a dose of 0.5 mg/kg was combined with nimodipine at doses of 6 and 10 mg/kg. Drug administration and data presentation are described in the legend of Fig. 1.

DISCUSSION

The major observation made from this study is that doses of MK-801 and nimodipine that have minimal anticonvulsant activity against PTZ produce a potent synergistic anticonvulsive effect when combined. The relative lack of effect of nimodipine on PTZ clonic convulsions is consistent with the finding that only higher doses of nimodipine (40–80 mg/kg) are anticonvulsant in a number of convulsive models (10, 14–16). Two important interactions between low doses of nimodipine [which do not produce any behavioral changes on their own (3,16)], and PTZ were noted however, namely an increase in the onset time and number of animals displaying tonic extension convulsions and death to PTZ. The first of these may be related to the blockade of neuronal 'L'-type (16) calcium channels. Such a mechanism has been postulated to explain the ability of low doses of nimodipine to block increased seizure activity recorded electroencephalographically in the rabbit following administration of PTZ, bicuculline and ischaemia (22–24). The delay in the convulsive onset time may also be due to the block of PTZ-mediated excitatory neurotransmitter release (i.e., glutamate and acetylcholine) by nimodipine (3, 25, 28). The ability of nimodipine to increase the appearance of tonic convulsive activity to PTZ may also be due to its ability to block neurotransmitter release. A number of dihydropyridine calcium channel antagonists (including nimodipine) have been reported to inhibit the release of dopamine and norepinephrine (3, 25, 28, 36). A reduction in the availability of either one or both of these neurotransmitters leads to a reduction of the seizure threshold to PTZ (21,29).

TABLE 2

CONVULSANT EFFECTS OF STR IN DRUG-TREATED MICE

Drug(s)	Onset Time (sec) for Clonic Convulsions	%-Convulsing	%-Mortality	N
STR 1 mg/kg	276 ± 20	85	54	26
The following drugs were injected 30 min prior to STR 1 mg/kg.				
MK-801 0.5 mg/kg	156 ± 11*	93	80	15
Nimodipine 10 mg/kg	234 ± 15	80	47	15
MK-801 0.5 mg/kg + Nimodipine 10 mg/kg	216 ± 2†	100	73	15

The animals were scored for the appearance of clonic convulsions which were severe enough to result in posture loss over 15 min. The data for onset time are presented ± S.E.M. of (N) animals. %-Convulsing and %-mortality represent the fraction of animals (N) having clonic convulsions and dying (see the Method section) respectively. Significantly different, *from STR, $p<0.05$, Student's t-test; †from MK-801 0.5 mg/kg, $p<0.001$, Student's t-test.

It is unlikely that the increased onset time to clonic convulsions mediated by nimodipine is due to its hypotensive effects (16), since verapamil and diltiazem, at doses which are hypotensive (16), had no effect on the onset time to PTZ convulsions. Therefore, low doses of nimodipine appear to be effective at delaying the onset of clonic convulsions, but increase the incidence of tonic-extension convulsions to PTZ.

In contrast to nimodipine, MK-801 is a behaviorally active drug. Several studies have reported behavioral and neurochemical similarities between MK-801 and phencyclidine (7,18); MK-801 being ten-fold more potent than phencyclidine behaviorally (18,27) and at the phencyclidine binding site (35). Prior studies have shown that MK-801 (0.5 mg/kg) produces increases in motor activity, ataxia, and hyperreactivity, while at doses between 1 and 5 mg/kg, MK-801 elcited "popcorn"-like vertical motor activity and wild running fits similar to high doses of phencyclidine (7,27). For these reasons, 0.1 and 0.5 mg/kg MK-801 were utilized to study anticonvulsant activity. Unlike nimodipine, MK-801 did not produce any change in the onset time to PTZ convulsions. However, MK-801 did protect against the lethal effects of PTZ. These observations are consistent with the anticonvulsant effects of the noncompetitive NMDA-receptor antagonist phencyclidine. Phencyclidine was shown to block the appearance of tonic convulsions but not clonic convulsions in mice (13). Thus, it appears that noncompetitive NMDA receptor antagonists are effective at blocking the tonic component of PTZ convulsions.

