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Paradoxical Facilitation of Pilocarpine-Induced Seizures in the Mouse by MK-801 and the Nitric Oxide Synthesis Inhibitor L-NAME

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STARR, M. S. AND B. S. STARR. *Paradoxical facilitation of pilocarpine-induced seizures in the mouse by MK-801 and the nitric oxide synthesis inhibitor* L-NAME. PHARMACOL BIOCHEM BEHAV 45(2) 321–325, 1993.—The sensitivity of pilocarpine-induced seizures to NMDA receptor blockade with MK-801, or to inhibition of synthesis of the second messenger nitric oxide (NO) with N^{ω}-nitro-L-arginine methyl ester (L-NAME), was studied in mice. The NO precursor L-arginine (100–500 mg/kg, IP) and L-NAME (1–125 mg/kg, IP) had no overt effects on animals' behaviour by themselves, while MK-801 (0.1–0.8 mg/kg, IP) caused motor excitability at low doses and sedation and paraplegia at high ones. Contrary to expectation, MK-801 and L-NAME failed to protect mice against limbic motor seizures induced by pilocarpine (400 mg/kg, IP), and L-arginine was not proconvulsant in mice challenged with a threshold convulsant dose of the cholinomimetic (100 mg/kg, IP). Surprisingly, both MK-801 and L-NAME were found to be proconvulsant when injected in conjunction with 100 mg/kg pilocarpine, and in both cases this convulsant action synergised with that produced by the dopamine D_1 agonist SK&F38393 (10 mg/kg, IP). Concomitant administration of L-arginine (500 mg/kg) prevented the convulsant effect of 5 mg/kg L-NAME but was ineffective against 25 mg/kg L-NAME and MK-801. It is concluded that glutamate, acting through the NMDA receptor and NO production, normally suppresses epileptogenesis in the mouse pilocarpine model of limbic epilepsy.

Epilepsy Mouse Pilocarpine MK-801 Nitric oxide

IN rodents, a high dose of pilocarpine given systemically is believed to activate muscarinic receptors in the hippocampus (18), thereby initiating spontaneously recurrent motor limbic seizures that have electrographic, behavioural, and neuropathologic features in common with partial complex seizures in man (17). Intractable status epilepticus is also readily achieved with pilocarpine, and this is believed to involve the recruitment of diverse neurochemical pathways in various parts of the brain, including those that utilise the excitatory amino acid transmitter glutamate, following secondary generalisation of the seizure.

Biochemical analyses of brains removed from animals subjected to lithium–pilocarpine seizures provided indirect evidence for the secondary involvement of excitatory amino acids in the initiation of epileptogenesis by cholinomimetics (20). Significant decreases in the tissue contents of glutamate and aspartate were detected in the hippocampus, as well as other limbic structures, consistent with a massive release of these amino acids having taken place as a result of seizure activity. These findings led discoverers to speculate that drugs that blocked the synaptic action of glutamate, or the second messengers it activated, could prove useful in the therapeutic management of human status epilepticus, especially in the later stages, when it can become refractory to conventional antiepileptic treatments.

Recent evidence suggests glutamate mediates epileptiform activity by stimulating NMDA type receptors, with the subsequent activation of nitric oxide (NO) synthesis intracellularly (14). Further, the NMDA receptor-channel blocker MK-801 (21), and the NO synthesis inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME) (12), have been reported to reduce the severity of seizures induced by the anticholinesterase tacrine (1) or electrical kindling (5), implicating NO-linked NMDA receptors in the evolution of partial complex seizures. In the present study, we tested MK-801 and L-NAME for their effectiveness as anticonvulsants in the mouse, in which this type of seizure was evoked with the muscarinic agonist pilocarpine.

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METHOD

Induction of Pilocarpine Seizures

Male mice of the inbred MF1/R2 strain, weighing 35–50 g, were used in this study. Animals were housed in groups of 8–10 at 22 ± 1°C, under fluorescent lighting from 0700–1700 h, and allowed free access to food and water.

