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Effects of Competitive and Noncompetitive NMDA Receptor Antagonists on Kindling and LTP

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MORIMOTO, K., K. KATAYAMA, K. INOUE AND K. SATO. *Effects of competitive and noncompetitive NMDA receptor antagonists on kindling and LTP.* PHARMACOL BIOCHEM BEHAV **40**(4) 893–899, 1991.—In the present study, comparative studies of the effects of competitive and noncompetitive antagonists of NMDA receptors (CPP, CGS19755 and MK-801) on two models of neuronal plasticity, kindling and long-term potentiation (LTP), were performed in rats. Systemic administration of CPP (5, 10 mg/kg), CGS19755 (5, 10 mg/kg) or MK-801 (1, 2 mg/kg) strongly retarded kindling development from the amygdala (AM), in which the early stage of kindled seizures and the growth of afterdischarges (ADs) recorded from the AM were significantly suppressed. After establishment of kindling, however, these compounds only reduced the previously AM-kindled seizure stage without shortening the AD duration. These NMDA receptor antagonists with the same dose sufficient for suppressing AM kindling almost completely blocked LTP of the synaptic component in the hippocampal dentate gyrus following high-frequency trains of the perforant path in urethane-anesthetized rats. These results further support the hypothesis that neuronal plasticity is induced by activation of the NMDA receptor complex and one of the basic neuronal mechanisms underlying kindling may be a long-lasting increase in synaptic transmission.

NMDA receptor Antagonist CPP CGS19755 MK-801 Kindling Long-term potentiation Neuronal plasticity

FOCAL electrical stimulation applied to limbic system or related forebrain structures initially causes only a brief afterdischarge (AD) and weak behavioral response. With spaced repetition of the stimulation there is a progressive intensification of the electrographic discharge, culminating in a generalized seizure. This phenomenon, called kindling (15), reflects a permanent change in brain function in the absence of any detectable tissue damage. Consequently, kindling is not only used as an experimental model of epilepsy, but is also regarded as an expression of neuronal plasticity relevant to neuronal mechanisms in learning and memory (16).

It is well documented that application of nonepileptogenic high-frequency stimulation can result in a long-lasting increase in synaptic efficacy (long-term potentiation: LTP) (3,36). A relationship between kindling and LTP has been shown in several studies (10, 12, 28, 41, 42). Although some authors suggest that LTP-like synaptic potentiation may be heavily involved in the initial stage of kindling development (28, 41, 42), others argue that different mechanisms may apply (6,27).

Recent evidence has indicated that N-methyl-D-aspartate (NMDA) receptors are critically involved in induction of both kindling (7, 14, 19, 26, 40) and LTP (8,32). We have recently demonstrated that daily pretreatment with a noncompetitive antagonist of NMDA receptors (MK-801) prior to each daily electrical stimulation to the amygdala (AM) powerfully retards kindling development (39). The NMDA receptor is a subtype of excitatory amino acid receptors and is believed to be a macromolecular complex which consists of at least the receptor site and associated ion channel.

To further clarify the role of NMDA receptors in kindling and LTP, a comparative study on the effects of competitive and noncompetitive antagonists of NMDA receptors was performed in these two models of neuronal plasticity. We used CPP (17) and CGS19755 (23) as a selective competitive antagonist (which blocks the NMDA receptor site) and MK-801 (44) as a selective noncompetitive antagonist (which blocks the associated ion channel) (Fig. 1).

METHOD

Experiment 1. Kindling

Effect on kindling development. Sixty male Sprague-Dawley rats weighing 250–300 g at the time of surgery were used. All rats were housed in a temperature-controlled colony with 12-h/12-h light/dark cycle and allowed free access to food and water

