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The Effect of the NMDA Receptor Antagonist, MK-801, on the Course and Outcome of Kindling

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MINTZ, M., I. C. ROSE AND L. J. HERBERG. *The effect of the NMDA receptor antagonist, MK-801, on the course and outcome of kindling*. PHARMACOL BIOCHEM BEHAV **35**(4) 815–821, 1990.—A rapid kindling procedure was used to distinguish between the anticonvulsant activity of drugs and their ability to retard the kindling process. MK-801 is a specific ligand at the phencyclidine (PCP) recognition site, and acts as a noncompetitive antagonist of NMDA-type glutamate/aspartate receptors. Intraperitoneal injections of MK-801 (0.5–4.0 mg/kg IP) significantly reduced the cumulated effect of 12 2-hr kindling stimulations, as determined from behavioral measures of seizure activity in immediately ensuing 24-hr drug-free kindling sessions; however, the corresponding electrographic effects did not reach significance. MK-801 also showed significant anticonvulsant activity when injected in fully kindled rats. Higher doses tested were accompanied by locomotor and postural effects. The anticonvulsant benzodiazepine, clonazepam, formulated with a proprietary diluent (as Rivotril, Roche), injected in anticonvulsant doses during the first 12 kindling sessions (0.64 mg/kg IP, repeated after 9 hr) did not significantly affect the course of subsequent sessions of drug-free kindling. Systemic injections of kynurenic acid (300–600 mg/kg IP 4 hours), a nonspecific antagonist of glutamate receptors in vitro, were without significant anticonvulsant or antikindling activity. Activity of NMDA-sensitive glutamate/aspartate receptors associated with the PCP recognition site may induce lasting facilitation of neural transmission; this facilitation may be responsible for the remote propagation and progressive enhancement of seizure activity kindled in the amygdala. The facilitatory process appears to be antagonised by MK-801.

Afterdischarges Amygdala Anticonvulsants Ataxia Clonazepam Epilepsy Glutamate Kindling Kynurenic acid MK-801 NMDA Seizures

RECENT findings have implicated excitatory amino acids (EAA) in the generation or propagation of brain seizure activity in various animal models of epilepsy, and several investigators have emphasised the possible importance of EAA antagonists as potential anticonvulsant agents [reviewed by Patel and colleagues (32)]. Unfortunately, the anticonvulsant activity of EAA antagonists can generally be seen only after direct intracranial injection (9,35), owing to their poor penetration of the blood-brain barrier. However, certain dissociative anaesthetics, among them ketamine and phencyclidine (PCP), cross freely into the brain where they act as noncompetitive NMDA antagonists at PCP recognition sites associated allosterically with the NMDA receptor. These compounds have well-documented anticonvulsant properties (6, 18, 31), and inhibit the expression of kindled seizures when injected systemically (3, 4, 5, 13). Unfortunately, the anti-NMDA activity of the dissociative anaesthetics is not easily disentangled from their affinity for sigma receptors (24,28); thus, the recent advent of MK-801, a novel and selective ligand for the PCP recognition site (44), affords a unique opportunity for investigating the anticonvulsant potential of the PCP-NMDA receptor complex (7,32). Recent investigations, confirming the potent anticonvulsant activity of MK-801, have shown that treatment with this compound may retard the development of the electrophysiological and behavioral manifestations of seizures kindled in the rat amygdala (15, 27, 39, 45). Anticonvulsant activity has also been reported against fully kindled seizures (39), but uncertainty remains as to the effect of MK-801 on the severity and duration of fully kindled electrophysiological seizures (15) or their behavioral expression (27,45). In the present study we have reexamined the anticonvulsant properties of MK-801 in an accelerated kindling paradigm which does not require repeated daily injection of the compound under test. The anticonvulsant and antiepileptogenic effects of MK-801 in this procedure were compared with those of kynurenic acid and clonazepam. Kynurenic acid is a nonselective competitive antagonist of glutamate receptors (10) that may enter the brain sparingly when injected systemically in high enough doses (32).