Mice were weighed and injected IP with methyl scopolamine (1 mg/kg) to prevent the peripheral autonomic effects of pilocarpine. They also received IP injections of water (controls), L-arginine (100–500 mg/kg; NO donor), SK&F38393 (10 mg/kg; D_1 agonist), MK-801 (0.1–0.8 mg/kg; NMDA antagonist), or L-NAME (1–125 mg/kg; NO synthase inhibitor) before being returned to their home cage. Thirty minutes later, mice were subjected to one of three forms of challenge with the convulsant compound pilocarpine: a) a subconvulsant 100-mg/kg dose; b) a 100-mg/kg dose made to give clonic convulsions by prior sensitisation with SK&F38393 [this combined treatment elicits limbic seizures that are identical in every respect to those produced by a higher dose of pilocarpine alone—see (18)—but are more reproducible]; c) a 400-mg/kg dose giving tonic convulsions. The first two treatments revealed drug treatments that facilitated seizure development, while the latter treatment detected anticonvulsant effects. All mice were subsequently observed for up to 3 h for characteristic signs of motor seizures (18), as well as gross changes in motor behaviour.

Statistical Analysis

Seizure frequencies and mortalities were compared by Fisher's exact probability test and seizure latencies by Student's *t*-test.

Drugs

All drugs were dissolved in demineralised water and administered IP in a dose volume of 5 ml/kg. L-Arginine, L-NAME, pilocarpine nitrate, and (−)-scopolamine methyl bromide were obtained from Sigma Chemical Co. (St. Louis, MO), while SK&F38393 and MK-801 were purchased from Research Biochemicals, Inc. (Natick, MA).

RESULTS

As noted in previous studies (3), 100 mg/kg IP pilocarpine elicited flank scratching and tremor in some mice but no seizure activity (0 of 27 convulsed). However, pretreatment with the selective dopamine D_1 receptor agonist SK&F38393 (10 mg/kg, IP) sensitised mice to the convulsant action of 100 mg/kg pilocarpine; 12 of 40 convulsed (none fatally) with an average latency of 38.3 ± 11.4 min (Fig. 1 and Table 1). These convulsions were characterised by a temporal sequence of head bobbing, rearing, and falling, interspersed with myoclonus of the forelimbs, leading eventually to status epilepticus. The combination of a subconvulsant amount of pilocarpine together with a sensitising dose of SK&F38393 has been found to produce clonic convulsions more reliably than using a higher dose of pilocarpine on its own (unpublished observations). At the higher dose of 400 mg/kg IP, pilocarpine elicited clonic-tonic convulsions in 12 of 15 animals (11 rapidly fatal) with a mean latency of 17.7 ± 1.4 min (Table 1).

Control injections of the NO precursor L-arginine (100–500 mg/kg, IP), the noncompetitive NMDA antagonist MK-801 (0.1–0.8 mg/kg, IP), or the NO synthase inhibitor L-NAME (1–125 mg/kg, IP) were unable to evoke convulsions by themselves (data not shown). Neither L-arginine nor L-NAME appeared to alter animals' behaviour at the doses tested. MK-801, on the other hand, induced hyperactivity at low doses (0.1–0.2 mg/kg) and progressively more pronounced sedation and ataxia at higher ones (0.4–0.8 mg/kg).

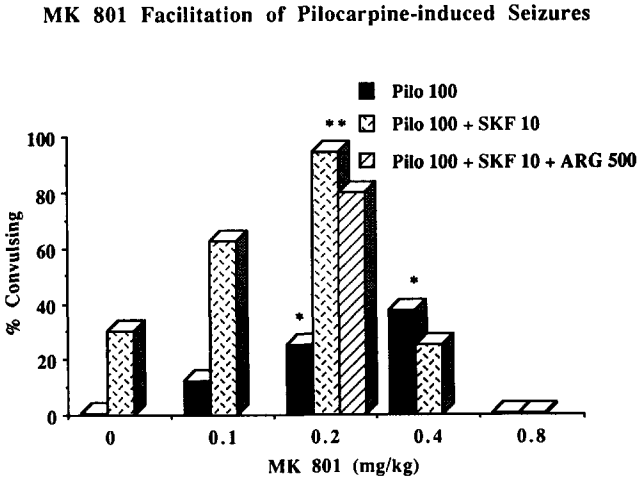

FIG. 1. Proconvulsant effect of MK-801 in pilocarpine-induced epilepsy in mice. Animals were pretreated IP with MK-801 together with vehicle or the dopamine D_1 receptor agonist SK&F38393 (SKF; 10 mg/kg), alone or in combination with L-arginine (ARG; 500 mg/kg), and 30 min later administered a subconvulsant dose of pilocarpine (PILO; 100 mg/kg, IP). Animals were then observed for 3 h for signs of seizure activity. Results are means of 9–17 experiments. $*p < 0.05$, $**p < 0.005$ vs. appropriate controls by Fisher's exact probability test.

