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Pharmacology, Biochemistry and Behavior 74 (2002) 141–147

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Characteristics of flurothyl-induced seizures and the effect of antiepileptic drugs on flurothyl-induced seizures in Mongolian gerbils

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Received 14 March 2002; received in revised form 3 June 2002; accepted 29 July 2002

Abstract

We investigated the characteristics of the flurothyl-induced seizures and the effects of antiepileptic drugs on the flurothyl-induced seizure model in a previously untested Mongolian gerbil species. Mongolian gerbils demonstrated tonic extension immediately after or within 1 min after the appearance of clonic convulsion. Very high amplitude spike waves appeared in these regions concurrent with the appearance of clonic convulsion. When the tonic extension appeared immediately after the clonic convulsion, the high amplitude spike waves continued during tonic convulsion. When the tonic extension occurred, high amplitude spike waves appeared in these three regions within a very short time, and afterward Mongolian gerbils died. Administration of valproic acid–Na (200 mg/kg), ethosuximide (100 and 200 mg/kg), clonazepam (2 mg/kg) and diazepam (0.5, 1 and 2 mg/kg) significantly prolonged the latency of clonic convulsion. Zonisamide–Na, phenytoin and carbamazepine, however, had no such effect. In Mongolian gerbils, tonic extension was demonstrated immediately after the appearance of clonic convulsion, yet, this effect was inhibited by all these drugs in a dose-dependent manner. Diazepam completely blocked the appearance of any behavioral changes in animals. These findings suggest that diazepam has a significant effect on flurothyl-induced seizures. Flurothyl-induced convulsions are associated with GABA receptors; hence, benzodiazepine (BDP) suppression may result from the strong relation between BDP and GABAnergic neurons.

Keywords: Flurothyl; Mongolian gerbils; Electroencephalogram; Tonic extension; GABA

1. Introduction

It was reported that an increase in the susceptibility of mice to seizures after repeated exposure to flurothyl (Appligate et al., 1997; Samoriski and Applegate, 1997; Ferland and Applrgate, 1998). In the flurothyl kindling model, eight flurothyl-induced generalized clonic seizures, dubbed forebrain seizures, and a subsequent 28-day stimulation-free interval changed the seizure phenotype of mice from purely forebrain seizures to seizures of a more complex phenotype. The generalized-onset, forebrain seizure progresses rapidly to a seizure with tonic manifestations, dubbed brain-stem seizures, when rechallenged with flurothyl. In addition to this finding, Ferland and Applegate (1999) reported a bidirectional transfer between the electrical and flurothyl kindling models. This shift suggests that the same phenomenon may occur in Mongolian gerbils, because they show the spontaneous generalized clonic seizure, which greatly resembles that of electrical kindled animals. Thus, we hypothesized that flurothyl-induced convulsion must develop rapidly in Mongolian gerbils.

Two independent neurocircuits in the brain mediate experimentally induced seizures (Applegate et al., 1991; Browning and Nelson, 1986; Browning et al., 1981; Browning, 1985; Browning et al., 1993). One neurocircuit mediates clonic seizures, while the other mediates tonic

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0091-3057/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0091-3057(02)00965-6

seizures. Maximal electroshock seizure demonstrates severe tonic extensor convulsion; pentylenetetrazol induces generalized clonic convulsion at low doses and generalized tonic convulsion at high doses. Clonic seizures begin in the forebrain structure, whereas tonic seizures depend on the brainstem structure (Appligate et al., 1997; Samoriski and Applegate, 1997; Ferland and Applrgate, 1998; Applegate et al., 1991). These findings suggest that a low threshold forebrain system mediates generalized clonic seizures and a high threshold brainstem system mediates generalized tonic seizures, although it is difficult to understand the independence of these neurocircuits.

In the present study, we investigated the characteristics of flurothyl-induced seizures compared with that of mice and monitored EEG change in Mongolian gerbils. In addition, antiepileptic drugs were evaluated using the previously untested Mongolian gerbil species in order to evaluate the effects of antiepileptic drugs on the progression from clonic convulsion to tonic convulsion.