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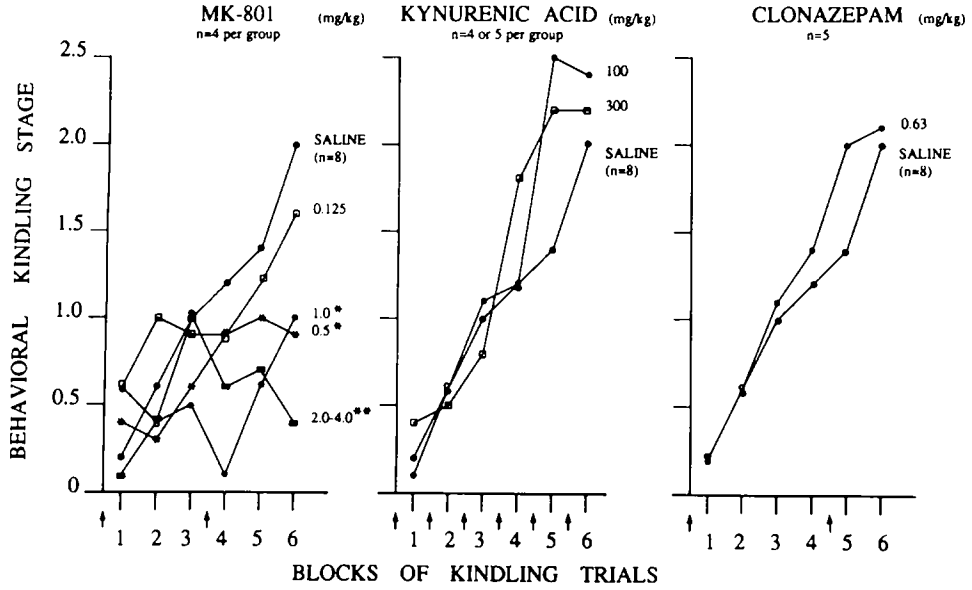

FIG. 1. Development of behavioural signs of seizure activity (Racine scale) during accelerated kindling (12 stimulations at 2-hr intervals). The plotted score of each block is the mean of two consecutive trials. Panels from left to right show the effects of MK-801, kynurenic acid and clonazepam. Arrows indicate the timing of injections. Data obtained with 2.0 and 4.0 mg MK-801 were similar, and have been pooled. The same saline control group is shown for each treatment. Significance tests, against saline controls, are based on the final kindling trial. $*p<0.05$; $**p<0.01$.

Kynurenic acid is also an antagonist (12) of strychnine-insensitive glycine receptors (22) that ordinarily potentiate the activity of the NMDA receptor (42). Clonazepam is a 1,4-benzodiazepine with anticonvulsant properties (36) that probably depend on GABAergic mechanisms (17).

METHOD

Subjects

Thirty-eight Wistar or Lister hooded rats were anaesthetised with nembutal and implanted with twisted bipolar stainless steel electrodes of 0.25 mm nominal diameter, insulated to within 0.5 mm of their tips. Electrodes were aimed at a point in the right amygdala with stereotaxic coordinates A6.8, L5.0, V6.6 in the atlas of Paxinos and Watson (33), and fixed in place with acrylic cement and screws. Electrode locations were verified on thionin-stained frozen sections at the end of the experiment. Rats with electrodes falling outside the amygdala were excluded from further analysis.

Drugs

MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine] (a gift from Merck Sharpe & Dohme Ltd.) was dissolved in saline. Kynurenic acid (4-hydroxyquinoline-2-carboxylic acid, Sigma) was dissolved in 30% NaOH and titrated to pH 6.0 with 2 M HCl. Clonazepam (Rivotril, Roche; including proprietary vehicle) was dispensed from pharmaceutical ampoules. Solutions were injected intraperitoneally in a volume of 1 ml/kg.

