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The Influences of Extremely Low Frequency Magnetic Fields on Drug-Induced Convulsion in Mouse

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This study investigated the effects of extremely low frequency magnetic fields (ELF-MFs) on the sensitivity of seizure response to bicuculline, picrotoxin and NMDA in mice. The mice were exposed to either a sham or 20 G ELF-MFs for 24 hours. Convulsants were then administered i.p. at various doses. The seizure induction time and duration were measured and lethal dose (LD_{50}) and convulsant dose (CD_{50}) of the clonic and tonic convulsion were calculated. The analysis of glutamate, glycine, taurine and GABA of mouse brain was accomplished by HPLC. The mice exposed to ELF-MFs showed moderately higher CD_{50}, LD_{50} and onset time on the bicuculline-induced seizure. However, the ELF-MFs did not influence them in the NMDA and picrotoxin-induced seizures. After the exposure to MFs exposure, the glutamate level was increased and GABA was decreased significantly in NMDA and picrotoxin-induced seizure. The level of glutamate and GABA were not changed by MFs in bicuculline-induced seizure. These results suggest that ELF-MFs may alter the convulsion susceptibility through GABAergic mechanism with the involvement of the level of glutamate and GABA.

Key words: Extremely low frequency magnetic fields (ELF-MFs), Convulsion, Glutamate, GABA

INTRODUCTION

Epilepsy is one of the most common neurological disorders. It is characterized by recurrent episodes of convulsive seizures, a loss of consciousness, sensory disturbances, or all of the above. At the neuronal level, either excessive excitatory activity or low inhibitory activity is believed to lead to seizures as a result of disturbances in specific membrane functions as well as a disruption in the concentrations of extra- and intracellular ions (Kondziella *et al*., 2002). Well-established models in epilepsy research are based on these hypotheses.

It has been reported that convulsions and epileptic seizures might be associated with exposure to electromagnetic fields (WHO, 1984, 1987, 1993). For example, a proconvulsant effect of naturally occurring alternating MFs (28 kHz atmospherics) has been reported in epileptic patients (Ruhenstroth_Bauer *et al*., 1995). In contrast, stimulated atmospherics and 100-Hz MFs resulted in a significant increase in latency to an audiogenic seizure in rats (Juutilainen *et al*., 1988). Therefore, attempts have been made to control seizures in both animal models and in humans with magnetic fields. However, these attempts have only been made in the early stages of development (Anninos *et al*., 1991).

The extremely low frequency (ELF, <300 Hz) magnetic fields (MFs) used in these experiments are generated as a consequence of the use of electricity. They induce a variety of behavioral and physiological functions in animals (Adey, 1981; Frey, 1993; Gould, 1984). Neurotransmission disorders are one of the major factors in the etiology of epilepsy (Ferraz *et al*., 2002). Among the amino acid neurotransmitters, glutamate and GABA have a critical role of regulating the balance in excitatory and inhibitory neurotransmission.

Glutamate is the major excitatory amino acid neurotransmitter in the central nervous system and the NMDA receptor is one of the glutamate receptors that are classified as ionotropic receptors including the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and

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kainate receptors (Ferreira *et al.*, 1999). The NMDA receptors, which are highly permeable to calcium and are distributed widely over the CNS neurons, are the major initiators of excitotoxicity.

γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter and exerts its effect through the $GABA_A$ and $GABA_B$ receptors. The $GABA_A$ receptors are composed of multiple subunits and binding sites. Both the GABA and benzodiazepine recognition sites are known to be extracellular, whereas several other sites, e.g. barbiturates and neurosteroids, may be located mainly at the transmembrane regions. Picrotoxin most likely binds to sites in the channels (Korpi *et al.*, 2002). Activation of the $GABA_A$ receptors, which are coupled directly to an ion channel, results in an increase in chloride conductance, inducing the early and short duration inhibitory post-synaptic potentials (Pittaluga *et al.*, 1987; Morrisett *et al.*, 1991). A blockade of the $GABA_A$ receptors by bicuculline, a competitive $GABA_A$ receptor antagonist, and by picrotoxin, a non-competitive $GABA_A$ receptor antagonist, induces clonic-tonic convulsions in mammals (Bowery, 1993; Pende *et al.*, 1993; Piredda *et al.*, 1985; Sperber *et al.*, 1989). These glutamatergic and GABAergic systems are rational targets for the development of antiepileptic drugs.

