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Effects of clobenpropit on pentylenetetrazole-kindled seizures in rats

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Abstract

The purpose of this study was to investigate whether or not clobenpropit, a selective and potent histamine H_3 receptor antagonist, can protect from pentylenetetrazole (35 mg/kg)-kindled seizures in rats. I.c.v. injection with clobenpropit (10 and 20 μg) significantly delayed the seizure stage and prolonged the latency to the onset of myoclonic jerks and the latency to the clonic generalized seizure in a dose-dependent manner. The protection by clobenpropit (20 μg) was completely antagonized by both immepip (5 and 10 μg, i.c.v.), a selective potent histamine H_3 receptor agonist, and α-fluoromethylhistidine (α-FMH, 50 μg, i.c.v.), a selective histidine decarboxylase inhibitor. In addition, clobenpropit markedly potentiated the histidine (100 and 200 mg/kg)-induced inhibition of pentylenetetrazole-kindled seizures. Pyrilamine (2 and 5 μg, i.c.v.) reversed the inhibition of pentylenetetrazole-kindled seizures induced by clobenpropit, whereas cimetidine had no effect even at a high dose of 5 μg. These results indicate that clobenpropit protects against pentylenetetrazole-kindled seizures in rats, and that its action is mainly due to the activation of endogenous histamine by blocking autoinhibitory presynaptic histamine H_3 receptors.

Keywords: Clobenpropit; Seizure; Endogenous histamine; Immepip; α-Fluoromethylhistidine

1. Introduction

Histamine, a biogenic amine, is an important neurotransmitter or neuromodulator in the mammalian central nervous system (Leurs et al., 1998; Schwartz et al., 1991). The histaminergic neuron system seems to be involved in various physiological and behavioral functions including sleep–wake cycles, emotion, appetite control, locomotor activity, stress behavior, neuroendocrine, learning and memory (Schwartz et al., 1991; Passani et al., 2000; Sakai et al., 1998) through histamine H_1, H_2 and H_3 receptors. The role of brain histamine in regulating seizure susceptibility has been documented, and a possible anticonvulsant action of endogenous histamine has been postulated (Scherkl et al., 1991; Toyota et al., 1998; Chen et al., 2003; Kamei et al., 1998). Several histamine H_1 receptor antagonists, such as diphenhydramine and chlorpheniramine, occasionally induced convulsions in epileptic patients and healthy children (Yokoyama et al., 1996). Kiviranta et al. (1995) found that the histamine concentration in the cerebrospinal fluid of children with febrile convulsions was significantly lower than that in febrile children without seizures. Moreover, i.p. injection of L-histidine (the precursor of histamine), metoprine (a histamine *N*-methyltransferase inhibitor), or i.c.v. injection of histamine itself could inhibit acute seizures induced by maximal electroshock (MES) and amygdaloid kindling seizure in mice or rats, whereas α-FMH (an irreversible histidine decarboxylase inhibitor) increased the duration of clonic convulsions induced by MES in mice (Leurs et al., 1998; Scherkl et al., 1991; Yokoyama et al., 1992). Both clinical and experimental data demonstrate that central histamine might play an inhibitory role in epilepsy and epileptogenesis.

However, there are discrepant or even contradictory results with regard to different substances, seizure test and animal species (Sturman et al., 1994; Wada et al., 1996). In addition, most of the above findings mainly concerned

