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Pharmacology, Biochemistry and Behavior 74 (2003) 909–915
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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Cessation of repeated administration of MK-801 changes the anticonvulsant effect against flurothyl-induced seizure in mice

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Received 3 June 2002; received in revised form 6 November 2002; accepted 3 January 2003

Abstract

The effects of acute and repeated administration of MK-801 on flurothyl (FE)-induced seizure were investigated in mice. In the acute effect of MK-801 (0.01–0.1 mg/kg ip) in naive and FE-kindled mice, there were no changes on the latencies of clonic seizures. However, MK-801 dose-dependently inhibited both latencies and incidence of tonic seizures in mice and suppressed the grade of seizure severity in FE-kindled mice. Repeated administration of MK-801 at doses of 0.01 and 0.1 mg/kg 2 h prior to each exposure to FE for 8 days did not show any effects on the latencies of clonic seizure. However, seizure severity was significantly exacerbated in the 0.1 mg/kg treated group when mice were reexposed to FE without MK-801 1 week after the last administration. A week after the repeated administration of MK-801 at a dose of 0.1 mg/kg for 8 days without exposure to FE, mice were exposed to FE 2 h after readministration of MK-801 until tonic seizure occurred. The latencies of clonic seizures were almost the same in the acute experiment in naive controls. The latency of tonic seizure was significantly delayed compared to the acute experiment with MK-801 at a dose of 0.1 mg/kg. These findings suggested that MK-801 possessed an anticonvulsant action against FE-induced tonic seizure. However, the efficacy of this acute effect of MK-801 was impaired at 1 week of withdrawal after repeated administrations. This may be related in part to the changes in sensitivity to NMDA receptors.

Keywords: Flurothyl; Clonic and tonic seizure; MK-801; NMDA receptor; Kindling; Mice

1. Introduction

Flurothyl (FE), a volatile convulsant agent, which has been established as an effective method for measuring seizure susceptibility, reliably elicits convulsions in animals, administered by inhalation (Adler et al., 1967). FE can express two different seizure phenotypes: forebrain and brainstem seizures. Forebrain seizure is expressed in animals exposed to FE with lower thresholds of clonus of the face and forelimb, while brainstem seizure is expressed with higher thresholds of tonus of the forelimb and hindlimb after forebrain seizure. Applegate et al. (1997) reported a model of epileptogenesis, which is based on the convulsant action of FE. C57BL/6 mice were exposed to FE until generalized seizure (forebrain seizure) was induced once daily for 8 days. After this period, mice were left undisturbed for 28 days and then were reexposed to FE and expressed brainstem seizure. Samoriski and Applegate (1997) reported that the number of generalized seizures and the duration of the stimulation-free interval are important factors for long-lasting reduction of seizure thresholds and for expression of brainstem seizure. In addition, the FE model can be observed as a behavioral seizure change in kindling development during the FE stimulation-free period and as a tonic extensor seizure, which cannot be seen in the electrical kindling model. However, it is unknown what happens during the stimulation-free period and the mechanism(s) of the propagation from forebrain seizure to brainstem seizure.

Epilepsy is a chronic brain disorder characterized by the recurrence of epileptic seizure. Imbalance of excitatory and inhibitory amino acids evokes epilepsy (Dingledine et al., 1990; Meldrum, 1992). A number of studies using animal models of epilepsy have indicated that, in particular, NMDA subtype glutamate receptors play important roles in epileptogenesis and in the expression of epileptic seizures (Dingledine et al., 1986; Anderson et al., 1987). MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-5,10-imine) is a potent noncompetitive NMDA receptor antagonist. This drug

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0091-3057/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(03)00013-3

possesses anticonvulsant effects in several experimental models of seizure (Tricklebank et al., 1989; Young et al., 1989), and it was suggested that MK-801 suppresses not only kindled seizure but also seizure development in the electrical kindling model (Gilbert, 1988; Morimoto et al., 1991). Applegate et al. (1997) reported that they administered MK-801 at a dose of 0.5 mg/kg twice daily for 28 days in periods in which mice were left undisturbed and showed that MK-801 had anticonvulsant effects on FE-kindled seizures.

