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Changes in the Incidence and Duration of Electroconvulsions After Acute or Subchronic Treatment With Methamphetamine in Mice

J. NAKAMURA,*†[1] S. YAMADA,† Y. HORIKAWA* AND I. NOSE*

**Department of Neuropsychiatry and †Institute of Brain Diseases, Kurume University School of Medicine, 67 Asahi-Machi, Kurume 830, Japan*

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NAKAMURA, J., S. YAMADA, Y. HORIKAWA AND I. NOSE. *Changes in the incidence and duration of electroconvulsions after acute or subchronic treatment with methamphetamine in mice.* PHARMACOL BIOCHEM BEHAV **45**(1) 173–177, 1993.—The effects of acute or subchronic treatment with methamphetamine on the incidence, intensity, and duration of electroconvulsion were investigated in mice. The convulsion was induced by electrical stimulation (100 Hz, 60 mA, 0.1-s duration) through electrodes located at each ear of mice, then analyzed by the vibration monitoring apparatus. Acute methamphetamine (3 mg/kg) reduced the incidence of the electroconvulsion in mice; however, the duration of each phase of the convulsion was prolonged by acute methamphetamine. Repeated administration of methamphetamine prolonged the duration of clonic phase of the convulsion and enhanced the acute methamphetamine-induced reduction in the incidence of electroconvulsion. These data indicate that the incidence of electroconvulsion is regulated by different mechanisms underlying the duration and intensity of the convulsion.

Convulsion Methamphetamine Dopamine Mouse

SYSTEMIC application of drugs that increase dopaminergic activity in the brain has been shown to attenuate or block generalized seizures in different species (1,7–10,14,20). γ-hydroxybutyrate, which blocks impulse flow of dopamine (DA) neurons, produces electroencephalographic and behavioral responses that resemble human petit mal seizures when administered to monkeys (19) and rats (2,4,19). These reports indicated that the electroconvulsive threshold level is at least partially modulated by the central dopaminergic system.

Repeated administration of methamphetamine caused a behavioral sensitization to a challenge dose of methamphetamine that is associated with the greater increase in DA release from DA nerve terminals (17,21). Therefore, this hyperdopaminergic state is expected to increase the electroconvulsive threshold level. In the present study, the sensitized state to methamphetamine was assessed by the incidence, intensity, and duration of the electroconvulsion.

METHOD

Experimental Animals and Methamphetamine Pretreatment

Adult male d-dy mice, weighing 20–30g, were used and were housed in groups of 12–18, fed ad lib, and maintained on a 12 L : 12 D cycle. Methamphetamine HCl (Dainihon Seiyaku Co.) was dissolved in isotonic NaCl solution. Mice were administered IP 3 mg/kg/day methamphetamine for 6 times at every 48-h interval, then kept for 7 days without the drug. To check the formation of the behavioral sensitization to methamphetamine, stereotyped behaviors after the challenge dose of methamphetamine (1 mg/kg, IP) was assessed according to the method of Ohi et al. (12). Observed movement such as sniffing, exploratory activity, head movement, gnawing, licking, and backlocomotion were assigned 0 points if absent, 1 point if present, or 2 points if movement was greatly enhanced scored 30 min after each pretreatment with methamphetamine.

Electrical Convulsions

Electrical convulsions were induced by a fixed current (60 mA), frequency (100 Hz), and duration (0.1 s) that was delivered through electrodes placed on the ears of mice. Animals were placed on the center of a round acryl board that was fixed onto the surface of a loudspeaker (38 cm i.d.) encircled with a tin plate 30 cm high. Vibration signals caused by electrical convulsion of a mouse were picked up by the pickup apparatus for minor tremor (Nihon Koden AB 621G), then amplified and monitored according to the method of Fukuda et al. (3) as shown in Fig. 1. Using this apparatus, each phase

[1] To whom requests for reprints should be addressed.