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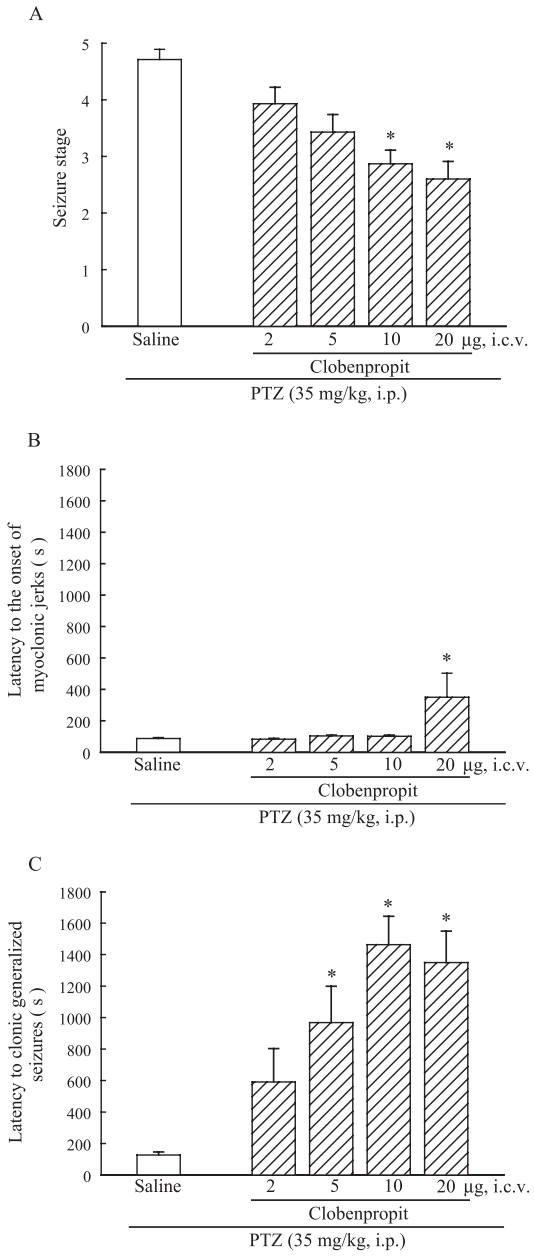

Fig. 1. Effects of clobenpropit on pentylenetetrazole-induced kindled seizures in rats. Clobenpropit was i.c.v. injected 30 min before pentylenetetrazole (35 mg/kg) treatments. Each value was expressed as the mean ± S.E.M. for 14–15 rats. *$P<0.05$ vs. pentylenetetrazole + saline-treated group.

convulsive effects on acute electroconvulsive or chemical seizures, and little was known as to whether or how histamine H_3 receptor antagonists are involved in pentylenetetrazole-kindled epilepsy in rats, a chronic animal model of epilepsy. Further experiments are needed to clarify the role of histamine H_3 receptors in seizure activity.

Clobenpropit has been considered one of the most potent and specific histamine H_3 receptor antagonists available, and has been widely used as a pharmacological tool to modulate the endogenous histaminergic system in the brain (Leurs et al., 1998; Fischer and Van der Goot, 1998; Zhang et al., 2003). Clobenpropit is now also known as a histamine H_4 receptor agonist (Gantner et al., 2002). Yet so far, there is only limited information about the effects of clobenpropit on chronic pentylenetetrazole-kindled epilepsy in rats. Therefore, the objectives of our investigations were to further