It has been shown that ELF-MFs can affect the progression of epilepsy (Keskil *et al.*, 2001; Ossenkopp and Cain, 1988; Potschka *et al.*, 1998). However, the results appear rather contradictory, and the processes underlying the observed effects are not fully explained.

Hence, the aim of this study was to determine if ELF-MFs could influence the susceptibility of convulsions related to glutamatergic or GABAergic mechanisms. Therefore, the glutamate, glycine, taurine and GABA concentrations were measured in a mouse brain in order to examine the roles of the excitatory and inhibitory amino acids in the mechanism responsible for the seizures.

MATERIALS AND METHODS

Animals

ICR mice (Hanlim, Korea) weighing 25-35 g were used in all experiments. The Mice were maintained in a temperature-controlled room (25±2 °C) and kept on a 12:12 light dark cycle (lights on at 08:00 h). Food and water were available ad libitum. The animals were housed individually. The experiments were carried out between 10:00 h and 16:00 h and each group consisted of 15-18 mice.

Magnetic fields

The MFs were generated with Helmholtz coils set parallel to each other in wood frame. The MFs consisted of 60 Hz time-varying fields. The generated MFs were within a range of 0-25 G intensity with the change of input voltage. This experiment used 20 G of MFs.

Convulsants and injection procedures

All drugs including bicuculline, picrotoxin and NMDA were purchased from Sigma (St. Louis, MO). Bicuculline was dissolved in 25% dihydroxybenzyl amine (DHBA). Picrotoxin and NMDA were dissolved in distilled water (D.W.). The diazepam was purchased from Roche (Seoul, Korea) and dissolved in D.W. All drugs were administered intraperitoneally (i.p.).

Convulsion test

The mice were exposed to MFs (20 G, 6 or 24 h) and convulsants were then injected into MFs exposure group and sham field exposure group. The convulsions induced by NMDA, picrotoxin and bicuculline at various doses were evaluated using the onset time, CD_{50} (convulsant dose) and LD_{50} (lethal dose), which were the doses required to induce seizure response and death in 50% of mice. The onset time for convulsions represents the time from the injection of the convulsants to the development of the first generalized seizures. Clonic convulsions were defined as seizures with a total loss of quadruped posture, while tonic convulsions were defined as seizures with a full body extension. Lethal toxicity was defined as death occurring within 6 h after the administration of the convulsants.

Sample preparation for brain neurotransmitters

After the convulsion test, the whole brain was rapidly removed, weighed to the nearest milligram and snap frozen rapidly in microcentrifuge tubes. The samples were stored at -70 °C. The brain regions were removed from the freezer, placed in an ice bath and given the appropriate amount of deionized water containing the internal standards. The tissue samples were disrupted by sonication and centrifuged at 13500 rpm for 3 min at 4 °C. Prior to the injection, 20 μL of the sample or a standard was reacted with a 10 μL *O*-phthalaldehyde solution for 10 min, and then filtered through a syringe filter.

Measurement of HPLC system

The brain neurotransmitters (glycine, taurine, glutamic acid or Γ-amino-n-butyric acid) were determined using a HPLC system consisting of a solvent delivery pump (Model PU-980 Pump, Jasco, Japan), an analytical C_{18} reversed-phase column (Luna 5u C18, 4.6 mm I.D. ×250 mm length, 5 μm particle size, Phenomenex, USA) and guard column. The internal standard used was L-homoserine. An electrochemical detector was set at +0.67 V at the working electrode. The flow rate was set at 1.20 mL/min. Centrally available reversed osmosis water was distilled and deionized. Mobile phase was 25% methanol (v/v)

water containing 0.1 M NaH_2PO_4 and 0.5 mM EDTA and adjusted to pH 4.5 with 1 M phosphoric acid. The buffers were allowed to sit overnight to allow the exothermic reaction to reach equilibrium. The buffer was filtered through a 0.45 μm membrane filter and degassed (Rowley *et al.*, 1995).

Chemicals

L-glutamic acid, L-homoserine, glycine, taurine and Γ-amino-*n*-butyric acid were purchased from Sigma (St. Louis, MO, USA) and prepared for the standards. The liquid reagents were obtained from Fisher (Seoul, Korea). The assay standards were diluted with water. All the standards and samples were derived using *O*-phthalaldehyde prior to the injection into the HPLC system.