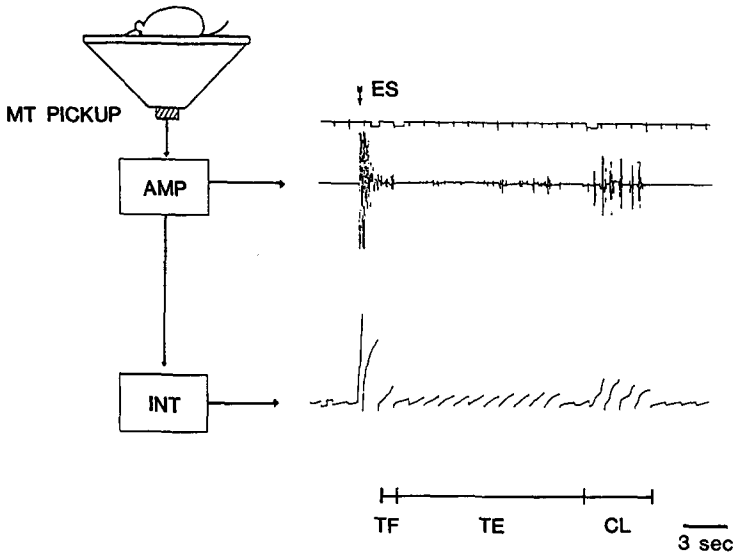

FIG. 1. Block diagram of the recording system of convulsion. Vibration signals caused by electroshock were picked up by the minor tremor (MT) pickup apparatus and then amplified (AMP) and recorded by the integrator.

of the electroconvulsion—tonic flexuous (TF), tonic extensine (TE), and clonic phase (CL)—could be monitored longitudinally on the monitoring paper. Electrical convulsions were induced 30 min after injection of methamphetamine (0.5, 1, 3 mg/kg, IP) to mice subchronically treated with saline or methamphetamine (1 or 3 mg/kg, IP). Data were expressed as the number of mice exhibiting death after tonic seizure, tonic-clonic seizure, incomplete seizure, and no seizure. Significant differences were calculated by χ^2-analysis. In mice exhibiting tonic-clonic seizure, the duration (seconds) of each phase of convulsion was measured from the monitor. To check the effect of DA antagonist on the changes in the electroconvulsion induced by methamphetamine, haloperidol was administered to mice 30 min prior to the electrical stimulation.

Significant differences in the duration of each phase of seizure were determined by analysis of variance (ANOVA) followed by Student's *t*-test.

RESULTS

The effect of repeated administration of methamphetamine on stereotyped behavioral response to the challenge dose of methamphetamine (0.5 mg/kg, IP) is shown in Fig. 2.

The scores for the methamphetamine-evoked behavioral changes were significantly greater in mice pretreated with repetitive methamphetamine than in mice pretreated with saline ($p < 0.05$).

As shown in Table 1, the electrical stimulation used in this experiment caused eight control mice to exhibit a typical tonic-clonic convulsion while the remaining mouse died. Only one mouse did not exhibit any seizure. Acute methamphetamine (3 mg/kg) significantly reduced the incidence of typical tonic-clonic convulsion to one mouse and elicited incomplete seizure in two mice, thereby increasing the incidence of no seizure to seven mice. One mg/kg methamphetamine was less effective than 3 mg/kg methamphetamine. Methamphetamine at a dose of 0.5 mg/kg had no effect on the incidence of electroconvulsion. Thus, the inhibitory effect of methamphetamine on the incidence of electroconvulsion appeared to be dose dependent.

On the other hand, the duration of each phase of the convulsion was prolonged by the acute treatment with methamphetamine (1 mg/kg, Fig. 3A).

Repeated administration of methamphetamine, which caused a behavioral sensitization to methamphetamine, significantly reduced the incidence of the tonic-clonic and incomplete convulsion to 42% in response to the challenge dose (0.5 mg/kg, IP) of methamphetamine when compared with that of the saline-treated group. The methamphetamine-induced reduction in the incidence of electroconvulsion was antagonized by pretreatment with haloperidol 30 min before the electrical stimulation (Table 2).