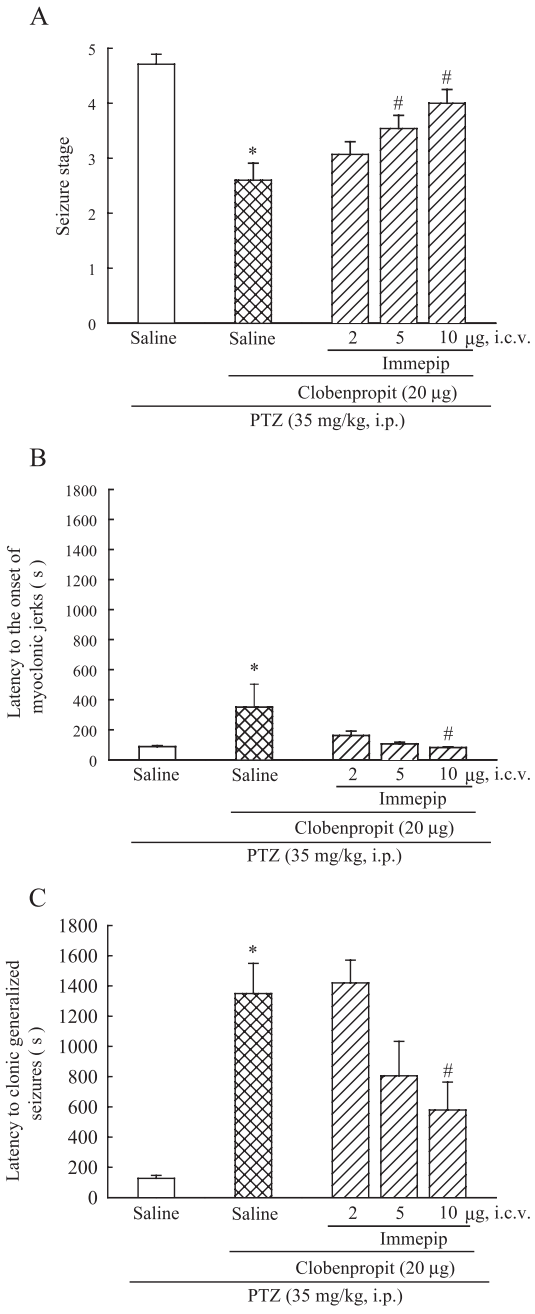

Fig. 2. Effects of immepip on the protective action induced by clobenpropit (20 μg, i.c.v.) on pentylenetetrazole-induced kindled seizures in rats. Clobenpropit was injected 30 min before pentylenetetrazole (35 mg/kg) treatments, and immepip was injected 5 min before clobenpropit treatments. Each value was expressed as the mean ± S.E.M. for 12–15 rats. #$P<0.05$ vs. pentylenetetrazole + clobenpropit (20 μg)-treated group. *$P<0.05$ vs. pentylenetetrazole + saline-treated group.

elucidate the pharmacological mechanisms of clobenpropit action on seizure activity.

2. Materials and methods

2.1. Animals

All experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animal. The animals used in this study were male Sprague–Dawley rats (♂, 220–300 g, Grade II, Certificate No. 22-9601018, Experimental Animal Center, Zhejiang University, China), maintained in individual cages with a 12-h light–dark cycle (lights on from 08:00 to 20:00). Water and food were given ad libitum. Experiments were carried out each day between 10:00 and 17:00.

2.2. Surgical procedure

The rats were anesthetized with sodium pentobarbital (35 mg/kg, i.p.), and fixed on a stereotaxic apparatus (Narishige, SR-5, Tokyo, Japan), and a guide cannula made of stainless steel tubing 700 μm outer diameter was implanted into the right lateral ventricle according to the following coordinates measured from the bregma (Chen et al., 1999; Chen et al., 2002): AP: − 1.0 mm, L: 1.5 mm, H: 3.8 mm from the skull. At least 10 days were allowed for recovery from the surgery. After the experiments, the rats were killed by decapitation, and the implantation of the electrode was checked by histological analysis.

2.3. Chemical kindling procedure

To induce kindling, a subconvulsant dose (35 mg/kg) of pentylenetetrazole was i.p. injected every 48 h (Chen et al., 2002; Zhang et al., 2003). After each pentylenetetrazole treatment, the rats were placed separately under glass funnels, and mortality as well as the appearance of clonic and tonic seizures was recorded during individual observation for 30 min. Seizure intensities were classified as follows: 0: no response; stage 1: ear and facial twitching; stage 2: convulsive waves through the body; stage 3: myoclonic jerks, rearing; stage 4: turn over onto one-side position; stage 5: turn over onto back position, generalized tonic–clonic seizures, or died within 30 min. In addition, the latency to the onset of myoclonic jerks and clonic generalized seizures was measured and analyzed statistically. In the absence of seizures within 30 min, the latency was taken as 1800 s. When the rats had a seizure score of 4 after three consecutive injections, it was defined as fully kindled. Eight of 136 rats which did not reach this criterion were excluded from subsequent tests. Three days after full kindling was completed, the rats were used for study. Studies of drug effect were carried out twice a week, on Wednesday and Sunday. The same animals were used repeatedly, and received all doses of each drug.

2.4. Drugs

During the drug test, pentylenetetrazole (Sigma, St. Louis, MO, USA) and L-histidine monohydrochloride (Sigma) were dissolved in saline and injected i.p. in a volume of 1 ml/kg. All other drugs, including clobenpropit and immepip (kindly supplied by Prof. Timmerman), α-FMH (Merck Sharp & Dohme Research Lab, Rahway, NJ), cimetidine (Sigma) and pyrilamine dihydrochloride (Sigma) were dissolved in sterilized saline and injected i.c.v. in a fixed volume of 5 μl over a period of 60 s at a constant speed with a continuous infusion pump (KN-201, Natsume, Tokyo, Japan).