Kindling

Kindling of seizures was carried out in transparent observation cages. An accelerated kindling schedule provided a total of twelve successive 1.5-sec, 50-Hz, 125-μA sinusoidal trains at 2-hr intervals over a 24-hr period. Intersession intervals of not less than 2 hr, as selected here, are long enough to ensure dissipation of short-term postictal inhibition which may else disrupt kindling (20,30). Kindling at 2-hr intervals is not less effective than at 24-hr intervals (38), and the shortened procedure has the advantage of minimising the number of repeated drug treatments needed to cover the period of kindling. Afterdischarges were recorded through the stimulating electrodes with a Grass 7C polygraph. Seizures were graded on Racine's 5-point scale (37). After the 12th stimulation, further stimulations were given at a rate of one stimulus every 24 hr until full Stage 5 seizures had developed.

Spontaneous behaviour and posture were monitored for 3 to 5 min before and after kindling sessions. The examiner in each case was aware of the treatment that had been given, and assessment was limited to a short list of objective criteria. Ataxia was assessed on a 3-point scale: (0)—Normal posture and gait; (+)—Signs of instability or incoordination present, but body supported on the four limbs when alerted; (++)—Rat rests or moves with body flat on the floor. Spontaneous activity was scored on a four-point scale: (−)—No spontaneous locomotion and no apparent bodily movement; (0)—Bodily movement present, with exploration of the kindling cage; (+)—Intermittent bursts of excessive locomotion; (++)—Continuous excessive locomotion and activity.

Procedure

Accelerated kindling, followed by daily kindling, commenced on the sixth day after surgery. Drug treatments were maintained throughout the period of accelerated kindling to assess their effect on the rate of seizure development, and drugs were given again in the final 24-hr sessions to assess their effect on fully developed seizures. Accelerated kindling started 45 min after injection of MK-801 or clonazepam, or 30 min after kynurenic acid. Booster injections of MK-801 were given at half the original dose, 1 hr

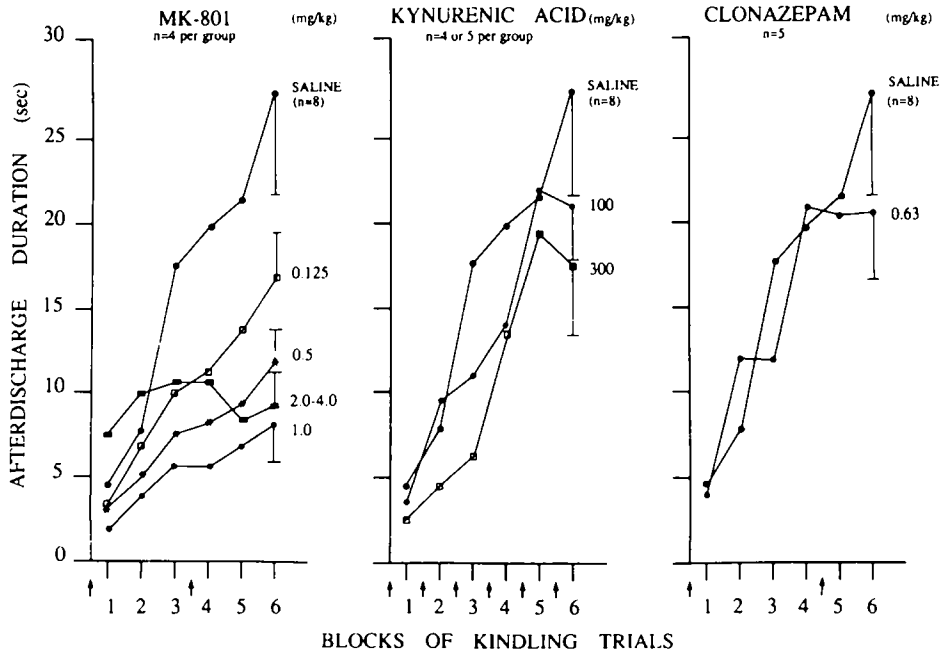

FIG. 2. The effects of MK-801, kynurenic acid, and clonazepam on the duration of amygdaloid afterdischarges (seconds ± sem) during accelerated kindling. Other details as in Fig. 1.