2. Materials and methods

2.1. Animals

One hundred and forty-five male Mongolian gerbils (8 weeks old, 60–70 g), obtained from Seac Yoshitomi (Fukuoka, Japan), and six male C57BL/6 mice (6 weeks age, 19–22 g), obtained from Charles River Japan (Yokohama, Japan), were housed in an air-conditioned room at 23 ± 1 °C. Light was provided on a 12-h light–dark cycle with lights off at 7:00 p.m. Food and water were provided ad libitum. All experiments were conducted according to the Guide for Animal Experimentation at Okayama University Medicine School.

2.2. Protochol for flurothyl experiment

All experiments were performed in the draft room. Mongolian gerbils or mice were placed in the 2-l closed Plexiglas chamber (Bell jar) individually. A 10% solution (in 95% ethanol) of flurothyl (2,2,2-trifluroethyl ether; Aldrich) was infused into the chamber (0.2 ml/min) using a 10-ml syringe driven by an infusion pump (KD Schientific Model 100, Neuroscience). The onset of forebrain seizure and tonic seizure was defined as a sustained loss of postural control and either bilateral forelimb and hindlimb tonic extensor, respectively. We recorded the latency from the start of flurothyl infusion to the sustained loss of posture control and tonic extension in mice and Mongolian gerbils. Eight mice and five Mongolian gerbils were used in this experiment. In addition, the effects of several antiepileptic drugs were examined using five Mongolian gerbils in each group, including the control group.

2.3. Chronic electrode implantation

The gerbils were anesthetized with a 50 mg/kg ip injection of pentobarbital–Na (Nenbutal, Dainippon Pharmaceutical). The electrodes to facilitate EEG-recording were then implanted, as previously described (Araki et al., 1986). These electrodes consisted of a pair of twisted stainless steel wires (tip diameter: 0.2 mm, polar distance: 0.5 mm); the wires were insulated for the entire length, except for the final 0.5 mm of the tips. The tips were implanted stereotaxically in the frontal cortex and either the dorsal hippocampus (P: 1.8, L: 2.8, H: 2.5) or the amygdala (A: 1.0, L: 4.0, H: 5.3) as designated by the coordinates given in a brain atlas (Thiessen and Yahr, 1977). Each electrode was connected to pins inserted in a small socket and fixed to the skull using dental cement. The effect of several antiepileptic drugs was examined

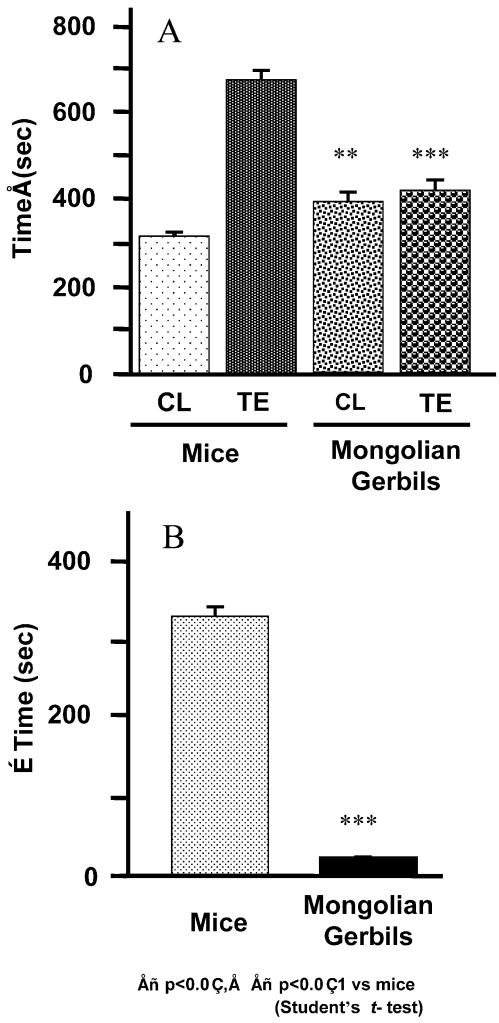

Fig. 1. Temporal differences between the latency of clonic convulsion and tonic extension in mice and Mongolian gerbils. Each group consisted of either six mice or five gerbils. Values are expressed as means ± S.E. (A) Latency of clonic convulsion and tonic extention: CL: clonic convulsion, TE: tonic extension. (B) Differences between the latency of clonic convulsion and tonic extensor (s).