However, the acute effect of MK-801 on FE-induced seizure development and clonic and tonic seizure in both naive and kindled mice is unknown. In addition, the effect of repeated administrations of MK-801 on FE-induced seizures during the initial 8 days is also unknown. Moreover, to elucidate what happens during a stimulation-free period, we observed the effects of 1 and 4 weeks of withdrawal after the last administration of MK-801 on FE-induced seizure severity and examined the effect of drug cessation on FE-induced seizures. By examining these effects of MK-801 on FE-induced seizures, the integrated evaluation of MK-801 will become possible.

2. Materials and methods

2.1. Animals

Adult (6 weeks of age at the beginning of experiments) male C57BL/6 mice were obtained from Charles River. An adaptational period (of at least 1 week) was allowed before the beginning of experiments. The animals were grouped in a temperature-controlled environment under a 12:12 h light/dark cycle (lights on at 7:00 a.m.). Food and water were provided ad libitum.

2.2. Experimental methods

Mice were individually placed in 2 l closed Plexiglas chambers. Seizures were elicited using 10% FE (2,2,2-trifluoroethyl ether, Aldrich) in 95% ethanol. FE was administered by infusion (0.2 ml/min) using a 10 ml syringe driven by an infusion pump (kd Scientific Model 100, Neuroscience). Sustained loss of posture control (>2 s) was defined as a clonic seizure. Latencies from the start of FE infusion to onset of clonic and tonic seizure were measured.

2.3. Behavioral seizure grade

To assess the seizure severity elicited by FE, generalized seizure behaviors were classified using the following behavioral grade system: Grade 1 = pure clonic seizure (loss of posture >2 s), Grade 2 = high-frequency/low-magnitude bouncing and/or backward motion, Grade 3 = running and bouncing, Grade 4 = forelimb and hindlimb treading, Grade 5 = forelimb tonic extension and hindlimb flexion, Grade 6 = forelimb and hindlimb tonic extension and Grade 7 = death. Grades 1 and 2 seizure behaviors are defined as a clonic seizure because these behaviors, myoclonus jerk, face and forelimb clonus, are elicited by weaker stimuli and depend on the forebrain network for expression. On the other hand, Grades 3–7 behaviors are defined as a tonic seizure because above Grade 3 they can be elicited by more severe stimuli in the absence of a forebrain connection and emanate from brainstem. The grade assigned reflects the highest seizure behavior expressed by the animals within a trial.

2.4. Drug

MK-801 hydrogen maleate was purchased from RBI. The drug was dissolved in saline, and the concentration of drug solution was adjusted so that the volume administered was constant at 10 ml/kg body weight of the mouse. MK-801 was administered intraperitoneally.

2.5. Procedure for experiments

2.5.1. Acute anticonvulsant effect of MK-801 on FE-induced seizure in naive mice

Thirty-five naive mice were used. They were divided into four groups: saline ($n = 9$), MK-801 0.01 mg/kg ($n = 9$), MK-801 0.05 mg/kg ($n = 8$) and MK-801 0.1 mg/kg ($n = 9$). Saline or MK-801 were administered 2 h prior to exposure to FE inhalation.

2.5.2. Acute anticonvulsant effect of MK-801 on FE-kindled mice

Mice were exposed to FE once daily for 8 days and then left undisturbed for 28 days. Mice were not administered saline or MK-801 at all during the initial 8 days and were left undisturbed for 28 days. We selected FE kindling mice, which were defined as mice that expressed above Grade 3 seizure phenotypes when they were reexposed to FE on day 36 (“pre” stated in Fig. 1A and B). After 1 week of this selection, mice were administered saline or MK-801 at doses of 0.01 mg/kg ($n = 13$), 0.05 mg/kg ($n = 14$) and 0.1 mg/kg ($n = 11$) 2 h prior to FE exposure (“post” stated in Fig. 1A and B). FE infusion was terminated when the mice expressed clonic seizure. Latencies from the start of FE infusion to onset of clonic seizure were measured, and seizure phenotype changes that occurred immediately after clonic seizure also were recorded.