before the 7th stimulation (i.e., 11:45 hr after the previous injection). This schedule was based on studies indicating persisting anticonvulsant effects (39) or behavioural effects (Mintz, unpublished) at periods of up to (and including) 12 hr after injection. Clonazepam at full dose was given 1 hr before the 5th stimulation (i.e., 7:45 hr after the previous injection). Full doses of kynurenic acid were given before every second stimulation. The pharmacokinetics of kynurenate are ill-defined, but profound depression of hypothalamic self-stimulation reported after intraperitoneal injection (300 mg/kg) showed no diminution after 1 hr (19). Control injections of saline matched the timing of the MK-801 or the kynurenic acid injections.

Anticonvulsant activity by MK-801 and kynurenic acid was also tested in fully kindled rats which had developed at least one Stage 5 seizure. For this purpose, MK-801, kynurenic acid or saline was injected 30 min (kynurenic acid) or 45 min (MK-801 or saline) before stimulation of the amygdala, and the intensity and duration of the ensuing seizure was compared with seizures recorded in the undrugged rat on days immediately before and after.

The effects of treatments were assessed by Kruskal-Wallis one-way analyses of variance, and group differences were tested where appropriate by Mann-Whitney summed ranks tests of significance (16).

RESULTS

PHASE 1: Accelerated Kindling

Seizure activity. All rats gave similar behavioural responses to the first stimulus of the kindling series, generally just a small head twitch. With further stimuli, the saline-treated group showed regular progression in the intensity of their reaction, culminating, in most cases, in their reaching Racine's Stage 2 (Fig. 1). This progression was not prevented by clonazepam or kynurenic acid, the latter tending even to accelerate the rate of kindling, as compared to saline. In contrast, MK-801 showed a dose-related ability to antagonise the development of seizures, higher doses (2.0 and 4.0 mg/kg) producing an almost complete suppression of progress. Group comparisons for the last (12th) kindling session showed a significant effect of treatment on seizure severity (Kruskal-Wallis, $H = 11.24$, $p<0.05$), particularly in groups treated with MK-801 in doses of 0.5 and 1.0 kg/kg (Mann-Whitney $p<0.024$), or 2.0–4.0 mg/kg ($p<0.004$).

Afterdischarges. Kynurenic acid or clonazepam had no significant effect on afterdischarge durations recorded at Session 12. Rats treated with MK-801 generally showed shorter mean durations than saline-treated rats, but the trend did not reach significance (Kruskal-Wallis, $H = 9.0$, $0.05<p<0.1$) (Fig. 2). Appreciable afterdischarge activity was observed (with about one-third of control durations) even after the highest doses of MK-801. Electrophysiological evidence of afterdischarge activity as recorded from the stimulated amygdala was generally accompanied by only minimal behavioural evidence of seizure activity (Fig. 3).

Motor effects. Rats treated with kynurenic acid or clonazepam showed no apparent alteration in general behaviour (posture, gait or cage exploration) during prekindling observation periods. MK-801, on the other hand, caused clear dose-dependent behavioural changes. In initial sessions, low doses (0.125 and 0.5 mg/kg) produced mild ataxia (+) and increased locomotor activity (++). Ataxia disappeared in subsequent sessions, but enhanced locomotion (+) persisted in 7/8 rats. Larger doses of MK-801 (1.0 to 4.0 mg/kg) were characterised by marked flaccidity, with the rats sprawled flat [ataxia = (++) in 7/8 rats], coupled with prolonged immobility from which the rats could be roused only by strong external stimuli [locomotor score = (−) in 7/8 rats]. In later sessions all the group regained the ability to support their bodies off the cage floor [ataxia score = (+)], but 7/8 rats now showed excess locomotor activity (++). Locomotion occurred as nontight circling.