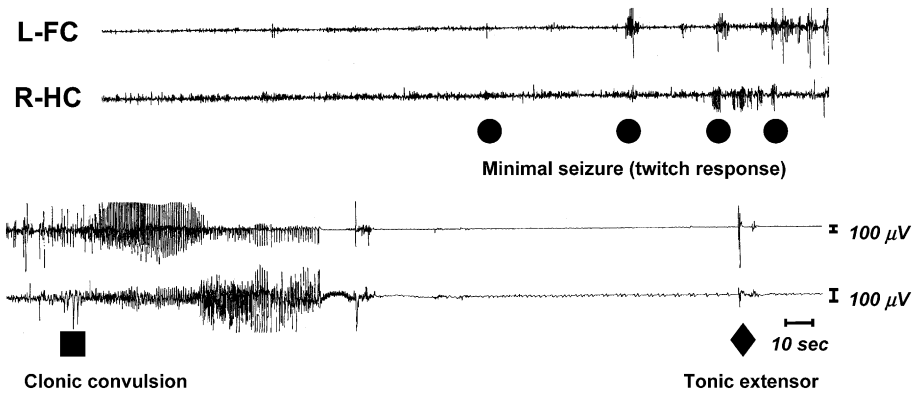

Fig. 2. Changes in EEG induced by flurothyl in a control animal. L-FC: left frontal cortex, R-HC: right hippocampus. (●) Minimal seizure, (■) clonic convulsion, (◆) tonic extensor.

using four Mongolian gerbils in the highest dose group in each drug.

2.4. EEG recording

After chronic implantation of the electrodes, animals were allowed to recover from the surgery for 1 week before commencing the experiments. Animals were transferred to a Bell jar placed in a draft room and allowed 15 min to adapt to the new environment. The EEG was recorded for 5 min before the start of flurothyl infusion; recording continued after flurothyl infusion until the animal demonstrated a tonic seizure. In experiments involving drug administration, the EEG recording continued for 20 min after the start of flurothyl infusion.

2.5. Drugs and administration

Drug dosages of the flurothyl-induced convulsion and EEG recording were as follows: zonisamide–Na (Dainippon Pharmaceutical) at 12.5, 25 and 50 mg/kg; phenytoin (Aleviatin, Dainippon Pharmaceutical) at 2, 5, 10 and 20 mg/kg; valproic acid–Na (Sigma) at 50, 100 and 200 mg/kg; ethosuximide (Sigma) at 50, 100 and 200 mg/kg; carbamazepine (Sigma) at 2, 5 and 10 mg/kg; clonazepam (Sigma) at 0.5, 1 and 2 mg/kg; diazepam (Cercine, Takeda Pharmaceutical) at 0.5, 1.0 and 2.0 mg/kg. Phenytoin and diazepam were used as injections of Aleviatin and Cercine, respectively, and diluted with saline. Valproic acid–Na and zonisamide–Na were dissolved in distilled water, and carbamazepine, ethosuximide and clonazepam were sus-