Data analysis

The data are presented as a mean ± S.E.M. (standard error mean). The CD_{50} values and their statistical comparison were calculated by computer probit analysis, according to Litchfield and Wilcoxon. An unpaired Student's *t*-test was used to calculate the differences in the seizure onset time, and ANOVA test was used to compare the brain neurotransmitter levels. P values less than 0.05 were considered statistically significant.

RESULTS

NMDA-induced convulsion test

A seizure was induced by NMDA in the control group and MFs exposure group (20 G, 6 or 24 h). There were no significant differences in CD_{50} and LD_{50} values in Fig. 1. The seizure induction time of MFs exposure group was unchanged compared with control group as shown in Table I.

Table I. Comparison of onset time of convulsants-induced seizure

Drug	Dose (mg/kg)	Onset time (sec) of seizures		
		Sham control	MF 6 h	MF 24 h
NMDA	120	605 ± 154	N. M.	417 ± 65
	130	226 ± 59		292 ± 38
	140	267 ± 22		254 ± 21
Picrotoxin	6	486 ± 10	570 ± 45	557 ± 23*
	8	430 ± 16	372 ± 10**	348 ± 6*
	10	425 ± 15	348 ± 8**	340 ± 19**
Bicuculline	3.5	104 ± 9	121 ± 7	128 ± 19
	4	73 ± 3	87 ± 4*	85 ± 4*
	4.5	70 ± 15	95 ± 9	84 ± 9

N. M., not measured

This table represents the induction time of first generalized seizure induced by each convulsing agents. The results are reported as mean values ± S.E.M. from 15-18 mice. Asterisks designate significant differences (*P<0.05, **P<0.01) compared with control group.

Picrotoxin-induced convulsion test

The MFs (20 G, 6 or 24 h) had no significant effects on the CD_{50} and LD_{50} values in picrotoxin-induced seizures in Fig. 2. The seizure onset time of the MFs exposure group at 8 and 10 mg/kg doses showed a significant decrease compared with the control group in Table I.

Bicuculline-induced convulsion test

The CD_{50} and LD_{50} values were increased significantly as a result of MFs exposure (20 G, 6 or 24 h) in the bicuculline-induced seizure, as shown in Fig 3. The seizure onset time increased significantly at 4 and 4.5 mg/kg doses of bicuculline (in Table I).

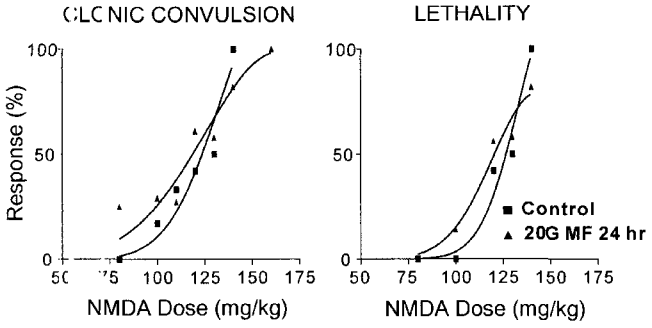

Fig. 1. Comparison of the CD_{50} and LD_{50} in an NMDA-induced seizure. The seizure response and lethality as a result of NMDA (80, 100, 110, 120 and 130 mg/kg) *i.p.* injection were evaluated in the control and MF exposure (20 G, 24 h). The CD_{50} was 110.1 mg/kg and 119.7 mg/kg in the control and MFs exposure. The LD_{50} was 119.9 mg/kg and 119.5 mg/kg in the control and MFs exposure. The values were calculated using computer probit analysis according to Litchfield and Wilcoxon.