2.5. Statistical analysis

All data were expressed as the means ± S.E.M. One-way analysis of variance (ANOVA) with Dunnett's multiple range test was used for calculating statistical significance. Statistical significance was set at $P < 0.05$.

Table 1
Effects of combined treatment with subeffective doses of clobenpropit and histidine on pentylenetetrazole-kindled seizures in rats

Drugs	Dose	*n*	Seizure stage	Latency to the onset of myoclonic jerks	Latency to the clonic generalized seizure
Pentylenetetrazole + saline	–	14	4.7 ± 0.2	87.9 ± 6.5	126.7 ± 19.7
Pentylenetetrazole + histidine (100 mg/kg) + saline	–	13	4.1 ± 0.3	83.3 ± 5.9	769.9 ± 199.4
Pentylenetetrazole + histidine (100 mg/kg) + clobenpropit	2 μg, i.c.v.	15	3.5 ± 0.3	141.1 ± 21.3	1088.4 ± 206.0
	5 μg, i.c.v.	15	2.8 ± 0.3[a]	242.7 ± 112.8[a]	1355.7 ± 205.0
Pentylenetetrazole + histidine (200 mg/kg) + saline	–	15	3.9 ± 0.3	89.4 ± 6.5	811.9 ± 218.0
Pentylenetetrazole + histidine (200 mg/kg) + clobenpropit	2 μg, i.c.v.	15	3.4 ± 0.4	108.8 ± 11.7	1040.0 ± 177.8
	5 μg, i.c.v.	15	2.7 ± 0.4[b]	346.8 ± 122.9[b]	1362.2 ± 194.1

Clobenpropit and histidine were given 30 min and 2.5 h before pentylenetetrazole (35 mg/kg) treatments, respectively. Each value was expressed as the mean ± S.E.M. for 13–15 rats.

[a] $P < 0.05$ vs. pentylenetetrazole + histidine (100 mg/kg) + saline-treated group.

[b] $P < 0.05$ vs. pentylenetetrazole + histidine (200 mg/kg) + saline-treated group.

3. Results

3.1. Effect of clobenpropit on pentylenetetrazole-kindled seizures in rats

I.c.v. injection of clobenpropit, a selective and potent histamine H_3 receptor antagonist, decreased the seizure stage, and prolonged the latency to the onset of myoclonic jerks and clonic generalized seizures in a dose-related manner in pentylenetetrazole (35 mg/kg)-induced chronic kindled seizure rats (Fig. 1A–C). Clobenpropit was injected 30 min before pentylenetetrazole (35 mg/kg) treatments. Clobenpropit at a dose of 5 μg significantly prolonged the latency to the onset of myoclonic jerks ($P<0.05$), and showed a tendency to inhibit the seizure stage. At a dose of 10 μg, clobenpropit significantly decreased the seizure stage and the latency to the onset of myoclonic jerks ($P<0.05$), and significantly inhibited all seizure types at a dose of 20 μg ($P<0.05$).

3.2. Effect of immepip on the protective action induced by clobenpropit (20 μg) on pentylenetetrazole-kindled seizures in rats

I.c.v. treatment with immepip, a selective histamine H_3 receptor agonist, dose-dependently antagonized the protective action of clobenpropit (20 μg). Clobenpropit was injected 30 min before pentylenetetrazole (35 mg/kg) treatments, and immepip was injected 5 min before clobenpropit treatments. As shown in Fig. 2A–C, immepip at doses of 5 and 10 μg significantly reversed the decrease of seizure stage induced by clobenpropit ($P<0.05$). The latency to the onset of myoclonic jerks and clonic generalized seizures was also markedly prolonged by immepip at a dose of 10 μg ($P<0.05$).

3.3. Effect of clobenpropit in combination with histidine on pentylenetetrazole-induced kindled seizures in rats

In addition, as shown in Table 1, clobenpropit and histidine were used 30 min and 2.5 h before pentylenetetrazole (35 mg/kg) treatments, respectively. Clobenpropit (5 μg) significantly decreased the seizure stage when combined treatment with histidine (100 and 200 mg/kg) ($P<0.05$), at a dose without appreciable protective effect when given alone. In addition, clobenpropit (5 μg) markedly prolonged the latency to the onset of myoclonic jerks when given in combination with histidine ($P<0.05$).