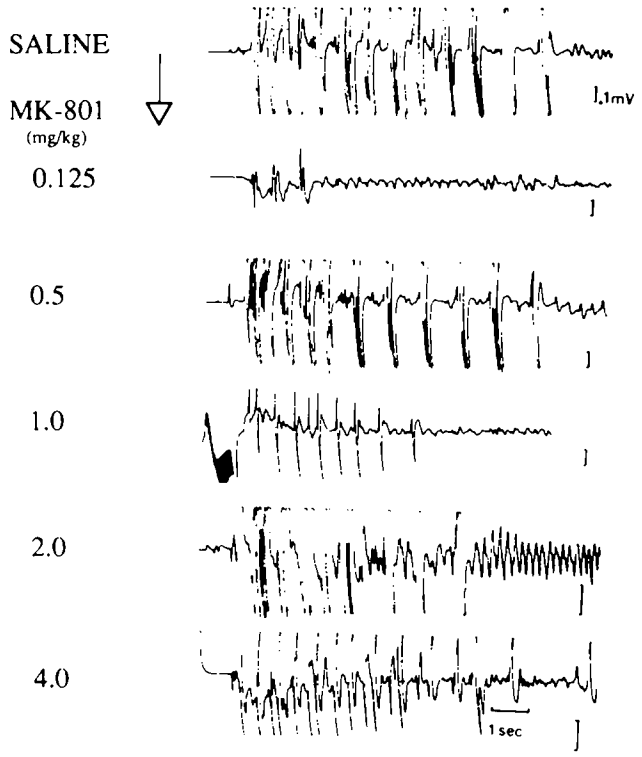

FIG. 3. Epileptic afterdischarges recorded from the amygdala during accelerated kindling in rats treated with MK-801. Arrow indicates onset of a 1.5-sec stimulus train. Vertical scales indicate 0.1 mV.

PHASE 2: Kindling at 24-hr Intervals

After drugs had been discontinued all rats in each group eventually went on to develop full Stage 5 seizures in response to additional once-daily stimulations. But Fig. 4 shows significant differences between groups in the number of additional stimulations needed to reach Stage 5 [Kruskal-Wallis, $H(4) = 13.6$, $p<0.01$]. The strongest effect was seen with rats previously treated with 1.0 mg/kg doses of MK-801: the rats in this group required an average of 17 additional stimulations to reach Stage 5, as compared to only 6 more stimulations for the saline controls ($p<0.01$). Significant antikindling activity was also seen with doses of 0.5 mg/kg (9 more stimulations, $p<0.05$), and 2.0–4.0 mg/kg (13 more stimulations, $p<0.01$). The effects of kynurenic acid (4 more stimulations), clonazepam (8 more stimulations) and the lowest dose of MK-801 (0.125 mg/kg; 8 more stimulations), were not significant.

PHASE 3: Fully Kindled Rats

Figure 5 (upper panel) indicates that MK-801 showed dose-dependent anticonvulsant activity against established behavioural seizures: seizural effects were significantly milder on drug days than on the preceding and following day [for doses of 0.5 and 2.0 mg/kg, Kruskal-Wallis, $H(2) = 9.5$–56.7, $p<0.01$]; doses of 0.25 and 1.0 mg/kg showed nonsignificant trends in the same direction (Kruskal-Wallis, $H = 5.6$–5.8, $0.5<p<0.1$). Kynurenic acid had no apparent effect on behavioural seizure intensity.

Kruskal-Wallis analysis of variance showed that afterdischarge durations were unaffected by MK-801 (Fig. 5, lower panel). Figure 6 shows that the appearance of afterdischarges was unaffected at the same time that treatment with MK-801 was producing a significant reduction in the intensity of the behavioural seizure. Anticonvulsant doses of MK-801 also induced changes in locomotor activity, as seen earlier during accelerated kindling. Locomotor effects included ataxia and hyperactivity or, at the highest doses, immobility. These effects occurred in all rats.