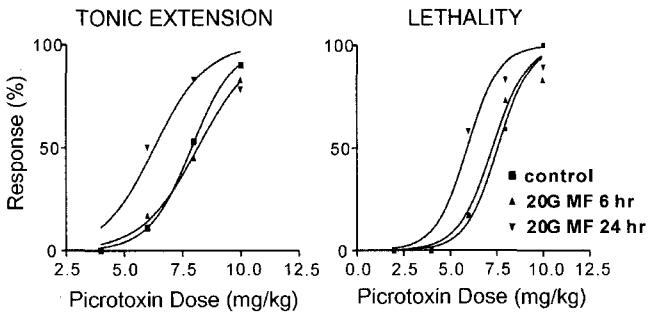

Fig. 2. Comparison of the CD_{50} and LD_{50} in a picrotoxin-induced seizure. The seizure response and lethality as a result of picrotoxin (4, 6, 8 and 10 mg/kg) *i.p.* injection were evaluated in the control and MF exposure (20 G, 6 or 24 h). The CD_{50} was 7.094 mg/kg, 8.167 mg/kg and 6.298 mg/kg in the control and MFs exposure for 6 h and 24 h, respectively. The LD_{50} was 7.582 mg/kg, 7.307 mg/kg and 5.944 mg/kg in the control and MF exposure for 6 hrs and 24 h, respectively. The values were calculated using computer probit analysis according to Litchfield and Wilcoxon.

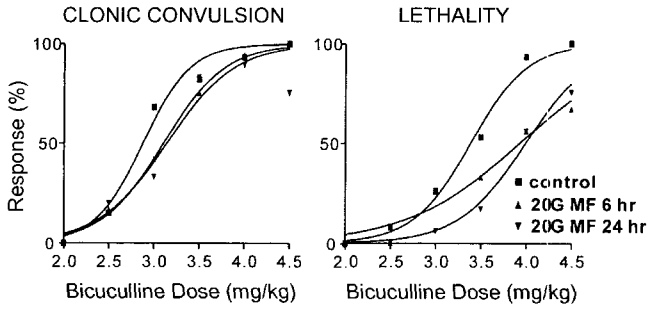

Fig. 3. Comparison of the CD_{50} and LD_{50} in bicuculline-induced seizure. The seizure response and lethality as a result of bicuculline (2.5, 3.0, 3.5, 4.0 and 4.5 mg/kg) *i.p.* injection were evaluated in the control and MFs exposure (20 G, 6 hrs or 24 h). The CD_{50} was 2.87 mg/kg, 3.10 mg/kg and 3.14 mg/kg in the control and MFs exposure group for 6 hrs and 24 h, respectively. The LD_{50} was 3.38 mg/kg, 3.93 mg/kg and 4.00 mg/kg in the control and MFs exposure group for 6 h and 24 h, respectively. The values were calculated using computer probit analysis according to Litchfield and Wilcoxon.

Effects of MFs on benzodiazepine system in bicuculline-induced seizures

Diazepam was administered at various doses 30 min before the bicuculline injection To determine if MFs influence benzodiazepine system. As shown in Fig 4, MFs (20 G, 24 h) exposure did not potentiate the anticonvulsant effects of diazepam in the bicuculline mice.

Effects of MFs on brain neurotransmitter after NMDA convulsion

Brain samples were obtained from the NMDA of LD_{80}-LD_{90} dose injected group. In Fig. 5, the glutamate concentration was increased as aresult of MFs (20 G, 24 h). When NMDA (130 mg/kg) was injected after the MFs exposure, the glutamate level increased significantly ($P< 0.01$) compared with NMDA alone group. The GABA concentration was significantly lower as result of the MFs or NMDA. In the NMDA-treated group after the MFs exposure, the lower GABA level was maintained compared with NMDA alone group. Glycine and taurine were reduced significantly by NMDA ($P<0.01$).

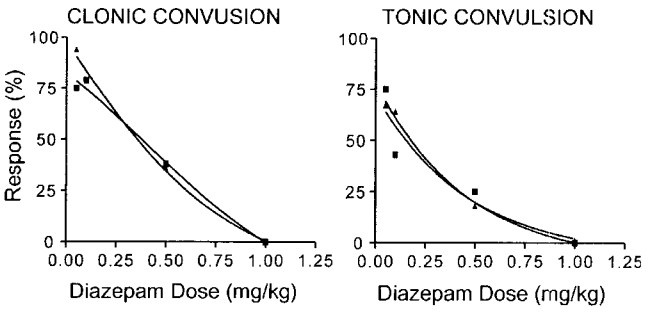

Fig. 4. The effects of diazepam after exposure of MFs. After exposure of MFs (20 G, 6 or 24 h), the mice were given diazepam (0.1, 0.5 and 1.0 mg/kg, *i.p.*) 30 min before the bicuculline (4 mg/kg) injection.