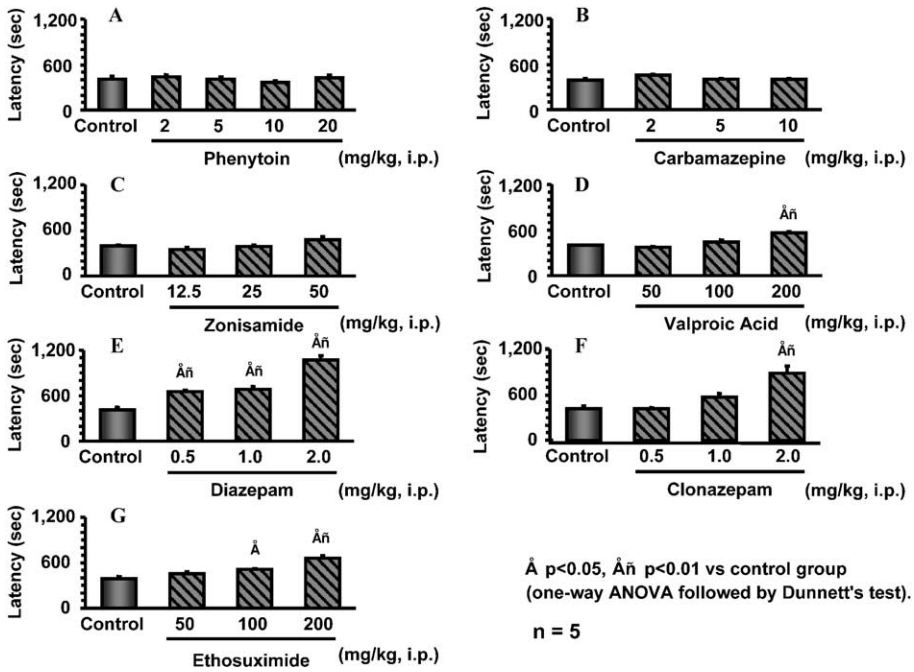

Fig. 3. Effects of various drugs on flurothyl-induced convulsions in Mongolian gerbils. (A) Phenytoin, (B) carbamazepine, (C) zonisamide–Na, (D) valproic acid–Na, (E) diazepam, (F) clonazepam, (G) ethosuximide. Latency is that of clonic convulsion. Values are expressed as means ± S.E. (s). * $P < .05$, * * $P < .01$ vs. control group (one-way ANOVA followed by Dunnett's test).

pended in 0.5% methylcellulose. All drugs were administered intraperitoneally at a volume of 0.1 ml/100 g body weight in Mongolian gerbils. Dosages were chosen to match those that previously demonstrated anticonvulsive action. Phenytoin, carbamazepine, valproic acid–Na, ethosuximide, diazepam and clonazepam were administered 30 min, and zonisamide–Na was administered 60 min before the beginning of flurothyl infusion. If gerbils showed a convulsion before the start of the experiment, and immediately after drug injection, the animals were excluded from the analyses. In the present experiment, only two animals showed the clonic convulsion immediately after drug injection.

2.6. Statistical analysis

The latency from the start of infusion to the sustained loss of posture control and tonic extensor was statistically evaluated by the analysis of variance (ANOVA) test followed by Dunnett's test. Data of the two groups were analyzed using Student's *t*-test. Probability values $<.05$ were considered to show a significant difference.

3. Results

3.1. The latency of flurothyl-induced clonic convulsion and tonic extension in mice and Mongolian gerbils

Upon treatment with flurothyl, mice exhibited a series of myoclonic jerks, losing postural control, exhibiting clonic convulsion, running and bouncing, forebrain and hindlimb treading, forebrain tonic extension and hindlimb flexion, forebrain and hindlimb tonic extension and then died. The time period between the latency of clonic convulsion and the onset of tonic extension was 272.7 ± 5.0 s (mean ± S.E.). The latency of myoclonic jerks and clonic convulsion in Mongolian gerbils was similar to that seen in mice. Mongolian gerbils, however, exhibited tonic extension immediately after the appearance of clonic convulsion. The time difference between the latency of clonic convulsion and the onset of tonic extension is reduced to 30.9 ± 8.0 s (Fig. 1). Some animals showed clonic–tonic convulsions almost simultaneously. Some the other animals showed clonic convulsion first and then recovered from it. Thereafter they stopped all behaviors and several tens of seconds after they showed tonic extension they suddenly died.