2.5.3. Effect of repeated administrations of MK-801 on the development of FE-induced kindling

Mice were divided into three groups: saline ($n = 9$), MK-801 0.01 mg/kg ($n = 9$) and MK-801 0.1 mg/kg ($n = 9$). MK-801 or saline were administered 2 h prior to each FE exposure once daily for 8 days. Latencies of clonic seizure were measured. Thereafter, 1 and 4 weeks without administration of MK-801, the mice were reexposed to FE to observe seizure severity during development of FE kindling. FE infusion was terminated when the mice expressed clonic

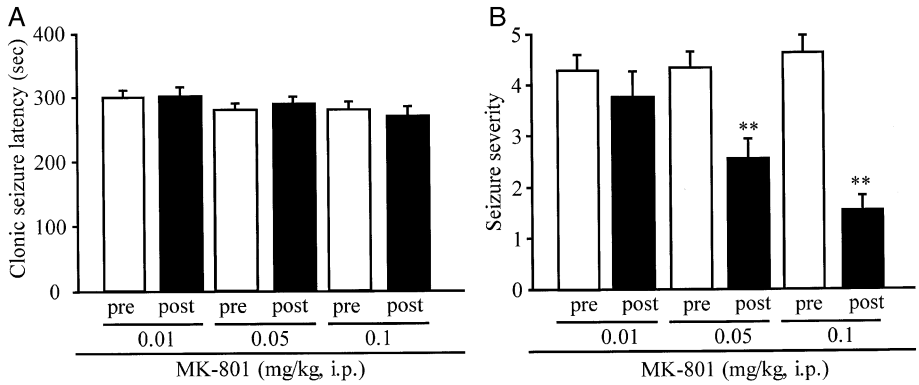

Fig. 1. Effect of MK-801 on FE-induced seizure severity in kindled mice. One week after establishment of kindling, mice were administered MK-801 or saline 2 h prior to exposure to FE. Each column represents the mean ± S.E.M. ** $P < .01$ significantly different from paired prestate using Kruskal–Wallis test. "pre" (black bars) is before drug administration, and it is the period when we selected kindled mice. "post" (open bars) is when we administered MK-801 after mice were established in the kindling state.

seizure. Latencies from the start of FE infusion to onset of clonic seizure were measured, and seizure phenotype changes that occurred immediately after clonic seizure also were recorded at days 15 and 36.

2.5.4. Effect of 1 week withdrawal after repeated administration of MK-801 on the anticonvulsant action against FE-induced seizure

MK-801 was administered repeatedly at a dose of 0.1 mg/kg once daily for 8 days without exposure to FE. After a 1 week withdrawal period, MK-801 was readministered 2 h prior to exposure to FE. Latencies from the start of FE infusion to the onset of clonic and tonic seizure and the differences between latencies of tonic and clonic seizures were compared to those of naive mice.

2.6. Statistic analysis

The latencies of each seizure component induced by FE were evaluated by analysis of variance (ANOVA) followed by Dunnett's test for multiple comparison, and the incidences of forelimb and hindlimb tonic extension were analyzed by the Kruskal–Wallis test followed by the Wilcoxon test. Probability values less than .05 were considered to show a significant difference.

3. Results

3.1. Acute anticonvulsant effect of MK-801 on FE-induced seizure in naive mice

The acute effects of MK-801 on FE-induced seizure in naive mice are summarized in Table 1. There was no significant difference in the latency of clonic seizure onset. In contrast to clonic seizure, MK-801 significantly suppressed the incidence of hindlimb tonic extensor in a dose-dependent manner. The differences between latencies of tonic and clonic seizures were significantly prolonged and the appearance of tonic seizures was completely delayed by MK-801 at a dose of 0.1 mg/kg.

3.2. Acute anticonvulsant effect of MK-801 on FE-kindled mice

Fig. 1A shows the effect of MK-801 on the latency of clonic seizure in previously kindled mice. There were no significant differences among any doses of MK-801 used. The grade of seizure severity was not affected with MK-801 at a dose of 0.01 mg/kg but was significantly suppressed at doses of 0.05 ($P < .01$) and 0.1 ($P < .01$) mg/kg compared to that of the paired "pre" state (Fig. 1B).