The combination of MK-801 and nimodipine at various doses produced a marked synergistic anticonvulsant action against PTZ. Most interesting was the significant reduction in the number of animals displaying clonic convulsions to PTZ, the extent of which being similar throughout the dose combinations tested. Similarly, there was a marked synergism between MK-801 and nimodipine (2 and 6 mg/kg) for increasing the onset time to clonic PTZ convulsions. The synergistic actions of MK-801 and nimodipine suggest that a common pathway mediates the marked anticonvulsant activity of this drug combination against PTZ. A putative pathway might be the NMDA-gated calcium channel. Previous studies have indicated that dihydropyridine calcium antagonists produced a specific and complete block of NMDA receptor-mediated deglutative responses originating in the nucleus tractus solitarius of the rat (12). Since the NMDA-gated calcium channel represents the site of action of MK-801, the interaction of nimodipine with this calcium channel via binding to the dihydropyridine binding site might further enhance the blockade of

neuronal NMDA-mediated calcium currents, resulting in a synergistic anticonvulsant effect. Alternatively, the dual blockade of NMDA-gated calcium channels and 'L' -type calcium channels located on excitatory interneurons (8,17) might be responsible for the synergistic anticonvulsant effect. However, given the multitude of physiologic processes mediated by calcium, the synergistic anticonvulsant effects of nimodipine and MK-801 may arise via interaction with any number of calcium-dependent processes.

The inability of MK-801 and nimodipine to completely block clonic convulsions to PTZ may be due to the constraints on the doses of drugs that were used for this study. However, the similar degree of protection observed at low and high dose combinations of nimodipine and MK-801 strongly suggests that a portion of the mechanisms contributing to PTZ convulsions are mediated by the mechanisms previously discussed.

Apart from an anticonvulsant synergism between MK-801 and nimodipine, other noteworthy effects of this drug combination on PTZ convulsions were observed. Firstly, MK-801 prevented the increased mortality from PTZ observed in the presence of 6 and 20 mg/kg nimodipine alone. Secondly, in animals administered combinations of MK-801 and nimodipine, the increased motor activity and hyperreactivity produced by MK-801 were greatly reduced. Nimodipine was also found to reduce the 'running fits' associated with higher doses of MK-801 (27). In total, these observations suggest that the combination of MK-801 and nimodipine can provide an anticonvulsant effect against PTZ in many ways superior to either agent alone.

In contrast to the convulsions generated by PTZ, those elicited by the spinal cord convulsant STR were relatively resistant to modification by either MK-801 and nimodipine or a combination of the two drugs. The inability of MK-801 to block STR convulsions is consistent with the lack of effect of phencyclidine on STR convulsions (13). These findings suggest that spinal cord NMDA-gated and 'L' -type calcium channels do not play a major role in mediating STR convulsions. An unexpected finding was that MK-801 decreased the onset time to STR convulsions and apparently increased the lethal effects of STR (Table 2). STR produces convulsions by antagonism of glycine receptors (11) which results in a disinhibition of sensory afferent information being conducted to the CNS and subsequently convulsions. The CNS excitation produced by MK-801 (27) may lead to an enhancement of STR convulsions despite the block of NMDA-gated and 'L' -type calcium channels.

In summary, a combination of MK-801 and nimodipine produced a synergistic and potent anticonvulsant action compared to either agent alone when PTZ but not STR was used as the convulsant. While our findings support the idea that low doses of either nimodipine or MK-801 may provide a basis for the development of therapeutically important anticonvulsants, the combination of both drugs, or derivatives thereof, may provide a far greater clinical utility (i.e., reduction of the untoward effects of MK-801) against generalized seizures. Quite clearly, further studies are necessary on the relationship between NMDA receptors, calcium channels and the activity of NMDA receptor antagonists and calcium channel blockers at these sites.