3.2. Flurothyl-induced EEG change in Mongolian gerbils

When these antiepileptic drugs were administered intraperitoneally, the EEG of the Mongolian gerbils was not markedly changed. The flurothyl-induced EEG changes, seen in Mongolian gerbils, demonstrated novel spike waves in the frontal cortex and hippocampus during minimal seizure (twitch response). During clonic convulsion, high amplitude spike waves also appeared in these regions immediately after clonic convulsion, tonic extension occurred, eventually leading to death. It was difficult to determine EEG changes during the transition from clonic convulsion to tonic extension (Fig. 2).

3.3. The effects of various drugs on flurothyl-induced seizures in Mongolian gerbils

We investigated the effects of acute treatment with zonisamide, phenytoin, valproic acid–Na, ethosuximide, carbamazepine and diazepam. The latency of clonic convulsion was prolonged significantly by the administration of valproic acid–Na, ethosuximide, clonazepam and diazepam in a dose-dependent manner (Fig. 3). The effects of diazepam were especially marked. Zonisamide–Na, phenytoin and carbamazepine, however, showed no effect on the latency of the clonic convulsion (Fig. 3).

All of the drugs investigated inhibited flurothyl-induced tonic extension. Zonisamide–Na, valproic acid–Na, carba-

Table 1
The effects of various drugs on the incidence of death within 20 min by either flurothyl-induced tonic extension or continued clonic convulsion in Mongolian gerbils

Drug	Dose (mg/kg)	Incidence of death by tonic extension	Incidence of death by continued clonic convulsion	Number alive after 20 min
Control	–	5/5	0/5	0/5
phenytoin	2	5/5	0/5	0/5
	5	3/5	2/5	0/5
	10	0/5	5/5	0/5
	20	0/5	4/5	1/5
Control	–	5/5	0/5	0/5
carbamazepine	2	4/5	1/5	0/5
	5	1/5	4/5	0/5
	10	1/5	3/5	1/5
Control	–	5/5	0/5	0/5
zonisamide	12.5	2/5	3/5	0/5
	25	1/5	3/5	1/5
	50	0/5	2/5	3/5
Control	–	5/5	0/5	0/5
valproic acid	50	5/5	0/5	0/5
	100	2/5	3/5	0/5
	200	0/5	4/5	1/5
Control	–	5/5	0/5	0/5
diazepam	0.5	0/5	2/5	3/5[a]
	1	0/5	3/5	2/5[a]
	2	0/5	0/5	5/5[a]
Control	–	5/5	0/5	0/5
clonazepam	0.5	1/5	3/5	1/5[a]
	1	2/5	0/5	3/5[a]
	2	0/5	0/5	5/5[a]
Control	–	5/5	0/5	0/5
ethosuximide	50	4/5	1/5	0/5
	100	1/5	3/5	1/5
	200	2/5	2/5	1/5

[a] Highlighted protective effect.