With the expectation that MK-801 and L-NAME would protect against pilocarpine-induced seizures [see (1)], these compounds were first tested in combination with the higher dose of the cholinomimetic. Table 1 shows that neither agent significantly altered the threshold or latency of onset of motor seizures or the mortality rate. L-arginine (100–500 mg/kg, IP) was similarly without effect and did not alter the seizure severity in mice that were subsequently challenged with a subconvulsant dose of pilocarpine (100 mg/kg), with or without pretreatment with SK&F38393 (10 mg/kg; Table 1).

Although not statistically significant, the consistently higher convulsion frequencies and mortalities we observed in the L-NAME-treated groups gave the impression that inhibition of NO synthesis might have exacerbated epileptogenesis. To test this, we repeated the MK-801 and L-NAME experiments with the lower dose of pilocarpine. Figure 1 shows that MK-801 pretreatment significantly increased the frequency of convulsions obtained with 100 mg/kg pilocarpine, in a bell-shaped dose-dependent manner, with latencies of 24.5 ± 10.3 and 50.0 ± 10.5 min at 0.2 and 0.4 mg/kg MK-801, respectively. No effect of 0.1 or 0.8 mg/kg MK-801 was detected. Convulsions were tonic in nature and no fatalities were recorded.

Interestingly, when low doses of MK-801 were coadministered with the D_1 agonist SK&F38393 (10 mg/kg, IP) the two proconvulsants interacted to produce a greater than additive seizure response (Fig. 1). This synergistic effect was most

TABLE 1

EFFECTS OF MK-801, L-NAME AND L-ARGININE ON PILOCARPINE-INDUCED MOTOR SEIZURES IN MICE

Treatment (mg/kg)	Number Convulsing	Mean Latency (min)	Number of Fatalities
Pilocarpine (100)	0/27	–	0/27
+ L-Arginine (100)	0/10	–	0/10
+ L-Arginine (500)	0/10	–	0/10
+ SK&F38393 (10)	12/40*	38.3 ± 11.4	0/40
+ SK&F38393 (10) and L-Arginine (500)	5/10	43.0 ± 5.3	0/10
Pilocarpine (400)	12/15	17.4 ± 1.4	11/15
+ L-Arginine (500)	8/8	14.8 ± 1.7	8/8
+ MK-801 (0.1)	7/8	16.7 ± 0.8	4/8
+ MK-801 (0.2)	7/8	19.9 ± 2.1	4/8
+ MK-801 (0.4)	7/8	18.8 ± 0.9	6/8
+ MK-801 (0.8)	7/8	20.0 ± 0.6	5/8
+ L-NAME (1)	10/10	18.0 ± 1.1	9/10
+ L-NAME (5)	10/10	16.3 ± 0.7	7/10
+ L-NAME (25)	9/9	16.2 ± 1.4	9/9
+ L-NAME (125)	10/10	15.9 ± 1.7	10/10

All animals received scopolamine methyl bromide (1 mg/kg) plus the treatments shown 30 min before pilocarpine. All drugs were administered IP and mice observed for 3 h.

*$p < 0.001$ by Fisher's exact probability test compared to pilocarpine (100 mg/kg) alone.

noticeable at 0.2 mg/kg MK-801, although the seizure latency remained unchanged at 21.7 ± 4.6 min (compared to MK-801 alone). No such facilitation was apparent with the SK&F38393/MK-801 drug cocktail when this involved higher doses of the NMDA antagonist (0.4–0.8 mg/kg). However, these results should be viewed with caution because animals were heavily sedated and prostrate and it was difficult to tell if they had convulsed or not. Hyperpnoea and continuous vocalisation were hallmarks of this combined treatment.

L-NAME was also found to be proconvulsant (Fig. 2). In the dose range 1–25 mg/kg IP, the NO synthesis inhibitor on its own did not potentiate pilocarpine-induced convulsions but was seen to do so at 125 mg/kg (five of eight convulsed, three fatally, mean latency 25.6 ± 9.3 min). However, there was a striking increase in the seizure rate when lower doses of L-NAME (5-25 mg/kg) and SK&F38393 (10 mg/kg) were administered together, consistent with the two drugs interacting in a synergistic fashion. Typically, though, the times of onset of seizures remained constant (32.0 ± 2.1 and 28.2 ± 5.6 min, respectively).

If NMDA receptors are linked to NO production in this test system, then it should be possible to reverse the MK-801- and L-NAME-induced facilitation of seizures with the NO donor L-arginine (10). We found that L-arginine, 500 mg/kg IP, was unable to modify the response to MK-801 (Fig. 1), while it reversed the convulsant effects of 5 mg/kg but not 25 mg/kg L-NAME (Fig. 2).