3.4. Effect of α-FMH on the protective action induced by clobenpropit (20 μg) on pentylenetetrazole-induced kindled seizures in rats

I.c.v. treatment with α-FMH, a selective and irreversible histidine decarboxylase inhibitor, reversed the clobenpropit-induced anticonvulsive effect in a dose-dependent manner (Fig. 3A–C). Clobenpropit and α-FMH were used 30 min and 2 h before pentylenetetrazole (35 mg/kg) treatments, respectively. α-FMH at a dose of 50 μg significantly reversed the decrease of seizure stage induced by clobenpropit ($P<0.05$). In addition, a tendency to shorten the latency to the onset of myoclonic jerks and clonic

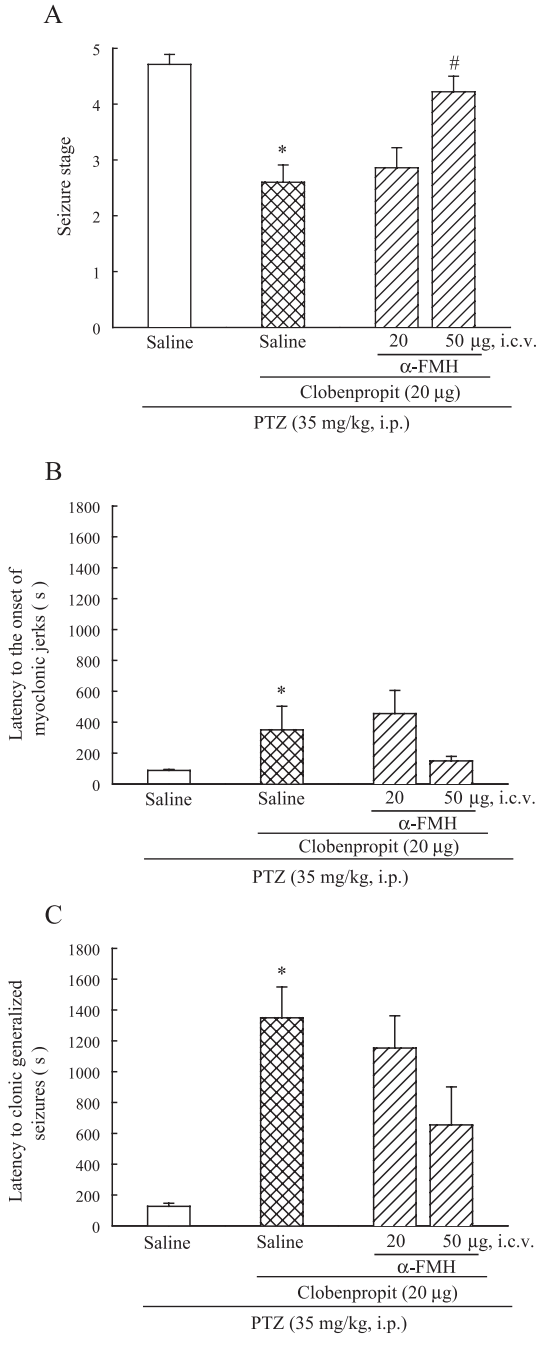

Fig. 3. Effects of α-FMH on the protective action induced by clobenpropit (20 μg, i.c.v.) on pentylenetetrazole-kindled seizures in rats. Clobenpropit and α-FMH were injected 30 min and 2 h before pentylenetetrazole (35 mg/kg) treatments, respectively. Each value was expressed as the mean ± S.E.M. for 12–15 rats. $^{\#}P<0.05$ vs. pentylenetetrazole + clobenpropit (20 μg)-treated group. $^{*}P<0.05$ vs. pentylenetetrazole + saline-treated group.