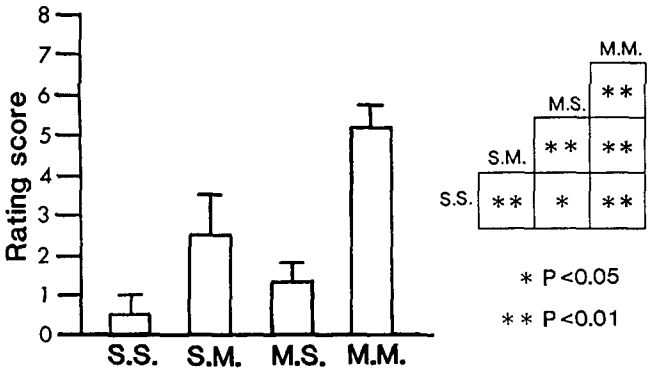

FIG. 2. Stereotypy from 1 mg/kg methamphetamine HCl in methamphetamine- and saline-pretreated mice (n = 8–9). The stereotypy was quantified with the stereotypy scale reported by Ohi et al. (12) as the stereotypy responses 30 min after the challenge dose of methamphetamine for 10 min. The distribution of scores from the stereotypy rating categories was analyzed using the Mann-Whitney *U*-test. *$p < 0.01$.

TABLE 1

NUMBERS OF MICE EXHIBITING ELECTROCONVULSION AFTER ACUTE TREATMENT WITH METHAMPHETAMINE OR SALINE

Acute Treatment	Tonic-Clonic Convulsion	Incomplete Convulsion	Dead	No Convulsion
Saline	8	0	1	1
MAP (0.5 mg/kg)	7	1	1	1
MAP (1 mg/kg)	5	3	0	2
MAP (3 mg/kg)	1*	2	0	7*

*$p < 0.01$ as compared with saline or MAP (0.5 mg/kg) group.

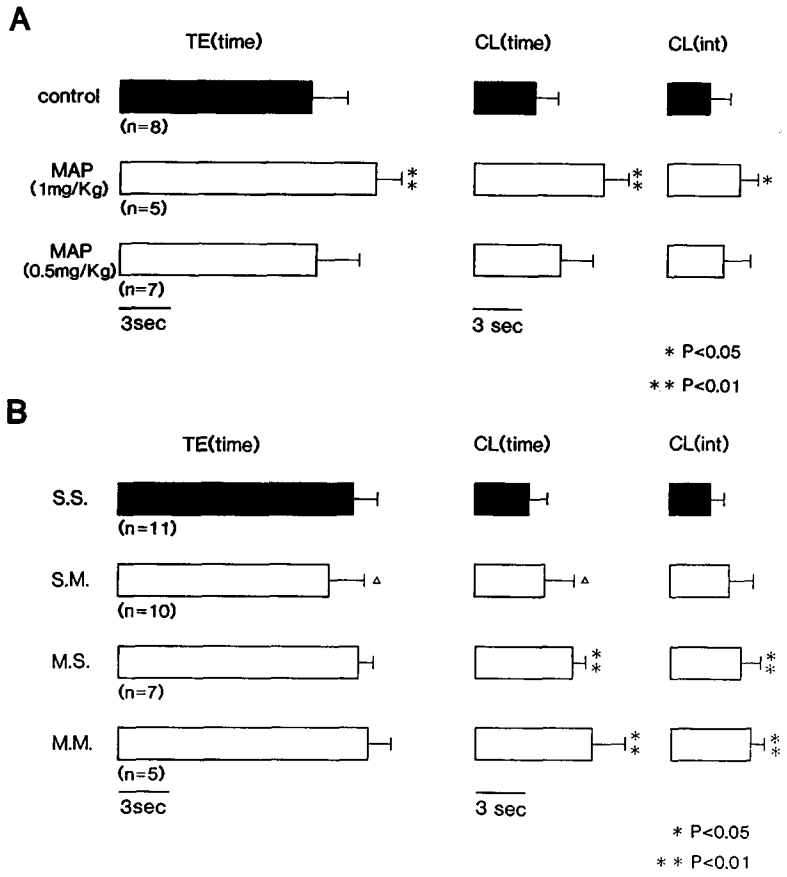

FIG. 3. Effects of acute (A) or repeated (B) treatment with methamphetamine on the duration and intensity of the electroconvulsion. Electroconvulsions were induced by a fixed current (60 mA), frequency (100 Hz), and duration (0.1 s) that was delivered through electrodes located on the ears of mice. Vibration signals caused by electrical convulsions were monitored by the pickup apparatus for minor tremor. Data represent mean seconds (±SEM, n = 5–8) of tonic extensine phase (TE) and clonic phase (CL) for the duration of convulsions and mean mm (±SEM, n = 5–8) for the intensity of convulsion. Note that (A) 1 mg/kg but not 0.5 mg/kg acute methamphetamine prolonged each phase of the convulsion and enhanced the intensity of clonic phase and (B) the duration and intensity of clonic convulsion are significantly enhanced by the repeated administration of methamphetamine (MS) compared with that of saline (SS). SS, repeated saline and acute saline; SM, repeated saline and acute methamphetamine (0.5 mg/kg); MS, repeated methamphetamine and acute methamphetamine.