3.3. Effect of repeated administration of MK-801 on the development of FE-induced kindling

The effects of repeated administration of MK-801 on the development of FE-induced kindling were examined. All mice showed a progressive decrease in the latency of clonic seizure for 8 days. Moreover, when the mice were reexposed

Table 1
Effects of MK-801 on latencies of FE-induced seizure components and on the incidence of tonic hindlimb extensors in naive mice

	n	Latencies (s)			Incidence
		Clonic	Tonic	Tonic–clonic	THE
Saline	8	375.4 ± 20.9	658.4 ± 18.4	283.0 ± 18.4	8/8
MK-801					
0.01 mg/kg	8	381.0 ± 22.3	666.3 ± 12.6	285.3 ± 29.1	8/8
0.05 mg/kg	9	387.3 ± 13.1	743.3 ± 11.0*	356.0 ± 22.1	4/9**
0.1 mg/kg	8	415.8 ± 11.2	819.8 ± 23.6*	404.0 ± 29.1*	0/8***

"Tonic-clonic" expresses the latencies between onset of clonic seizure and onset of tonic seizure.
THE: tonic hindlimb extensor.
Mice were administered MK-801 or saline 2 h prior to exposure to FE. Each value represents the mean ± S.E.M.
* Significantly different from saline: Dunnett's test ($P < .01$).
** Significantly different from saline: Kruskal–Wallis test ($P < .05$).
*** Significantly different from saline: Kruskal–Wallis test ($P < .01$).

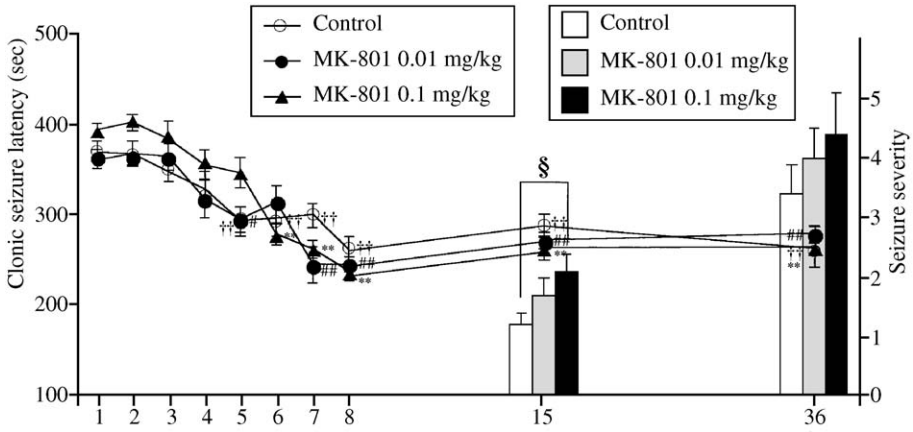

Fig. 2. Effect of MK-801 on the FE-induced clonic seizure latency during the development of FE-induced kindling for 8 days. Mice were administered MK-801 or saline once daily 2 h prior to each trial. Cessation of repeated administration of MK-801 changes the anticonvulsant effect against FE-induced seizure. However, at days 15 and 36, mice were exposed to FE without administration of MK-801 or saline. Each point and column represents the mean ± S.E.M. $^{\S}P<.05$, significantly different from saline group using Dunnett's test. $^{\#}P<.05$, $^{\#\#}P<.01$, significantly different from the first day of control. $^{**}P<.01$, significantly different from the first day of 0.01 mg/kg of MK-801. $^{\dagger\dagger}P<.01$, significantly different from the first day of 0.1 mg/kg of MK-801.

to FE at 1 (day 15) and 4 (day 36) weeks without administration of MK-801 or saline, latencies of clonic seizure were almost maintained. In each group, in contrast to each first day, latencies of clonic seizure were significantly decreased from days 5 to 36 ($P<.01$) for saline, from days 5 ($P<.05$) and 7–36 ($P<.01$) for 0.01 mg/kg and from days 6 to 36 ($P<.01$) for 0.1 mg/kg of MK-801. However, there were no significant differences in the latencies among the groups for the drug session. Although the seizure phenotype, which occurred immediately after clonic seizure, was not changed at day 36, on day 15 (1 week after the last exposure to FE) it was significantly enhanced in mice that were previously treated with MK-801 at a dose of 0.1 ($P<.05$) mg/kg for 8 days (Fig. 2).

3.4. Effect of 1 week withdrawal after repeated administration of MK-801 on the anticonvulsant action against FE-induced seizure

Fig. 3 shows the effect of 1 week withdrawal after repeated administration of MK-801 on the anticonvulsant action against FE-induced seizure. There was no significant difference in the latency of clonic seizure onset. Although the latency of tonic seizure and the difference between latencies of tonic and clonic seizures were significantly longer when mice were acutely administered MK-801 at 0.1 mg/kg, the anticonvulsant action of MK-801 was impaired when mice were administered 1 week withdrawal after repeated administration of MK-801.