DISCUSSION

Anticonvulsant activity by MK-801 has previously been demonstrated in vitro (24) and in animal models of bicuculline- and electroshock-induced epilepsy (7), and with audiogenic and photosensitive seizures (32). The present study, and four other reports in the past 12 months (15, 27, 39, 45), extend these findings to include limbic seizures induced by kindling. It is of particular

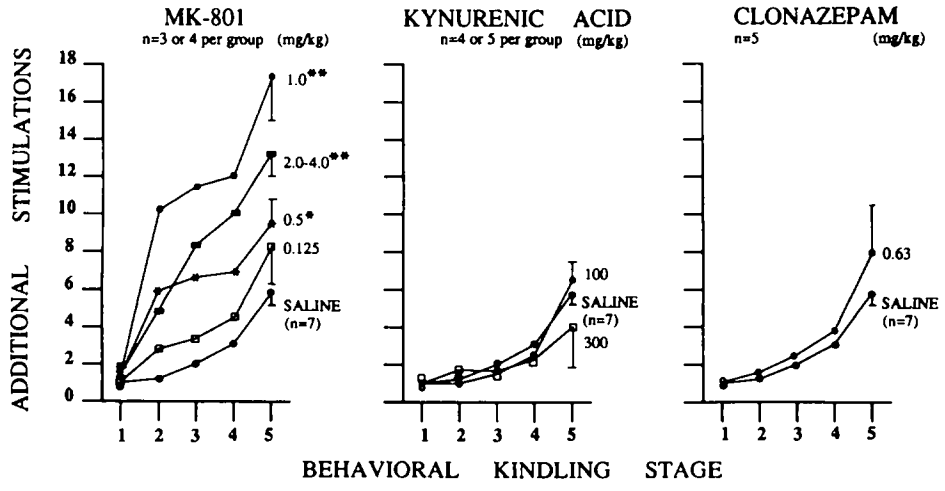

FIG. 4. Number of additional daily stimulation sessions (± sem) required to reach each of the five behavioural stages of Racine. All rats had previously received 12 stimulations at 2-hr intervals during accelerated kindling. Panels from left to right show results obtained in groups previously treated with MK-801, kynurenic acid or clonazepam during the course of accelerated kindling. *$p<0.05$; **$p<0.01$ (compared to saline).