DISCUSSION

The results of this study showed, unexpectedly, that pretreating mice with the noncompetitive NMDA receptor antagonist MK-801, or with the NO synthase inhibitor L-NAME, was conducive to seizure development by the muscarinic agonist pilocarpine. This finding contrasts directly with recent reports in which MK-801 and L-NAME were found to be anticonvulsant in other models of secondarily generalised partial complex seizures. First, Gilbert (5) announced that IP pretreatment with MK-801, in a similar dose (0.5 mg/kg) to those used here, lessened the severity of motor seizures induced by electrical kindling of the hippocampus. This is perhaps not

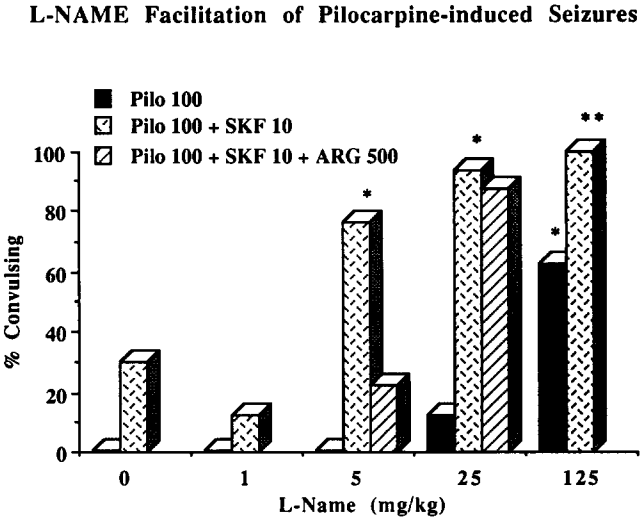

FIG. 2. Proconvulsant effect of L-NAME in pilocarpine-induced epilepsy in mice. Animals were pretreated IP with L-NAME together with vehicle or the dopamine D_1 receptor agonist SK&F38393 (SKF; 10 mg/kg), alone or in combination with L-arginine ARG; 500 mg/kg), and 30 min later administered a subconvulsant dose of pilocarpine (PILO; 100 mg/kg, IP). Animals were then observed for 3 h for signs of seizure activity. Results are means of 10 experiments. *$p < 0.05$, **$p < 0.005$ vs. appropriate controls by Fisher's exact probability test.

surprising in view of the high density of NMDA receptors in the hippocampus, but it does not explain why MK-801 facilitated the comparable epileptic condition elicited by chemical stimulation of the hippocampus with pilocarpine (18).

Second, Bagetta et al. (1) demonstrated that L-NAME prevented the seizures and brain damage produced by the anticholinesterase tacrine in LiCl-treated rats. Once again, the origin and behavioural characteristics of the motor limbic seizures evoked by the two cholinomimetics would appear to be closely similar, if not identical. So, the clue to the opposing actions of L-NAME in these two studies is to be found either in the mechanisms by which lithium sensitises rats to tacrine-induced epilepsy or in the mode of administration of the enzyme inhibitor, which in turn will determine its site(s) of action in the brain.

NMDA is strongly convulsant by the ICV route (7), and so it is likely that by injecting L-NAME directly into the ventricles Bagetta et al. (1) succeeded in deactivating the same population of glutamate receptors as were activated by NMDA. If these receptors lie at the epileptic focus, then their stimulation will promote paroxysmal cell firing (2). It must be emphasised, however, that there are NMDA receptors in other parts of the brain that, when stimulated, can have the opposite effect and inhibit seizures. Turski's group has shown that NMDA microinjected into the corpus striatum (19) or substantia nigra pars compacta (16) acts to release mediators (e.g., GABA and dopamine, respectively) that curtail pilocarpine-induced seizure propagation. Thus, if the overriding effect of systemic L-NAME, as used in the present study, is to cross into the brain and remove the protective action of endogenous glutamate within the basal ganglia a facilitation rather than a diminution of the seizure response will be the outcome. Discrete stereotaxic injection of L-NAME into the brain sites in question (i.e., striatum and substantia nigra) should provide a simple test of this hypothesis.