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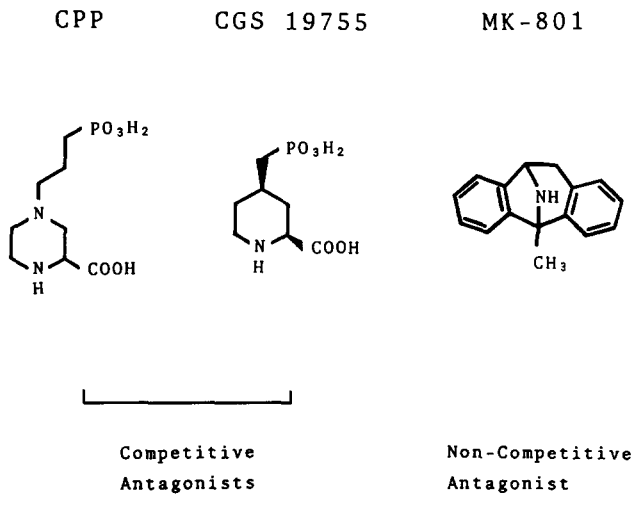

FIG. 1. Competitive and noncompetitive antagonists of NMDA receptors. CPP: 3-(2-carboxy-piperazine-4-yl)propyl-1-phosphonoic acid; CGS19755: cis-4-(phosphomethyl)-2-piperidine carboxylic acid, MK-801: [(+)-5-methyl]-10, 11-dibenzo [a,b]-cyclo-heptene-5,10-imine meleate.

except for the time during experimental sessions. Under pentobarbital anesthesia (50 mg/kg, IP), all rats stereotaxically received tripolar electrodes (Diamel-insulated Nichrome wire, 0.18 mm in diameter) in the left amygdala (AM: 0.6 mm posterior and 4.8 mm lateral from the bregma, and 8.0 mm below the dura). All coordinates were with the incisor bar 5.0 mm above the interaural plane. In addition, a screw electrode was placed in the right frontal skull as a reference for recording EEG.

After a recovery period of one week, all rats received kindling stimulation with a 1-s train of 60 Hz sine wave at 200 μA peak-to-peak amplitude to the AM on day 1. Stimulation was delivered through two poles of the tripolar electrode, whereas EEG was recorded between the remaining pole and skull screw electrode on a Nihonkoden 5109 electroencephalograph. Then the rats were divided into 9 groups, matched for seizure stage and AD duration, as follows: CPP groups, 0 mg/kg (N=7), 5 mg/kg (N=7), 10 mg/kg (N=7); CGS19755 groups, 0 mg/kg (N=6), 5 mg/kg (N=6), 10 mg/kg (N=6) and; MK-801 groups, 0 mg/kg (N=7), 1 mg/kg (N=7), 2 mg/kg (N=7). All drugs were dissolved in sterile 0.9% saline.

From day 2 to day 4, the animals received IP administration of these NMDA receptor antagonists. Two hours following the injection, the kindling stimulation was delivered to the AM six times a day at 2-h intervals. From day 5, the drug administration was stopped while kindling stimulation was continued, once daily, until fully kindled generalized seizures appeared.

AM kindling development was assessed using a modification of Racine's classification (34): stage 0, no response or behavior arrest; stage 1, rhythmic mouth and facial movement; stage 2, rhythmic head nodding; stage 3, forelimb clonus; stage 4, rearing and bilateral forelimb clonus; stage 5, rearing and falling. The development of kindled seizure stage and growth of the AD duration were measured and compared with each control.

Effect on previously kindled seizures. The rats kindled from the AM in the control groups of the previous experiment were used. They showed stable stage 5 seizures. The generalized seizure triggering threshold (GST) was determined in each rat by application of trains that were increased in intensity at 50 μA steps at an interval of 20 min.

Two hours after drug administration with various doses (CPP: 0, 5, 10, 20 mg/kg; CGS19755: 0, 10 mg/kg; MK-801: 0, 1, 2 mg/kg), the animals received electrical stimulation to the AM at the intensity of GST. The sequence of the dose was randomly assigned and each drug trial was separated by at least 48 h. The effects of these drugs on the seizure stage and AD duration were measured and compared with each control.