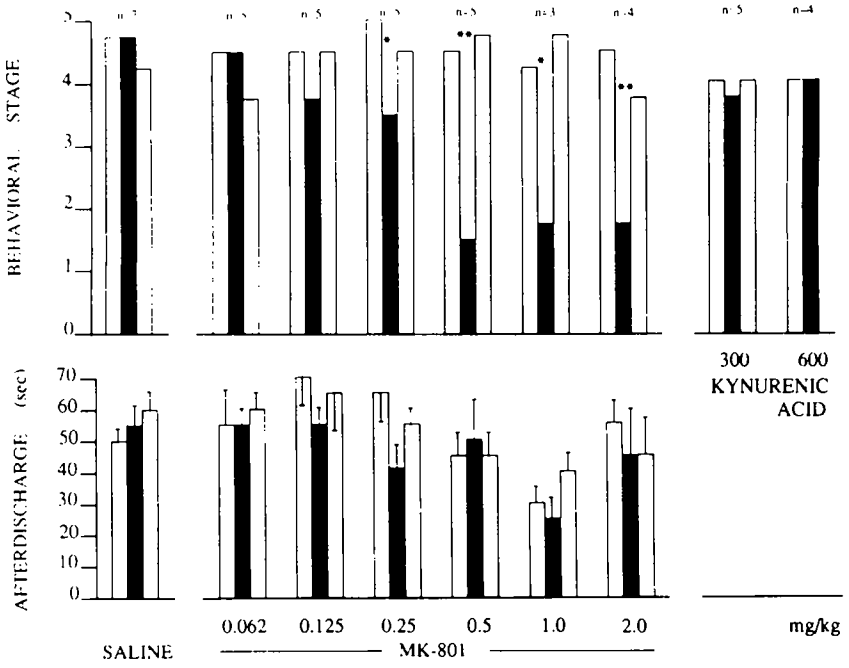

FIG. 5. Effect of MK-801 and kynurenic acid on mean behavioural seizure score (top panel), and on the duration of amygdala afterdischarges (seconds ± sem) in fully kindled rats. Data obtained under drug treatment (solid columns) were compared to drug-free data obtained one day before and one day after (open columns). $*p<0.1$; $**p<0.01$ (Kruskal-Wallis).

interest that MK-801 proved to be effective not only in suppressing fully fledged seizures, but also in slowing the rate at which seizures were kindled.

This result may be qualified, however, by two further observations. Firstly, MK-801 was relatively ineffective against kindled afterdischarges. Secondly, the behavioural evidence of its anticon-

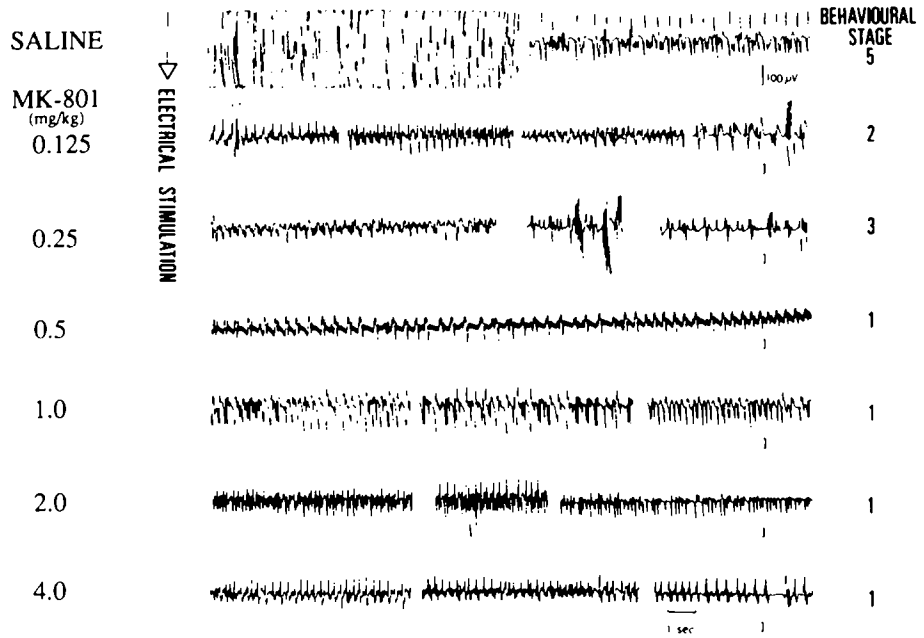

FIG. 6. Afterdischarges recorded from the amygdala of fully kindled rats stimulated under different doses of MK-801. The behavioural stage reached on the occasion of the recording is indicated on the right of each trace.

vulsant activity was contaminated by prominent side-effects, ranging from locomotor hyperactivity to flaccid immobility and ataxia, as noted also in previous studies (15, 27, 39, 45). Thus, it could be argued that motor 'side-effects' of MK-801 might have masked the standard behavioural signs of seizure staging (37), and hence led to underestimation of seizure activity and to a spurious impression of anticonvulsant activity. However, other features of the results seem to rule out any simple explanation on these lines. First, anticonvulsant activity by MK-801 reached significance even at doses (0.5 mg/kg) at which motor side-effects were relatively slight; secondly, the antikindling, 'protective' activity of MK-801 was inferred from the increased number of drug-free kindling sessions that were needed to reach Stage 5 seizures long after completion of the initial 12 drugged sessions. There seems to be no way in which the injections of MK-801 could have affected kindled responses at this stage of the study, other than through having conferred a genuine protection against the first 12 kindling sessions.