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REFERENCES

1. Aanosen, L. M.; Wilcox, G. L. Phencyclidine selectively blocks a spinal action of N-methyl-D-aspartate in mice. Neurosci. Lett. 67: 191–197; 1986.
2. Bolger, G. T.; Weissman, B. A.; Bacher, J.; Isaac, L. Calcium antagonist binding in cat brain tolerant to electroconvulsive shock. Pharmacol. Biochem. Behav. 27:217–221; 1987.
3. Bolger, G. T.; LeSieur, P.; Basile, A. S.; Skolnick, P. Modulation of neurotransmitter metabolism by dihydropyridine calcium channel ligands in mouse brain. Brain Res. 438:101–107; 1988.
4. Bolger, G. T.; Rafferty, M. F.; Crawley, J. N.; Paul, S. N.; Skolnick, P. Effects of calcium antagonists on phencyclidine behaviors. Pharmacol. Biochem. Behav. 25:45–49; 1986.
5. Bongianni, F.; Carla, V.; Moroni, F.; Pellegrini-Giampietro, D. E. Calcium channel inhibitors suppress the morphine withdrawal syndrome in rats. Br. J. Pharmacol. 88:561–567; 1986.
6. Chapman, A. G.; Meldrum, B. S.; Nanji, H.; Watkins, J. C. Anticonvulsant action and biochemical effects in DBA/2 mice of CPP (3((±)-2-carboxypepierazin-4-yl)-propyl-1-phosphonate), a novel N-methyl-D-aspartate antagonist. Eur. J. Pharmacol. 139:91–96; 1987.
7. Contreras, P. C.; Monahan, J. B.; Lanthorn, T. H.; Pullan, L. M.; DiMaggio, D. A.; Handelmann, G. E.; Gray, N. M.; O'Donohue, T. L. Phencyclidine, physiological actions, interactions with excitatory amino acids and endogenous ligands. Mol. Neurobiol. 1:191–211; 1987.
8. Cortes, R.; Supavilai, P.; Karaobath, M.; Palacios, J. M. The effects of lesions in the rat hippocampus suggest the association of calcium channel blocker binding sites with a specific neuronal population. Neurosci. Lett. 42:249–254; 1983.
9. Croucher, M. J.; Collins, J. F.; Meldrum, B. S. Anticonvulsant action of excitatory amino acid antagonists. Science 216:899–901; 1982.
10. DeSarro, G. B.; Nistico, G.; Meldrum, B. S. Anticonvulsant properties of flunnarizine on reflex and generalized models of epilepsy. Neuropharmacology 25:695–701; 1986.
11. Faingold, C. L. Strychnine effects on the sensory response patterns of reticular formation neurons. Electroencephalogr. Clin. Neurophysiol. 50:102–111; 1980.
12. Hashim, M. A.; Bolger, G. T.; Bieger, D. Functional evidence for a link between voltage-operated calcium channels and NMDA receptors in the rat solitary complex. Can. Fed. Biol. Soc. Abstr. 453:138; 1988.
13. Hayes, B. A.; Balster, R. L. Anticonvulsant properties of phencyclidine-like drugs in mice. Eur. J. Pharmacol. 117:121–125; 1985.
14. Hoffmeister, F.; Benz, U.; Heise, A.; Krause, H. P.; Neuser, V. Behavioral effects of nimodipine in animals. Arzniemittelforschung 32:347–359; 1982.
15. Isaacson, R. L.; Thomas, R. J. Effect of a calcium slow channel inhibitor (nimodipine) on picrotoxin-induced seizures. Soc. Neurosci. Abstr. 12:1193; 1986.
16. Janis, R. A.; Silver, P. J.; Triggle, D. J. Drug action and cellular calcium regulation. Adv. Drug Res. 16:309–591; 1987.
17. Jones, S. M.; Snell, L. D.; Johnson, K. M. Inhibition by phencyclidine of excitatory amino acid-stimulated release of neurotransmitter in the nucleus accumbens. Neuropharmacology 26:173–179; 1987.
18. Koek, W.; Kleer, E.; Mudar, P. J.; Woods, J. H. Phencyclidine-like catalepsy induced by the excitatory aminoacid antagonist DL-2-amino-5-phosphonovalerate. Behav. Brain Res. 19:257–259; 1986.
19. Lehmann, J.; Schnieder, J.; McPherson, S.; Murphy, D. E.; Bernard, P.; Tsai, C.; Bennett, D. A.; Pastor, G.; Steel, D. J.; Boehm, C.; Cheney, D. L.; Liebman, J. M.; Williams, M.; Wood, P. L. CPP, a selective N-methyl-D-aspartate (NMDA)-type receptor antagonist: characterization *in vitro* and *in vivo*. J. Pharmacol. Exp. Ther. 240:737–745; 1986.
20. McCaslin, P. P.; Morgan, W. W. 2-Amino-7-phosphonoheptanoic acid, a selective antagonist of N-methyl-D-aspartate, prevents barbital withdrawal-induced convulsions and the elevation of cerebellar cyclic GMP in dependent rats. Neuropharmacology 26:731–735; 1987.
21. Mason, S. T.; Corcoran, M. E. Catecholamines and convulsions. Brain Res. 170:497–507; 1979.
22. Meyer, F. B.; Anderson, R. E.; Sundt, T. M.; Yaksh, T. L.; Sharbrough, F. W. Suppression of pentylenetetrazole seizures by oral