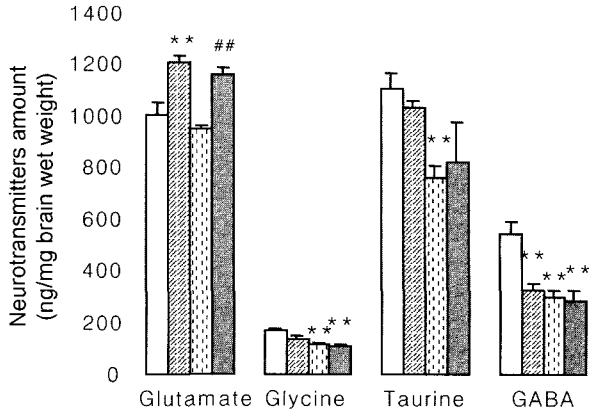

Fig. 5. The effects of MFs on brain neurotransmitter after NMDA convulsion the glutamate, glycine, taurine and GABA concentration in mouse brain were measured in the vehicle (□), the MFs exposure group (24 h, ▨), the NMDA (130 mg/kg) alone group (⊡) and NMDA (130 mg/kg) injected group after MFs exposure (24 h, □). The concentrations are expressed as a mean ± S.E.M. * and # denote significant differences compared with the control (**P<0.01) and NMDA alone group (## P<0.01), respectively.

Effects of MFs on brain neurotransmitter after picrotoxin convulsion

Brain samples were obtained from picrotoxin of LD_{80}-LD_{90} dose injected group. As shown in Fig. 6, the glutamate concentration was increased as a result of MFs (20 G, 24 h) and decreased by picrotoxin (8 mg/kg). When picrotoxin was injected after the MFs exposure, the glutamate level increased significantly ($P<0.01$) compared with the picrotoxin alone group. The GABA concentration

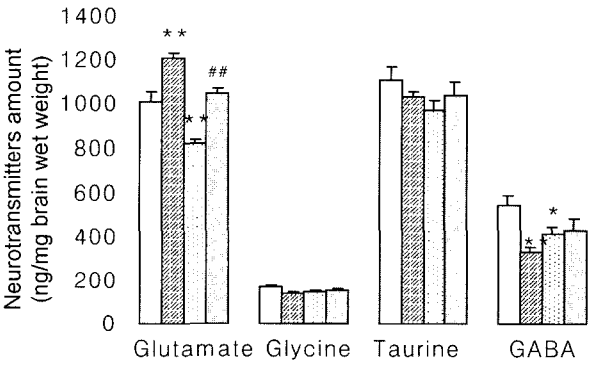

Fig. 6. The effects of MFs on brain neurotransmitter after picrotoxin convulsion. The glutamate, glycine, taurine and GABA concentration in the mouse brain were measured in the vehicle (□), the MFs exposure group (24 h, ▨), the picrotoxin (8 mg/kg) alone group (⊡) and picrotoxin (8 mg/kg) injected group after MFs exposure (24 h, □). The concentrations are expressed as a mean ± S.E.M. * and # denote significant differences compared with the control (**P<0.01) and picrotoxin alone group (## P<0.01), respectively.

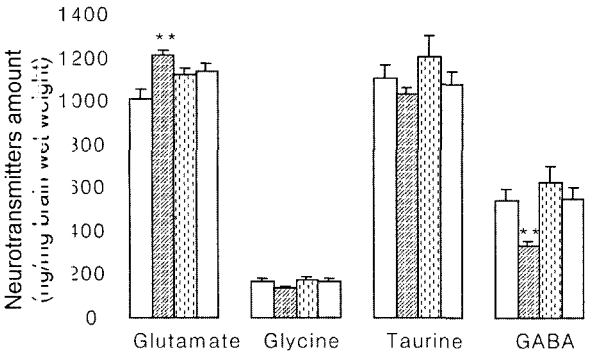

Fig. 7. The effects of MFs on brain neurotransmitter after bicuculline convulsion. The glutamate, glycine, taurine and GABA concentration in a mouse brain were measured in the vehicle (□), the MFs exposure group (24 h, ▨), the bicuculline (4 mg/kg) alone group (▦) and bicuculline (4 mg/kg) injected group after MFs exposure (24 h, □). The concentrations are expressed as a mean ± S.E.M. * denotes significant differences compared with the control (**P<0.01).

was significantly reduced by MFs (P<0.01) and picrotoxin (P<0.05). In the picrotoxin group after the MFs exposure, the GABA level did not show any significant differences compared with the picrotoxin alone group. Glycine and taurine were not influenced by picrotoxin and MFs.