Experiment 2. Long-Term Potentiation (LTP)

Fifty-two male Sprague-Dawley rats were anesthetized with urethane (1.2–1.5 g/kg, IP). A monopolar recording electrode (Teflon-coated stainless-steel wire: 0.05 mm in diameter) and a stimulating electrode (Diamel-insulated Nichrome wire: 0.18 mm in diameter) were implanted stereotaxically into the hilus of the dentate gyrus (3.2 mm posterior and 2.5 mm lateral to bregma, and 3.0 mm below the dura) and the ipsilateral perforant path (4.5 mm lateral to lambda, and 3.1 mm below the dura). In this experiment, the incisor bar was 3 mm below the interaural plane.

All stimuli were constant current diphasic pulses sequenced and timed by a programmable stimulator (2). Before the experiment the current intensity required to evoke the population spike >2 mV at 250 μs pulse duration (150–500 μA) was determined. This value was used, for each rat, for the remainder of the experiment. All evoked potentials were amplified (Nihonkoden VC-11), sampled as 640 voltage levels at 50 μs intervals, digitized and stored on a magnetic disk for later analysis. The slope of the rising phase of the excitatory postsynaptic potential (EPSP) and height of the population spike were measured for each evoked response, as described in Fig. 2. To examine synaptic strength and construct input/output (I/O) curves, the EPSPs were plotted against the log of stimulus intensity. I/O curve determination consisted of 32 single test pulses ranging in intensity from 10 to 250 μs duration, delivered at 15-s intervals in an ascending-descending sequence. LTP was induced by 10 high-frequency (400 Hz) and high-intensity (250 μs pulses) trains of 20 ms duration at 1-s intervals. Test pulses of 250 μs duration were delivered at 30-s intervals before and after LTP-inducing trains. Rectal temperature was monitored and maintained at 36.5–37.0°C by a heating lamp. Two hours after IP administration of CPP, CGS19755 or MK-801 at the same doses used to test the effects on kindling development in Experiment 1, the first I/O curve was measured, and then LTP-inducing trains were delivered to the perforant path. The second I/O curve was measured 45 min after the LTP-inducing trains. Test stimuli, at 250 μs pulse duration, were also delivered immediately before and after the trains. LTP was evaluated in terms of the percent increase in the slope of the EPSP and height of the population spike between the average of 5 potentials evoked immediately before and after trains [{(after trains − before trains)/before trains} × 100]. LTP of the EPSP was also evaluated by comparison between the first and second I/O curve.

Statistics

All data obtained were expressed as mean ± S.E.M. The changes in the AD duration and percent increases in the evoked potential were compared by one-way ANOVA, followed by two-tailed Student's *t*-test. The change of the seizure stage was compared by Kruskal-Wallis test, followed by Mann-Whitney's U-test.

RESULTS

Experiment 1: Kindling

Effect on kindling development. Figure 3 illustrates the effects of the drugs on seizure development. In each control group, all

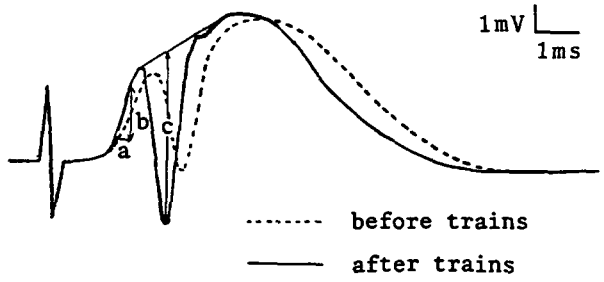

FIG. 2. Field potentials evoked in the dentate gyrus before and after LTP-inducing high-frequency trains of the perforant path. Marked potentiation of the slope of the population EPSP (b/a) and the amplitude of the population spike (c) can be seen.