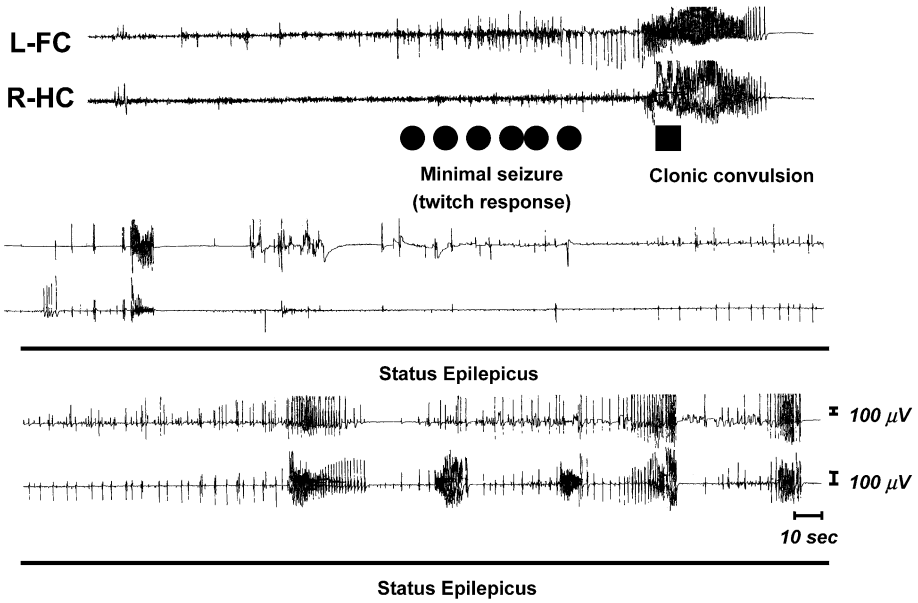

Fig. 4. The effects of zonisamide–Na on EEG changes induced by flurothyl inhalation in Mongolian gerbils. L-FC: left frontal cortex, R-HC: right hippocampus, R-AM. (●) Minimal seizure, (■) clonic convulsion, (▬) status epilepticus (continued clonic convulsion).

mazepine and ethosuximide produced inhibition at doses of 12.5, 100, 5 and 200 mg/kg, respectively (Table 1). Phenytoin, clonazepam and diazepam completely inhibited tonic extension at doses of 10, 2 and 2 mg/kg, respectively (Table 1). When the tonic extension was inhibited in zonisamide–Na administered animals, the EEGs of the cortex, hippocampus and amygdala were characteristic. Burst-like high amplitude spike waves appeared in these three regions and they continued for a long time (Fig. 4; EEG of amygdala is not shown). In the diazepam-injected animals, the high amplitude spike waves were completely inhibited in these three regions.

4. Discussion

In Mongolian gerbils, flurothyl inhalation resulted in clonic convulsion, followed immediately by tonic extension. A near-complete, bidirectional transfer between the electrical and flurothyl kindling models was recently reported (Ferland and Applegate, 1999), in which mice previously exposed to either electrical or flurothyl kindling showed both increased seizure susceptibilities and altered seizure phenotypes when exposed to the other seizure paradigm. These results suggest that the proepileptogenic processes initiated by exposure to either electrical or flurothyl kindling are similar. In the present study, Mongolian gerbils demonstrated low threshold induction of generalized tonic seizures upon treatment with flurothyl. This finding suggests that the same processes underlie the changes in seizure susceptibility in the electrical stimulation, spontaneous epileptogenesis and the flurothyl models as the animals mature.

Mongolian gerbils, animals that demonstrate spontaneous epileptiform seizures (Thiessen et al., 1968; Goldblatt et al., 1971; Loskotoa and Lomax, 1975), were utilized as an experimental model of human epilepsy. These animals spontaneously exhibited generalized clonic seizures, not generalized tonic seizures, emulating the electrical kindling model. Mongolian gerbils demonstrated low threshold induction of generalized tonic seizures upon treatment with flurothyl. Therefore, spontaneous epileptigenesis is necessary for bidirectional transfer of seizure susceptibility in the flurothyl kindling model. This finding suggests that the same processes underlie the changes in seizure susceptibility in the electrical stimulation, spontaneous epileptigenesis and flurothyl models as animals mature. The development of behavioral manifestations resulting from hippocampal kindling was similar to that seen following amygdaloid kindling; a transfer phenomenon was observed between the amygdalal and hippocampal kindling models (Araki et al., 1985). In general, the amygdala is highly involved in the electrical kindling phenomenon (Araki et al., 1985; Tanaka, 1972; McIntyre, 1980). Therefore, the amygdala and hippocampus may also have an important role in flurothyl seizure induction. So, we investigated EEG changes in the amygdala and hippocampus following inhalation of flurothyl. It was difficult to define differences between EEGs resulting from clonic convulsion or tonic extension. We attempted to determine the regions responsible for initiating the flurothyl-induced seizure. Although spike and spike/wave complexes predominate in the cortex with a high frequency, high voltage activity appears in the hippocampus and amygdala. Two independent networks in the brain control clonic convulsion and tonic extension. A low-threshold forebrain system controls clonic convulsion and a high threshold

brainstem system controls tonic extension (Appligate et al., 1997). In the Mongolian gerbil model of epilepsy, tonic convulsion occurs immediately after clonic convulsion, suggesting that the networks between clonic and tonic convulsion preexist in Mongolian gerbils. It is conceivable that spike waves will be found in the regions of TE incidence when TE occurs. However, it was not possible to find the brain region where TE occurs from the present examination. Detailed electrophysiological examinations will be needed to define this activity precisely.