Effects of MFs on brain neurotransmitter after bicuculline convulsion

Brain samples were obtained from the bicuculline of LD_{80}-LD_{90} dose injected group. Fig. 7 showed that the MFs (20 G, 24 h) exposure increased the glutamate concentration. Bicuculline (4 mg/kg) did not influence the glutamate level. When bicuculline was injected after MFs exposure, the glutamate level did not show significant changes (P<0.01) compared with the vehicle and bicuculline alone group. The GABA concentration was significantly lowered by the MFs (P<0.01). In the bicuculline treated group after MFs exposure, the GABA level did not show any significant differences compared with the vehicle and bicuculline alone group. Glycine and taurine were not influenced by bicuculline and the MFs.

DISCUSSION

In this experiment, the ELF-MFs had different influences on the susceptibility of the seizures to different convulsants. The MFs had no significant effects on CD_{50} and LD_{50} values in the NMDA and picrotoxin-induced seizures. However, increased CD_{50} and LD_{50} values were observed in bicuculline injected group. Considering the mechanism of NMDA, MFs may affect the inhibitory activity through GABA receptor. They, however, have no effects on the excitatory activity through the NMDA receptor in seizure.

Although bicuculline and picrotoxin are antagonists for the $GABA_A$ receptor, which is part of a larger GABA/drug receptor-Cl^- ion channel complex, bicuculline and picrotoxin have different binding sites and action mechanism. Bicuculline binds to the GABA sites competitively and exerts its inhibitory action in Cl^- ion currents by decreasing the opening frequency and the mean open time of channel (Macdonald and Olsen, 1994). Picrotoxin, as a channel blocker, binds to picrotoxin site in the channel directly and causes a decrease in mean channel open time (Macdonald and Olsen, 1994). Therefore, the different results of the bicuculline and picrotoxin-induced seizures, suggest that the properties influenced by the MFs can be either GABA binding sites or Cl^- ion channels.

Several reports have suggested that MFs can modulate benzodiazepine action positively (Jeong *et al.*, 2000; Min *et al.*, 2001). The benzodiazepine receptor is an integral part of the $GABA_A$ receptor-Cl^- channel complex and enhances GABAergic transmission. These benzodiazepines increase the frequency of channel opening in response to GABA and benzodiazepine site are coupled allosterically to the barbiturate and picrotoxin site (Macdonald and Olsen, 1994). In this study, CD_{50} and LD_{50} values of diazepam and bicuculline-treated group were not affected by the MFs. This finding demonstrates that the effects of the MFs shown in bicuculline-induced seizure are not potent enough to intensify the anticonvulsant action of benzodiazepine.

Many investigators have reported that an imbalance between the excitatory and inhibitory neurotransmitter plays a role in genesis or the spread mechanism of a seizure (Goto *et al.*, 2001; Lott *et al.*, 1978; Sejima *et al.*, 1997). This study found that the glutamate, glycine, taurine and GABA concentrations were influenced by either the MFs or convulsants in a mouse brain. MFs exposure without the resulted in an increased in the glutamate level and a decreased in the GABA level significantly. The concentrations of neurotransmitters were altered differently by each convulsant. In NMDA and picrotoxin-induced convulsion, the MFs exposure group showed an increased glutamate level but there were no significant effects on the glutamate level as a result of MFs in bicuculline-induced convulsions. Although the increased glutamate level as a result of MFs in the picrotoxin and NMDA-induced seizure did not cause an excitatory result in the convulsion response *in vivo* test, there is the possibility that it can contribute to different results between bicuculline and the others.

Another finding observed in the present study was different GABA levels. While the GABA concentrations were reduced as a result of NMDA, picrotoxin or in combination with the MFs, there were no significant changes in the GABA levels in the bicuculline-injected group. This constant GABA level in the bicuculline group compared

with the other groups may be further evidence for the MFs effects on the in vivo result of bicuculline-induced seizure.

In conclusion, MFs may alter the convulsion susceptibility via a GABAergic mechanism. The glutamate and GABA levels can influence the modulatory effects of MFs. Further studies will be needed to elucidate the accurate mechanism of MFs on the seizure susceptibility.

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