rats showed a progressive increase in both the seizure stage and AD duration, and the average of the seizure stage on 19th stimulation (the last stimulation of the drug sessions) was 4.4, 4.7, 4.5 in the CPP, CGS19755 and MK-801 control groups, respectively. In contrast, treatment with the NMDA receptor antagonists significantly suppressed the development of the seizure stage and growth of the AD duration, especially in the early stages of AM kindling (stage 0–2). The average of the seizure stage on 19th stimulation was 3.5 and 0.4 in the 5 and 10 mg/kg CPP, 3.0 and 2.3 in the 5 and 10 mg/kg CGS19755, and 0.4 and 0.3 in the 1 and 2 mg/kg MK-801 groups. In control rats, 13.7 kindling stimulations were required to elicit the first stage 5 of kindled generalized seizures. The numbers required for the drugged groups were 15.0 and 25.3 for the 5 and 10 mg/kg CPP, 19.6 and 20.7 for the 5 and 10 mg/kg CGS19755, and 23.7 and 27.3 for the 1 and 2 mg/kg MK-801 groups.

Figure 4 shows examples of ADs recorded from the kindled AM in the control, CPP and MK-801 groups. In the control rat, during kindling, the AD duration was progressively prolonged with a more complex waveform and higher frequency. In the CPP- or MK-801-pretreated rats, however, these changes in ADs were markedly reduced.

Effect on previously kindled seizure. Figure 5 describes the effects of the three antagonists of NMDA receptors on previously kindled seizures from the AM. Although CPP, CGS19755 and MK-801 all significantly reduced the seizure stage in a dose-dependent manner, these drugs did not show any significant effects on the AD duration, even at the doses which significantly suppressed kindling development.

Experiment 2: LTP

Figure 6 demonstrates the time course of the percent increase in the EPSP and population spike in the dentate gyrus following LTP-inducing trains in anesthetized rats. In each control group, all rats showed clear LTP following trains. Substantial increases in both the EPSP and population spike were observed (Fig. 2) and lasted for at least 45 min (16.9–32.7% in the EPSP and 62.8–75.2% in the population spike). Systemic administration of CPP, CGS19755 and MK-801, however, markedly suppressed LTP of the EPSP and significantly reduced LTP of the population spike in a dose-dependent manner. The average of the percent increases in the EPSP measured 45 min after trains was only −2.8% and 1.9% in the 5 and 10 mg/kg CPP, −1.5% in the 10 mg/kg CGS19755, and 3.2% and 5.3% in the 1 and 2 mg/kg MK-801 groups.

These effects of CPP and MK-801 on LTP of the EPSP were confirmed by comparison between the first and second I/O curves, as described in Fig. 7. All animals in the control group showed a substantial increase in the slope of the second I/O curve (45 min after trains), compared with the first I/O curve (immediately before trains). Both CPP and MK-801 blocked these increases in the slope.

DISCUSSION

In the present study, we have shown that an antagonism of either the receptor site or the associated ion channel of the NMDA receptor complex strongly retards kindling development from the AM. These results are consistent with previous reports in which the competitive antagonist 2-amino-5-phosphonovalerate (APV, ICV injection) (7,19) and noncompetitive antagonists,