administration of a dihydropyridine Ca^{++} antagonist. Epilepsia 28: 409–414; 1987.
23. Meyer, C. B.; Anderson, R. E.; Sundt, T. M.; Sharbrough, F. W. Selective central nervous system calcium channel blockers—a new class of anticonvulsive agents. Mayo Clin. Proc. 61:239–247; 1986.
24. Meyer, F. B.; Tally, P. W.; Anderson, R. E.; Sundt, T. M.; Yaksh, T. L.; Sharbrough, F. W. Inhibition of electrically induced seizures by a dihydropyridine calcium channel blocker. Brain Res. 384:180–183; 1986.
25. Middlemiss, D. N. The calcium channel activator, BAY K 8644 enhances K^+-evoked efflux of acetylcholine and noradrenaline from rat brain slices. Naunyn Schmiedebergs Arch. Pharmacol. 331: 114–116; 1985.
26. Middlemiss, D. N.; Spedding, M. A functional correlate for the dihydropyridine binding site in rat brain. Nature 314:94–96; 1985.
27. O'Neill, S. K.; Bolger, G. T. Phencyclidine and MK-801: A behavioral and neurochemical comparison of their interactions with dihydropyridine calcium antagonists. Brain Res. Bull.; submitted.
28. Pileblad, E.; Carlsson, A. *In vivo* effects of the Ca^{2+} antagonists nimodipine on dopamine metabolism in mouse brain. J. Neural Transm. 66:171–187; 1986.
29. Snead, O. C. On the sacred disease: The neurochemistry of epilepsy. Int. Rev. Neurobiol. 24:93–180; 1983.
30. Swearengen, E.; Chavkin, C. NMDA receptor antagonist D-APV depresses excitatory activity produced by normorphine in rat hippocampal slices. Neurosci. Lett. 78:80–84; 1987.
31. Trouve, R.; Nahas, G.; Latour, C.; Sitbon, M.; Demus, J. F. Ca^{++} modulators as antidotes to imipramine lethal toxicity in the rat. Br. J. Pharmacol. 90:183P; 1987.
32. Turski, L.; Klockgether, T.; Sontag, K-H.; Herrling, P. L.; Watkins, J. C. Muscle relaxant and anticonvulsant activity of 3-(($\pm$)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid, a novel N-methyl-D-aspartate antagonist, in rodents. Neurosci. Lett. 73:143–148; 1987.
33. Weissman, B. A.; Bolger, G. T. The effects of chemically and electrically-induced convulsions on [^{3}H]nitrendipine binding in mouse brain. Brain Res. Bull. 19:673–678; 1987.
34. White, E. J.; Bradford, H. F. Enhancement of depolarization-induced synaptosomal calcium uptake and neurotransmitter release by BAY K 8644. Biochem. Pharmacol. 35:2193–2197; 1986.
35. Wong, E. H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83: 7104–7108; 1986.
36. Woodward, J. J.; Leslie, S. W. BAY K 8644 stimulation of calcium entry and endogenous dopamine release in rat striatal synaptosomes antagonized by nimodipine. Brain Res. 370:397–400; 1986.