TABLE 2

NUMBERS OF MICE EXHIBITING ELECTROCONVULSION AFTER CHRONIC TREATMENT WITH METHAMPHETAMINE OR SALINE

Chronic Treatment	Tonic-Clonic Convulsion	Incomplete Convulsion	Dead	No Convulsion
SS	11	2	2	3
SM	10	3	3	2
MS	8	5	3	3
MM	5	3	0	11*
MM + H	8	2	0	0†

SS, chronic saline and acute saline; SM, chronic saline and acute methamphetamine; MS, chronic methamphetamine and acute saline; MM, chronic methamphetamine and acute methamphetamine; MM + H, chronic methamphetamine and acute methamphetamine and haloperidol (0.5 mg/kg).

*$p < 0.01$ as compared with SM group.

†$p < 0.01$ as compared with MM group.

The duration and intensity of the clonic phase but not the TE phase of convulsion was significantly prolonged by repeated administration of methamphetamine. However, acute effects of methamphetamine on the duration of convulsion were unchanged by repeated administration of methamphetamine (Fig. 3B).

DISCUSSION

Methamphetamine has a DA-releasing action from DA nerve terminals in the brain. This indirect DA-agonistic action of methamphetamine is responsible for the methamphetamine-induced behavioral changes and the increase in a convulsive threshold level. In the present study, methamphetamine reduced incidence of the electroconvulsion in mice and haloperidol antagonized the effect. The results suggest that the electroconvulsive threshold level is modulated by the activity of DAergic neurons, in agreement with the report by Riffee et al. (15) and others (1,7,9,10,20) that the IV pentylenetetrazol seizure threshold is increased by a single 2.5-mg/kg injection of (+)-amphetamine.

The repeated administration of methamphetamine, which is associated with behavioral sensitization to the challenge dose of methamphetamine, reduced the incidence of the electroconvulsion in mice compared with saline-treated mice after the challenge dose of methamphetamine. The results indicate that the repeated administration of methamphetamine increases the electroconvulsive threshold level in response to challenge dose of methamphetamine. The repeated administration of methamphetamine results in an increase in DA release from the striatum in vivo (17) and striatal slices of rats in vitro (21) in response to low doses of methamphetamine and in a supersensitivity of D_1 receptors and subsensitivity of D_2 receptors (5). As the methamphetamine-induced reduction in the incidence of electroconvulsion was prevented by the pretreatment with haloperidol, the mechanism underlying the increased convulsive threshold level may be due to enhanced DA release from DA nerve terminals in response to the challenge dose of methamphetamine. Karler et al. (6) reported that subchronic treatment with amphetamine enhanced the increase in the bicuculline-induced convulsive threshold level more than 30 days after the last injection of amphetamine, which associated with the behavioral sensitization to amphetamine. These findings indicate that the bicuculline-induced convulsive threshold level is modulated by the DAnergic system.

In the present study, the duration and intensity of clonic convulsion were enhanced after repeated administration of methamphetamine, while the incidence of electroconvulsions was unchanged. Moreover, acute effects of methamphetamine on the duration and intensity of clonic convulsion were unchanged by the repeated treatment with methamphetamine, while acute methamphetamine reduced the incidence of electroconvulsions, when compared with the saline-treated group. These findings indicate that the incidence of electroconvulsion is modulated by different mechanisms underlying the duration and intensity of electroconvulsion. The mechanism underlying the prolongation of clonic convulsion after repeated administration of methamphetamine remains unclear. Karler et al. (6) reported that the NMDA, glutamate agonist, induced convulsive threshold level is reduced by acute amphetamine. Moreover, repeated amphetamine enhances the reduction of the threshold level of NMDA-induced convulsion. The data indicate that repeated methamphetamine could change glutamatergic functions as well as DAergic functions. The changes in glutamatergic functions after repeated methamphetamine may account for the prolongation of the duration or intensity of clonic convulsion in the rat sensitized with methamphetamine.

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