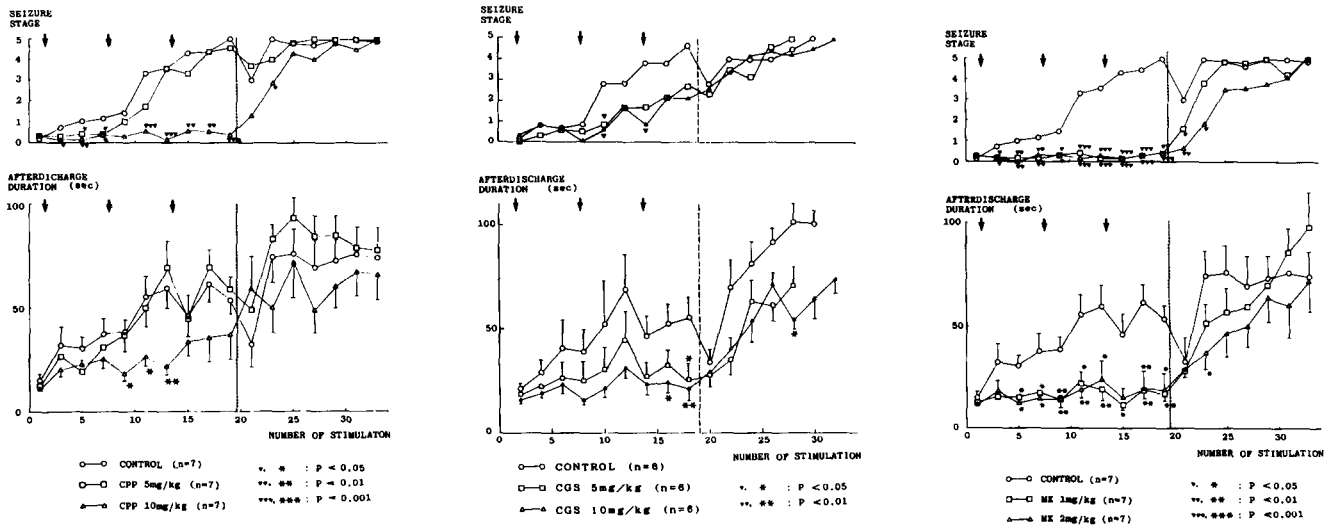

FIG. 3. The effects of CPP (left), CGS19755 (middle) and MK-801 (right) on kindling seizure development from the amygdala in rats. The rats received IP administration of the drugs once daily for consecutive 3 days (arrows), and the amygdala was stimulated 6 times a day at 2-h intervals (drug sessions). After 19 stimulations, drug administration was stopped and only electrical stimulation was delivered once per day (nondrug sessions). Note that all drug pretreatments significantly suppress the kindled seizure stage and afterdischarge duration, especially in the early stage of kindling.

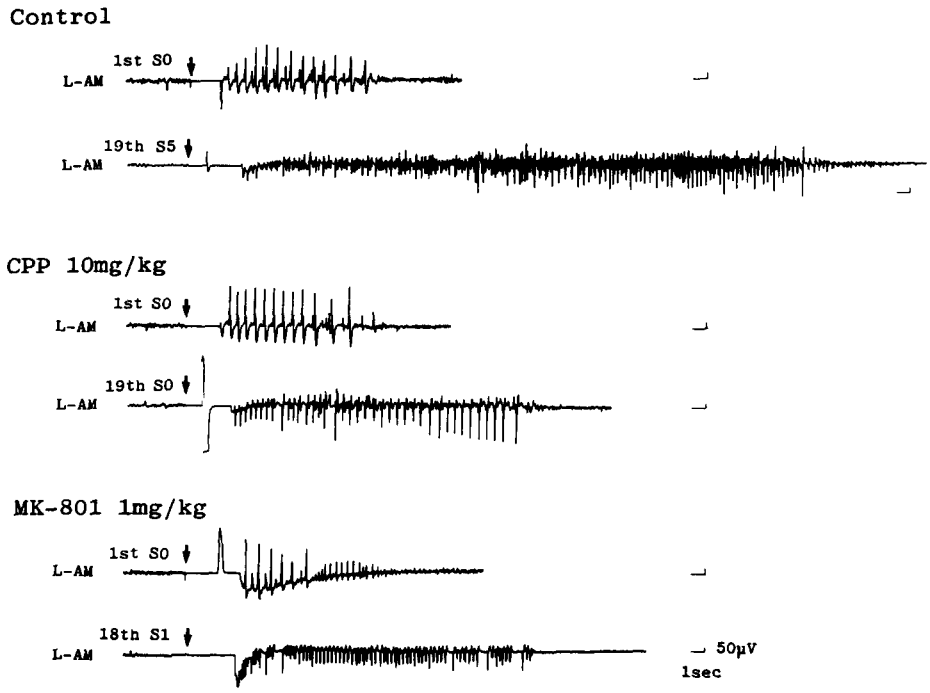

FIG. 4. Examples of afterdischarges recorded kindled left amygdala (L-AM) in control (top) and CPP- (middle) or MK-801- (bottom) treated rats. Arrows indicate the beginning of electrical stimulation. Note that, in the rats treated with 10 mg/kg CPP or 1 mg/kg MK-801, the duration of afterdischarges is markedly shorter and the waveform is relatively simple, compared with the control.