Antiepileptogenic activity of MK-801 appears to have been clearly demonstrated by behavioural evidence, and, in at least some cases, by electrographic evidence. Our failure to find a significant reduction of afterdischarge durations during kindling must therefore be treated with caution. Nevertheless, our negative finding agrees with that of Gilbert (15), who found MK-801 (1.0 mg/kg) to be effective against behavioural but not electrographic seizures in amygdala-kindled rats. Sato and colleagues [(39): vide Table 1] made similar observations, reporting that MK-801 (1.0–2.0 mg/kg) was more effective against the behavioural than against the electrographic signs of kindled seizures. The insubstantial effect of MK-801 on afterdischarge durations during accelerated kindling, and the absence of any apparent effect on fully kindled afterdischarges, may thus offer a clue to its locus of action. Binding sites for MK-801 (25,44) are distributed in close parallel to high-affinity sites for NMDA (8,41), and include structures thought to be critical for the propagation of limbic seizures, especially the substantia nigra and frontal neocortex (11,21). Thus, it seems important to consider whether kindled activity may be propagated to these structures by NMDA pathways sensitive to MK-801, unlike spiking in the kindled amygdala itself, which appears to be maintained by cell populations relatively insensitive to MK-801.

Experimental and anatomical evidence are consistent with this hypothesis. NMDA receptors in the amygdala are closely associated (as in other structures) with receptors sensitive to quisqualate or kainate (8). NMDA as well as non-NMDA local systems would thus be equally subject to kindling stimulation by amygdaloid electrodes, but afterdischarge activity sustained by quisqualate or kainate would not be directly affected by MK-801, and (as we found) would not be appreciably shortened in duration. On the other hand, wider propagation of seizures appears to be critically dependent on NMDA terminals situated outside the amygdala, particularly in the substantia nigra reticulata, where injections of a selective NMDA antagonist (2-AP7) have been shown to protect against pilocarpine-induced limbic seizures (43). It would thus be of much interest at this stage to learn whether local application of NMDA antagonists in the substantia nigra prevents spread of seizures kindled in the amygdala, in the same way as nigral application of GABAergic agents is known to do (21,23). The kindling process presumably represents a plastic change at synapses following repeated use, and the NMDA receptor seems the most likely substrate (29).

Antikindling activity was not seen with the other two compounds tested, clonazepam and kynurenic acid. Kynurenic acid is believed to act as a potent broad-spectrum EAA antagonist (14,34), resembling MK-801 in its ability to inhibit transmission at the NMDA synapse. Surprisingly, in view of this common feature, kynurenic acid did not affect the development or expression of kindled seizures. Brain entry was probably adequate, since systemic injections (<600 mg/kg IP) have been shown to confer significant protection against metrazol seizures (Mintz, unpublished), and to produce dose-dependent depression of electrical self-stimulation (19). However, small intracerebroventricular injections of kynurenic acid (5 μg in mice) may actually *induce* convulsions (40); this untoward property of kynurenic acid might be related to its inefficacy as an anticonvulsant in the present study.

The initial dose of clonazepam (0.63 mg/kg) equalled or exceeded previously reported anticonvulsant ED_{50} values, ranging between 0.28 and 0.64 mg/kg, for suppression of seizures in fully kindled rats (1, 2, 26); plasma half-life, in man, exceeds 24 hr (36). Yet this dose of clonazepam, supplemented by a subsequent booster dose, did not confer protection against kindling. Unlike MK-801 (0.5, 1.0 and 2.0–4.0 mg/kg), it did not increase the number of stimulations needed subsequently to bring about full convulsive seizures. The anticonvulsant action of clonazepam is believed to derive from enhanced inhibitory GABAergic activity (17,36) rather than from blockade of glu/aspartatergic transmission. Thus the differing effects of clonazepam and MK-801 in kindling underline the critical role of EAA transmission in the acquisition of propagated seizure activity.

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