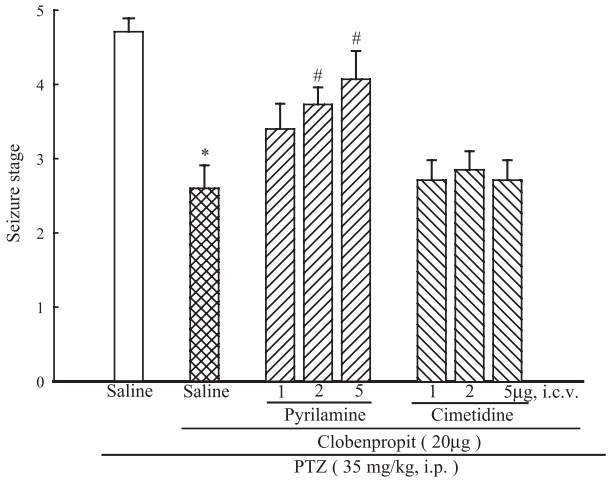

Fig. 4. Effects of pyrilamine and cimetidine on the protective action of clobenpropit (20 μg, i.c.v.) on pentylenetetrazole-induced kindled seizures in rats. Clobenpropit was injected 30 min before pentylenetetrazole (35 mg/kg) treatments, and pyrilamine or cimetidine was injected 5 min before clobenpropit treatments. Each value was expressed as the mean ± S.E.M. for 13–15 rats. $^{\#}P<0.05$ vs. pentylenetetrazole + clobenpropit (20 μg)-treated group. $^{*}P<0.05$ vs. pentylenetetrazole + saline-treated group.

generalized seizures was observed, although it was not significant.

3.5. Effects of pyrilamine and cimetidine on the protective action of clobenpropit (20 μg) on pentylenetetrazole-induced kindled seizures in rats

The histamine H_1 receptor antagonist, pyrilamine, and H_2 receptor antagonist, cimetidine, were injected 5 min before clobenpropit treatments. I.c.v. treatment with pyrilamine dose-dependently inhibited the protective action of clobenpropit. A significant effect was observed at doses of 2 and 5 μg ($P<0.05$) (Fig. 4). On the other hand, cimetidine did not appreciably change any of the seizure types, even at a high dose of 5 μg.

4. Discussion

It is generally known that histamine H_3 receptors regulate the release and synthesis of neuronal histamine, and clobenpropit, which is considered as a potent and selective histamine H_3 receptor antagonist (Leurs et al., 1998; Barnes et al., 1993), can activate the central histaminergic system increasing histamine release from nerve terminals (Jansen et al., 1998). In the present study, it was found that clobenpropit significantly inhibited the pentylenetetrazole-kindled seizure stage, and prolonged the latency to the onset of myoclonic jerks and clonic generalized seizures in a dose-dependent manner. In addition, the clobenpropit-induced antiseizure action was reversed by immepip, a selective histamine H_3 receptor agonist, at a dose with no apparent effect on pentylenetetrazole-induced chronic kindled seizure when given alone. This observation demonstrated that the effects of clobenpropit are mediated through the autoreceptors located on histaminergic neurons, i.e. the histamine H_3 receptors. Results of some other investigations were consistent with our findings. Fischer and Van der Goot (1998) found that clobenpropit dose-dependently raised the electroconvulsive threshold for tonic seizures, and this protective action was reduced by immepip. Clobenpropit could significantly and dose-dependently decrease the duration of the electrically induced convulsive phase in mice (Yokoyama et al., 1994b). We have also recently reported that clobenpropit protected against pentylenetetrazole-induced chronic seizure development in rats (Zhang et al., 2003). Our data yielded the preliminary results that clobenpropit had a protective effect on pentylenetetrazole-induced chronic kindled seizure. Similar results have also been reported for amygdaloid kindled seizures in rats (Kakinoki et al., 1998). Therefore, one can presume that clobenpropit might play an important role in both prevention and treatment in epilepsy.