such as phencyclidine (4), ketamine (5) and MK-801 (14, 26, 39) (IP injection), all significantly reduced AM kindling. Thus it is suggested that repeated activation of the NMDA receptor complex may be essential for kindling. In our study, the effects of the noncompetitive antagonist MK-801 seemed to be more potent than those of competitive antagonists (CPP and CGS19755) on kindling (see Fig. 3). However, the 1 and 2 mg/kg doses of MK-801 caused severe ataxia and sedation, while 10 mg/kg of CPP and CGS19755, which significantly suppressed kindling, only caused mild sedation. The assessment of behavioral seizures might be more reliable following application of the competitive NMDA receptor antagonists. Therefore, there may be

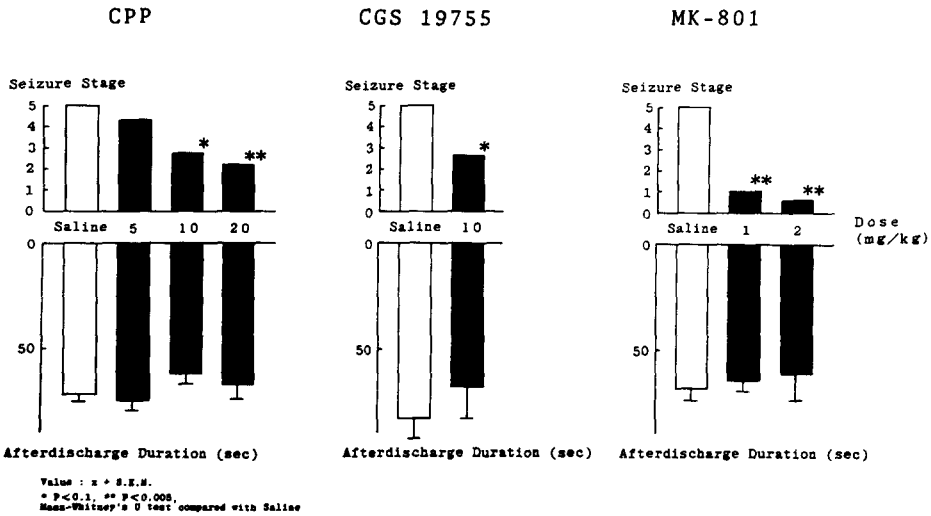

FIG. 5. The effects of CPP (left), CGS19755 (middle) and MK-801 (right) on previously kindled seizures from the amygdala. All drugs significantly reduced the kindled seizure stage without shortening the afterdischarge duration.