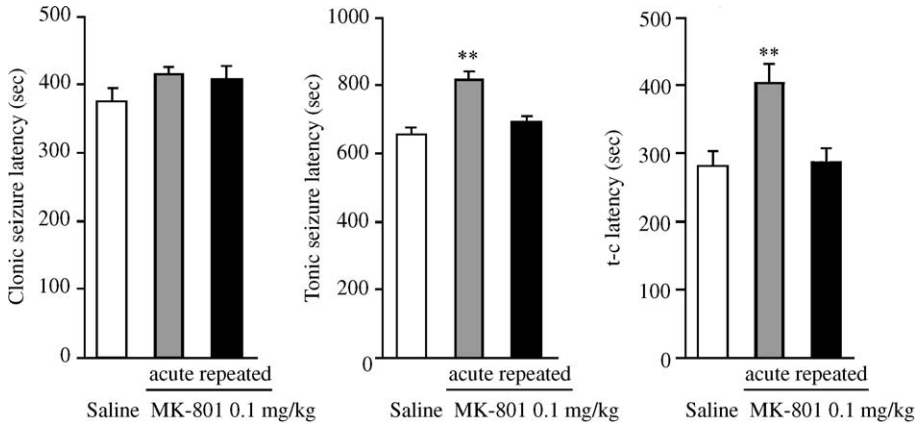

Fig. 3. Comparison of acute and repeated administration of MK-801 on the anticonvulsant effect against FE-induced seizure. Mice were administered MK-801 for 8 days without exposure to FE. At 1 week of withdrawal, mice were readministered MK-801 (0.1 mg/kg) 2 h prior to exposure to FE. "t-c" expresses the latencies between onset of clonic seizure and onset of tonic seizure. Each column represents the mean ± S.E.M. $^{**}P<.01$, significantly different from saline group using Dunnett's test.

4. Discussion

The acute administration of MK-801 in naive mice did not affect the clonic seizure latency but suppressed both latency and incidence of tonic seizure in a dose-dependent manner. There have been many studies reporting that MK-801 possesses an anticonvulsant action in several models of seizure such as electroshock- and pentylenetetrazol-induced seizure (Clineshmidt et al., 1982; O'Neill and Bolger, 1989; Tricklebank et al., 1989). Thus, the anticonvulsant action of MK-801 on this FE-induced seizure model also was recognized. Velisek et al. (1995) reported similar findings in the FE model, although there was a difference in species and age compared to the present study. Sato et al. (1988) suggested that MK-801 did not elevate clonic seizure thresholds in an electrical kindling model. With regard to these findings, it was suggested that MK-801 might be especially effective against a tonic seizure threshold of FE-induced seizure but not a clonic seizure threshold. The differential efficacy of MK-801 on these two seizures may be related to the anatomical structures that are dependent on these seizures. Gale (1992) reported that clonic seizures are believed to begin in a forebrain structure, whereas tonic seizures are dependent on an intact brainstem structure. The previous findings that systemic injection of NMDA elicits only a tonic seizure but never elicits a clonic seizure (Mares and Velisek, 1992) also support the present results. Therefore, it is conceivable that brainstem, but not forebrain, NMDA receptors play an important role in FE-induced tonic seizures.

The strain used in this study was C57BL/6. In general, it is well known that seizure susceptibility is affected by strain differences (Ferraro et al., 2002). Particularly, DBA/2 and C57BL/6 mice have been studied with regard to their differential susceptibility regarded as seizure sensitive and resistant, respectively (Ferraro et al., 1995; Golden et al., 2001). In experiments using FE as a convulsant agent, strain differences in sensitivity to FE-induced seizure were shown in various strains of mice, including C57BL/6 (Marley et al., 1986; Wehner and Marley, 1986). However, these reports showed the effect of only single-seizure activity. Reports on the effects of repeated seizure activity on seizure threshold are limited to the C57BL/6 strain, and because the C57BL/6 elicited reliably kindling by repeated exposure to FE, we used this same strain as Applegate et al. (1997).

It was reported that high doses (>0.5 mg/kg) of MK-801 could suppress the fully kindled seizure in the electrical kindling model. However, the efficacy of MK-801 on kindled animals differs depending on when it is administered (McNamara et al., 1988) and which brain region is stimulated (Sato et al., 1988; Clifford et al., 1990). In the present study, clonic seizure latencies were not affected by MK-801. We used relatively low doses of MK-801 (0.01–0.1 mg/kg) compared to those of previous studies, since high doses (0.5 mg/kg) have exhibited abnormal behavior, for example, sedation, ataxia and jumping in mice. The focus of seizure is decided in electrical kindling, while it is unknown where the focus of seizure is in the FE model.