The NMDA receptor-channel blocker, MK-801, was also paradoxically proconvulsant in the present study. In general, all of the various types of NMDA receptor antagonists, not just MK-801, have been shown to be potently anticonvulsant in a wide variety of in vitro and in vivo models of epilepsy [see (4)]. Moreover, some authors have argued that blocking excitatory amino acid receptors, or their associated second messenger systems, may be the only feasible way of arresting seizure activity at its source in the later stages of human status epilepticus (20). The intractable convulsions that develop after animals have been challenged with pilocarpine are believed to closely mimic this clinical condition (17). It seems ironic, therefore, that reality was the very antithesis of prediction, that is, these seizures were made worse, not better, by MK-801, possibly because the drug (as speculated for L-NAME) was removing a beneficial influence of glutamate within basal ganglia pathways that normally contain seizure spread.

The results of O'Neill and Bolger (11), who found that MK-801 similarly potentiated strychnine-induced convulsions, provide indirect support for this suggestion. Strychnine convulsions are believed to originate at the spinal level and to be modulated by the substantia nigra via its efferent connections with reticulospinal systems (13). Given that the nigra also exerts a profound influence on the propagation of limbic seizures (15), the blockade of NMDA receptors in this nucleus would explain how MK-801 is able to facilitate both strychnine and pilocarpine convulsions.

McAllister (9) recently commented on the difficulties associated with the assessment of MK-801 in seizure models. High doses of MK-801 (i.e., >0.4 mg/kg) are strongly hypnotic and cause paraplegia, and these debilitating effects are apparently accentuated by the epileptic condition itself [see (8)]. Thus, while we were able to demonstrate a clear proconvulsant response to MK-801 in the dose range 0.1–0.2 mg/kg, when animals exhibited amphetamine-like hypermotility, the lack of any such effect at 0.4–0.8 mg/kg may have been related to their motor incapacity.

In earlier studies, we noticed that pilocarpine-induced seizure activity is markedly accentuated by drugs that stimulate dopamine D_1 receptors in the brain (3). Also, the increases in motor activity effected by D_1 stimulant drugs in dopamine-depleted animals are greatly potentiated by MK-801 (6), strongly suggesting that a functional interdependence occurs between D_1 and NMDA receptors in the control of certain behaviours. We saw a similar synergism between the proconvulsant actions of the selective D_1 agonist, SK&F38393, and those of L-NAME and MK-801 in this study. Thus, intermediate doses of L-NAME and MK-801, which showed little or no tendency to cause convulsions, either when administered alone or in the presence of a threshold convulsant dose of pilocarpine (100 mg/g), greatly enhanced the proconvulsant action of SK&F38393 in the presence of the cholinomimetic (Fig. 2). It is possible, therefore, that other responses mediated by D_1 receptors in the brain will be found to involve a collaboration with glutamate acting at NMDA receptors, which in turn are linked to the NO signal transduction system.

NO is a cellular messenger released in response to NMDA receptor activation (14). It is derived from L-arginine in the body, and Mollace et al. (10) recently reported that L-arginine injected ICV potentiated the epileptogenic property of a subconvulsive amount of NMDA. It is tacitly assumed, therefore, that MK-801 and L-NAME owe their proconvulsant actions in the present study to a similar interference with NO production. Our attempt to confirm this suspicion, by administering a large dose of L-arginine systemically to restore NO synthesis that had been suppressed by MK-801 and L-NAME, was not entirely successful. This treatment reversed the convulsant effect of 5 mg/kg L-NAME but not that of 25 mg/kg L-NAME or 0.2 mg/kg MK-801. The role of NO in the convulsant response to MK-801 in this model must therefore remain speculative. In all probability, insufficient quantities of L-arginine were able to gain access to the brain following systemic injection because even with a large dose (500 mg/kg, IP) we never saw signs of the behavioural excitation that had previously been reported to occur with ICV delivery of the amino acid (10). Further experiments are required to test whether intracerebral L-arginine is antiepileptic in this test system.

In conclusion, the present study demonstrates that MK-801 and L-NAME, compounds that exhibit anticonvulsant activity in other animal models of partial complex seizures, paradoxically accentuate rather than alleviate the convulsions associated with pilocarpine-induced epileptiform activity in mice. As stimulation of NMDA receptors has been linked with NO synthesis, and a similar lowering of seizure threshold also occurred with the NO synthase inhibitor L-NAME, it is suggested that excitatory amino acid transmission, acting through the NO system, is essential for curbing epileptogenesis initiated by muscarinic overactivity in the hippocampus. The pilocarpine model of epilepsy would therefore appear to behave differently from other models of secondarily generalised motor limbic seizures, with regard to MK-801 sensitivity and NO involvement.

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