We previously reported that histidine (500 and 1000 mg/kg), the precursor amino acid of histamine, had a protective effect against pentylenetetrazole-induced seizure development and kindled seizures in a dose-dependent manner, and its action was reversed by α-FMH (Chen et al., 2002; Zhang et al., 2003). In the present study, we were interested to find that clobenpropit could markedly potentiate the histidine (100 and 200 mg/kg)-induced inhibition of pentylenetetrazole-kindled seizures, at doses which had no apparent effects when given alone. Clobenpropit can enhance the synthesis and release of endogenous histamine from nerve terminals by blocking autoinhibitory presynaptic histamine H_3 receptors (Leurs et al., 1998; Schwartz et al., 1991; Zhang et al., 2003). Histidine was reported to potentiate the histamine release induced by histamine H_3 receptor antagonists (such as thioperamide), and there is evidence for a good correlation between epileptogenic activity and brain histamine levels (Itoh et al., 1991; Onodera and Miyazaki, 1999). These findings provide more evidence that the protection of clobenpropit against pentylenetetrazole-kindled seizures was due to an increase in histamine synthesis and release from histaminergic nerve terminals. In addition, it is interesting to observe that α-FMH reversed the clobenpropit-induced effects at doses which had no apparent effects when given alone. This result suggests that a decrease in histamine synthesis induced by α-FMH might reduce the presynaptic histamine release stimulated by the treatment with clobenpropit.

On the other hand, histamine H_3 receptors are now considered as heteroreceptors in addition to autoreceptors in both central nervous system and peripheral nervous system, regulating the release of a wide variety of various other neurotransmitters including GABA which is recognized as an important inhibitory neurotransmitter (Fink et

al., 1990; Schlicker et al., 1988; Schlicker et al., 1993; Vohora et al., 2001). It is thought that the convulsant properties of pentylenetetrazole are mainly due to an impairment of GABAergic neurotransmission (Frey et al., 1979; Croucher et al., 1983). Therefore, the possible role of GABA in the observed effects cannot be ignored. In addition, there is a close relationship between histamine and GABA. For example, Ericson et al. (1991) found that neurons of the histaminergic tuberomammillary nucleus contain the neurotransmitter GABA, and that the GABA brain content of ICR mice was decreased to 85% of the control level 12 h after α-FMH administration (Sakai et al., 1996). Vohora et al. (2001) have recently reported that GABAergic mechanisms are involved in the protection against seizures induced by the histamine H_3 receptor antagonist, thioperamide. We also found that bicuculline reversed the protective action of clobenpropit (data not shown). Similar results described were when we reported that certain GABAergic drugs such as diazepam, sodium valproate and muscimol significantly potentiated the inhibition of amygdaloid kindled seizures induced by clobenpropit (Ishizawa et al., 2000). Therefore, it is likely that the protection by clobenpropit against pentylenetetrazole-kindled seizures is at least in part mediated by active GABAergic neurotransmission. Further studies are needed to investigate the role of GABAergic mechanism in the protection by clobenpropit against kindled seizures.

The protective effect of clobenpropit was reversed by the histamine H_1 receptor antagonist, pyrilamine, but not by the histamine H_2 receptor antagonist, cimetidine. These data are consistent with results of studies showing, e.g. that histamine H_1 receptor antagonists including diphenhydramine, pyrilamine, and ketotifen accelerate the development of the process of amygdaloid kindling in rats, and promote convulsive effects on acute electroconvulsive seizure in mice (Yokoyama et al., 1996). In addition, 2-thiazolylethylamine, a selective histamine H_1 receptor agonist, decreases seizure susceptibility in mice (Yokoyama et al., 1994a).

In conclusion, our data suggest that clobenpropit enhances histamine release from histaminergic presynaptic terminals, and that the released histamine depresses pentylenetetrazole-kindled seizures via activation of histamine H_1 receptors. Clinical data show that long-term epilepsy, or taking antiepileptic drugs over time, can result in cognitive deficits (e.g. memory or attention problems, especially in children), and other mental side-effects, such as depression (especially in the elderly), vigilance, abnormalities of psychomotor speed, somnolence, asthenia, dizziness, etc. (Kwan and Brodie, 2001). On the other hand, histamine H_3 antagonists, like clobenpropit, have been demonstrated to ameliorate learning and memory in several cognition-deficit animal models (Chen, 2000; Miyazaki et al., 1997). Besides, recent studies have shown that histamine H_3 receptor antagonists also have antidepressive effects (Perez-Garcia et al., 1999; Ito, 2000). Therefore, histamine H_3 receptor antagonists might prove to be useful antiepileptic drugs or adjuncts to existing antiepileptic drug therapy.

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