When MK-801 was administered 2 h prior to each exposure to FE once daily for 8 days, both control and MK-801-treated animals progressively shortened the latencies of clonic seizure from days 1 to 8. There were no significant differences between groups. This result is consistent with a previous observation (Velisek et al., 1995), suggesting that MK-801 does not exert latencies of clonic seizures even though acutely or repeatedly administered. In a stimulation-free period, latencies of clonic seizure were not affected 1 and 4 weeks after the last administration of MK-801. However, as shown in Fig. 2, the mice treated with MK-801 at a dose of 0.1 mg/kg exhibited higher seizure severity compared to control 1 week after the last exposure to FE. Together with Applegate et al.'s (1997) report, the present results suggest that the change of seizure phenotype from clonic to tonic seizure may be related to the NMDA receptor in a stimulation-free period. Therefore, we performed the experiment of repeated administrations of MK-801.

In the experiment of the effect of repeated administration of MK-801 for 8 days without exposure to FE, and then after 1 week, mice were exposed to FE 2 h after administration of MK-801 until tonic seizure occurred. The acute anticonvulsant action of MK-801 disappeared against the FE-induced latency of tonic seizures and the incidence of forelimb tonic extension by repeated administration of MK-801. If there was no change in NMDA receptors, it is conceivable that impairment of the anticonvulsant effect of MK-801 could not be observed. So, it is suggested that this alteration to MK-801 may be due to changes in NMDA receptor up-regulation after 1 week of withdrawal after repeated administration. McNamara et al. (1988), in an electrical kindling model, reported that MK-801 suppressed the seizure stage only during the drug treatment. After drug cessation, the seizure stage rapidly reached Stage 4 or 5 compared to another excitatory amino acid antagonist. Hanania et al. (1999) reported that rats treated chronically with the NMDA antagonist phencyclidine (20 mg/kg once per day for 5 days) showed a marked increase in locomotor activity when phencyclidine (3.2 mg/kg) was readministered after 3 or 8 days of withdrawal. They reported that an up-regulation of the NMDA receptor subunit NR1 was related to this phenomenon. In the electrical kindling model, it was easily kindled when the NMDA antagonist was administered repeatedly and the electrical stimulation was performed after drug cessation (Gorter et al., 1991; Namba et al., 1994; Kodama et al., 1999). It has been demonstrated that chronic treatment with NMDA receptor antagonists can lead to an increased density of NMDA receptors that may complicate the therapeutic efficacy of such drugs. Williams et al. (1992) and McDonald et al. (1990) showed that treatment with an NMDA receptor antagonist, but not AMPA/kainate receptor antagonists, produced an up-regu-

lation of the NMDA receptor, namely an increase in B_{max} of NMDA receptor binding sites in vivo and in vitro. Moreover, it was reported (Kalluri and Ticku, 1999) that the NMDA receptor subunit NR2B, which is one of the MK-801 recognition sites, was up-regulated after chronic treatment with MK-801 or AP-5 but not with CNQX, an AMPA/kainate receptor antagonist (McDonald et al., 1990; Brooks et al., 1991; Williams et al., 1992; Follesa and Ticku, 1996). The present findings together with previous observations about alterations in NMDA receptors after repeated administration suggest that enhancement of seizure severity at 1 week of withdrawal after repeated administration of MK-801 may be related to the up-regulation of the NMDA receptor.

In conclusion, clonic seizures induced by FE were not affected by acute or repeated treatment with MK-801. However, tonic seizure was suppressed in both naive and kindled states, suggesting that NMDA receptors played an important role only in the tonic seizures in this model. With regard to the effect of MK-801 on the duration of stimulation-free period, pretreatment with MK-801 significantly exacerbated the grade of seizure severity, suggesting that the anticonvulsant action of MK-801 is impaired by 1 week of withdrawal after chronic administration of the drug.

Acknowledgements

This work was supported by the Japanese Health Science Foundation and a Grant-in Aid for Scientific Research (No. 11672262) from the Japanese Ministry of Education, Science, Sports and Culture.

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