All of the antiepileptic drugs tested interfered with the flurothyl-induced tonic seizures in Mongolian gerbils. Phenytoin and diazepam completely inhibited the appearance of tonic extension. Phenytoin possesses a marked inhibitory effect on the maximal electrical shock-induced tonic extension, but has no effect on clonic convulsion. The area of the brain responsible for tonic convulsion may be inhibited by phenytoin. This drug, however, may not have any effect on the area of the brain affected in clonic convulsion, resulting in the continuation of clonic convulsion. On the other hand, diazepam completely blocks the appearance of clonic and tonic convulsion. Krasowski (2000) reported that antagonism of the GABAA receptor might account for the convulsant effects of flurothyl. BDZs are potent anticonvulsants, used in a wide variety of experimental and clinical seizure disorders. BDZs act via modulatory sites associated with the GABAA receptor. The development of compounds acting either as partial agonists at the BDZ binding site on the $GABA_A$/BDZ receptor complex or on selective $GABA_A$/BDZ receptor subtypes has confirmed them to be extremely effective treatments (Haefely et al., 1990; Stephens et al., 1993). It was reported that diazepam mainly acts on the limbic system of the brain (Poldinger, 1975). In the hippocampal kindling model, diazepam completely inhibits behavioral convulsion. Although diazepam did not block hippocampal after-discharge, it did inhibit high amplitude spike waves in the amygdala, cortex and reticular formation (Aihara et al., 1982). Taken together, these results suggest that the inhibitory effect of diazepam on the amygdala plays a role in the inhibition of both clonic and tonic convulsion. Importantly, high amplitude spike waves were completely inhibited in the amygdala in the present flurothyl exposure model upon administration of diazepam. The effects of these antiepileptic drugs on flurothyl-induced convulsion were very similar to those of pentylenetetrazol-induced clonic–tonic convulsion. However, as the flurothyl doses are able to increase cumulatively, it is easy to decide the changes in the threshold of convulsion.

Clinical and basic researchers have struggled to identify the regions of the brain responsible for augmenting seizure activity up to the point of fully generalized motor expression. Clonic convulsion begins in forebrain structure, whereas tonic extension is dependent on intact brainstem structures (Browning et al., 1993). Recently, it was reported that claustrum is important for both the kindling and the propagation of kindled seizures from the amygdala (Wada and Kudo, 1997; Mohapel et al., 2000). The sites of action of these drugs, which inhibit the occurrence of tonic extension in the brain, are also related to these brain regions. Ultimately, further study will be necessary to determine the mechanism of flurothyl-induced seizures and the action of antiepileptic drugs. In the flurothyl-induced epileptic model, it is clear that the rapid progression from clonic convulsion to tonic convulsion occurred in Mongolian gerbils. In mice, this structure is too small to investigate the mechanism involved in the progression of convulsion. However, it is possible to perform studies with experimental brain lesions (electrical lesions and drug-induced lesions) and microinjection of some drugs (neurotransmitter agonist, antagonist, antiepileptic drugs, etc.). Mongolian gerbils are very convenient for investigating the mechanism of flurothyl-induced convulsion and changes in seizure phenotype. Although it is possible to investigate this phenomenon using other animals, e.g., rats, the progression period for the phase change is lengthy. Many species can be used to help clarify the mechanism of the changes in seizure phenotype.

In conclusion, flurothyl-induced convulsion is closely tied to the GABA receptor. BDZ-like compounds, which activate GABA receptors, may inhibit both clonic convulsion and tonic seizures in Mongolian gerbils. Antiepileptic drugs working through another mechanism are likely to inhibit flurothyl-induced tonic extension even though they cannot inhibit the occurrence of flurothyl-induced clonic convulsion.

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 in Japan.

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