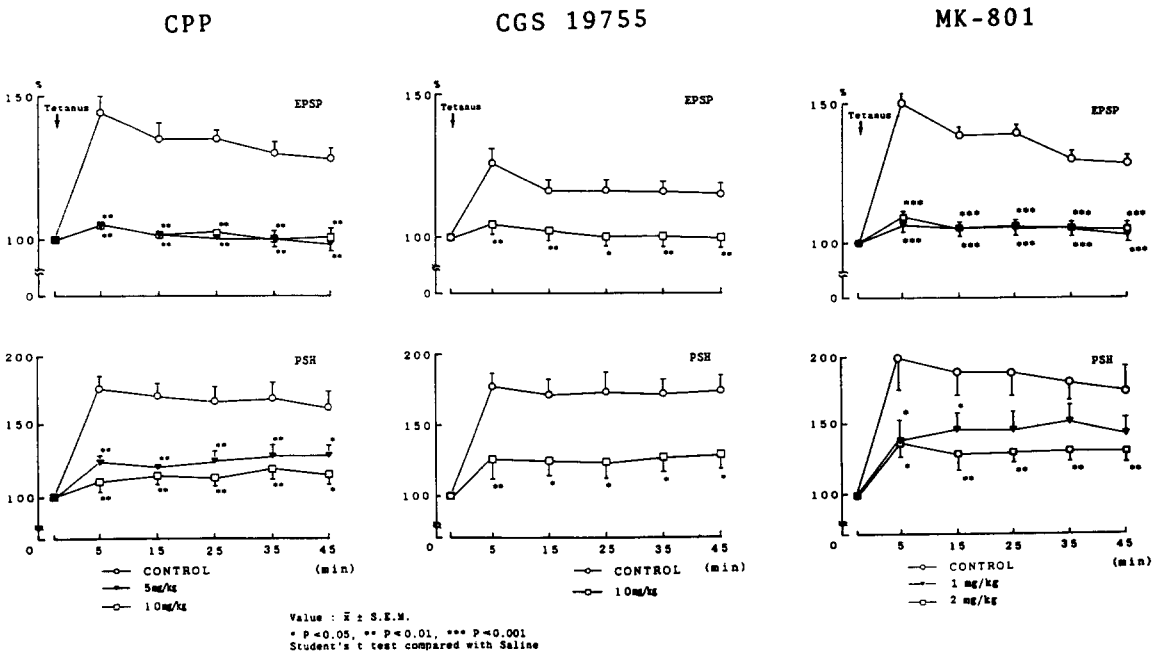

FIG. 6. The effects of CPP (left), CGS19755 (middle) and MK-801 (right) on long-term potentiation in the dentate gyrus of urethane-anesthetized rats. The time course of the percent increase in the population excitatory postsynaptic potential (EPSP: top) and population spike height (PSH: bottom) following high-frequency trains of the perforant path (arrows). Note that all drugs almost completely suppress the potentiation of the EPSP in the early phase as well as the late phase of LTP.

little or no difference between competitive and noncompetitive antagonists for their neuropharmacological effects on kindling.

In our analyses, the effects of these two types of NMDA receptor antagonists on AM kindling could be characterized as follows: 1) The growth of ADs recorded from the kindled AM was markedly suppressed; 2) The initial stages of AM kindling were particularly suppressed, resulting in a large delay of the appearance of secondary generalized seizures; and 3) After drug

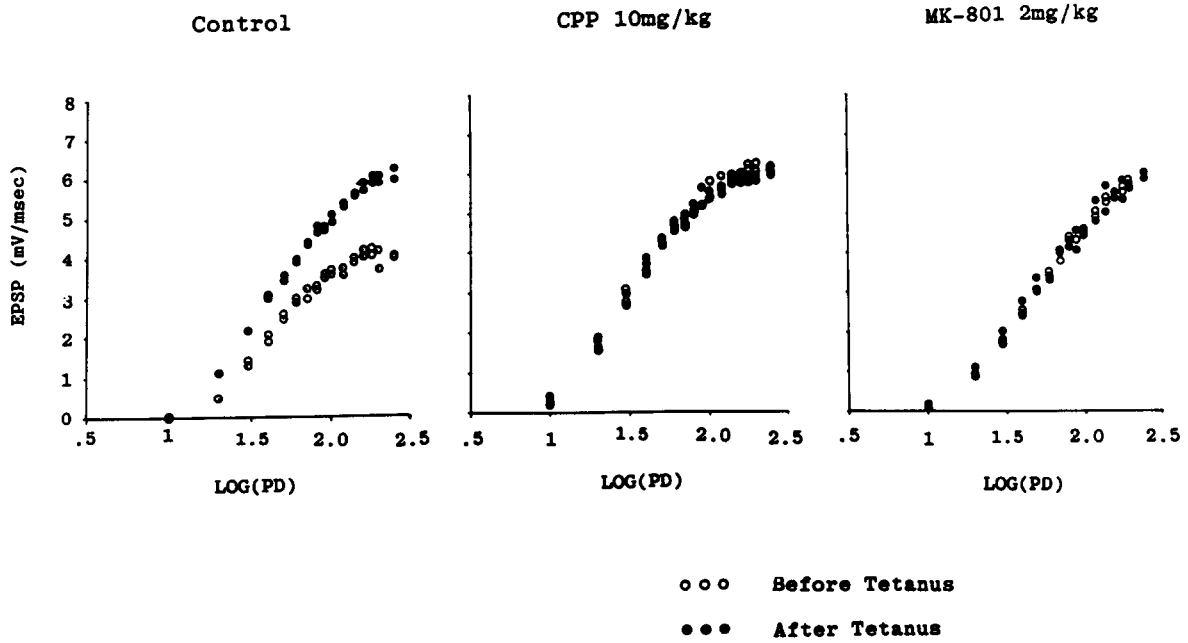

FIG. 7. Examples of input/output curves generated from a stimulus intensity (pulse duration: PD) series before and after LTP-inducing trains in control (left) and CPP- (middle) or MK-801- (right) treated rats. Although the marked increase in the slope of the curves was induced after trains in the control rat, there was very little change in the CPP- or MK-801-treated rats.

administration was stopped, kindling was not immediately induced, and some additional electrical stimulations were required to complete kindling. Although one might consider that the latter effect was related to the delayed refractority to kindling which follows massive stimulation procedure (6 times per day), similar effect could be observed in ordinary kindling procedure (once per day stimulation) in our previous study (39). Furthermore, in our previous study, it was shown that the effect of MK-801 on AM kindling was not due to elevating the focal AD threshold (39). Thus, taken together, the main mechanism of the action of these NMDA receptor antagonists is considered to be a blockade of focal epileptogenic changes in and around the kindled focus.

It is of interest that, in contrast to the potent effects on kindling development, these compounds only reduced the AM-kindled seizure stage and had little effect on the AD duration in previously kindled animals. This dissociation of the effects between kindling development and previously kindled seizures is consistent with the previous results in in vitro hippocampal slice studies with APV (1,40). Since previous biochemical studies have not revealed any lasting changes in either the receptor site or in the ion channel of the NMDA receptor complex in the kindled brain (22,33), the diminished effect after kindling is not explained by changes in sensitivity of the complex to these compounds. It is more likely that kindling may result in a change in the second messenger systems, for example the protein kinase C (PKC) system (9), via the NMDA receptor complex.

LTP-like synaptic potentiation has been proposed as a basic mechanism for kindling. This hypothesis is based upon demonstrations of kindling-induced increases in evoked responses in various target brain sites (10, 12, 28, 35, 41), which is long-lasting in some reports (12,28), and significant facilitation of perforant path kindling after induction of LTP in the hippocampal dentate gyrus (42). However, the opposite view has also been suggested (6,25). In this study, it appeared that both competitive and noncompetitive antagonists of NMDA receptors with the same doses sufficient for suppressing AM kindling development almost completely blocked LTP of the synaptic component (EPSP) in the dentate gyrus of the hippocampus, in the early phase (measured 5 min after trains) as well as the late phase (45 min after trains) of LTP. These results are consistent with previous results in in vitro (8,18) or in vivo (32) studies and further imply that activation of the NMDA receptor complex is critical for the induction mechanism of neuronal plasticity. Although the brain areas and train parameters in our experiments were different in kindling and LTP, it is still possible that, in the kindled brain, abnormal neuronal circuits with an increased synaptic efficacy may be permanently established by repeated activation of the NMDA receptor complex, at least in the early stage of kindling. To clarify this possibility, it must be examined whether or not synaptic potentiation in the dentate gyrus during kindling can be successfully blocked by these NMDA receptor antagonists.

We have recently suggested that collapse of inhibitory GABA systems during kindling-inducing trains in the kindled focus is a primary seizure-triggering mechanism in kindling (29–31). Such a disinhibition of GABA systems should facilitate opening of the voltage-dependent NMDA channel and increase Ca influx into the neuron (11,20). This, in turn, could activate the intracellular PKC system (24, 27, 38), which is known to regulate neuronal outgrowth (21). In fact, it has recently been demonstrated that kindling induces a long-lasting increase of PKC activity in neuronal membrane (9), a positive immunoreactivity of c-fos oncogene (13), and a synaptic reorganization (sprouting) (37,42). This chain of biological changes may be triggered, in part, by activation of the NMDA receptor complex and contribute to the kindling process.

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