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2-Thiazolylethylamine, a Selective Histamine H_1 Agonist, Decreases Seizure Susceptibility in Mice

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YOKOYAMA, H., K. ONODERA, K. IINUMA AND T. WATANABE. *2-Thiazolylethylamine, a selective histamine H_1 agonist, decreases seizure susceptibility in mice.* PHARMACOL BIOCHEM BEHAV 47(3) 503-507, 1994.—The effects of intracerebroventricular (ICV) administration of histamine and its selective agonists on electrically and pentylenetetrazole-induced convulsions in mice were studied. The ICV administration of histamine decreased seizure susceptibility on electrically and pentylenetetrazole-induced convulsions significantly and dose-dependently. The inhibitory effects of histamine were well antagonized by centrally acting histamine H_1 antagonists such as pyrilamine (or mepyramine) and ketotifen, but not by a peripherally acting histamine H_1 antagonist, astemizole, or a centrally acting H_2 antagonist, zolantidine. The ICV administration of 2-thiazolylethylamine, a selective histamine H_1 agonist, also decreased seizure susceptibility, which could be antagonized by centrally acting histamine H_1 antagonists, whereas dimaprit, a selective histamine H_2 agonist, did not affect seizure susceptibility. These findings strengthened the idea that the central histaminergic neuron system plays an inhibitory role in convulsions.

Histamine 2-Thiazolylethylamine Electrically-induced convulsions Pentylenetetrazole-induced convulsions

HISTAMINE has been established to be a neurotransmitter or neuromodulator (14,17,20). Intracerebroventricular (ICV) administration of histamine caused several behavioral changes (6) to the sleep-wakefulness cycle (7), locomotor activity (11), and learning and memory (8), and also induced catalepsy (12). Histamine is considered to be involved in maintaining homeostasis in the brain (14,17,20) by, for example, inhibiting convulsions (13,16,23-26).

However, the effects of the ICV administration of histamine on seizure susceptibility are still unclear (4,18). The administration of histamine (ICV, 12.5-200 μg) had no effect on pentylenetetrazole-induced seizure in mice (4). However, other authors showed that the administration of histamine (ICV, 20-40 μg) significantly decreased both frequency and severity of convulsions induced by picrotoxin, but did not decrease those induced by pentylenetetrazole in mice (18). The doses of histamine used in these studies seem to be relatively high with regard to the physiological importance, since the content of histamine in the brain of rodents is about 40 ng/g (22). We reevaluated the effect of ICV histamine on electrically and pentylenetetrazole-induced convulsions.

2-Thiazolylethylamine is a more selective and potent histamine H_1 agonist than other agents (3), whereas dimaprit is known to be a selective and potent histamine H_2 agonist (3). We studied the effects of these drugs on electrically and pentylenetetrazole-induced convulsions in mice.

MATERIALS AND METHODS

Animals

Six-week-old male ddY mice (Funabashi Farm Co., Funabashi, Japan) weighing 23-27 g were used. They were housed in a room at 22 ± 2°C with a 12-h light/dark cycle (lights on

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at 0700) and supplied with food and water ad lib. All experiments were performed between 1300 and 1600.

Electrically Induced Convulsions

Convulsions were induced as described in detail elsewhere (26). Briefly, electroconvulsive shock was induced by applying an electric current through ear-clip electrodes with electroencephalograph paste. These electroshock seizures were induced by 100-Hz square waves with 30 mA for 0.1 s. The seizure susceptibility was evaluated as the durations of convulsive states. The tonic phase was regarded as a period between the onset of hindlimb extension and the beginning of myoclonic jerks, the clonic phase as that during myoclonic jerks, and the convulsive coma phase as that between the end of myoclonic jerks and the recovery of the righting reflex.

Pentylenetetrazole-Induced Convulsions

Mice received pentylenetetrazole SC at a dose which produced clonic convulsions in almost all mice treated with vehicles. Clonic convulsions were defined as at least three consecutive seconds of myoclonic activity of limbs. The mice were observed for a further 30 min after the administration of pentylenetetrazole, and the numbers of mice that exhibited clonic convulsions were recorded.

Drugs

Histamine dihydrochloride (Wako, Tokyo, Japan), 2-thiazolylethylamine dihydrochloride, and dimaprit dihydrochloride (gifts of Dr. Parsons, Smith-Kline Beecham Pharmaceuticals, London) were dissolved in Ringer's solution (Otsuka Pharmaceuticals, Tokyo) and administered ICV by the technique described previously (11). Pyrilamine maleate, ketotifen fumarate (Sigma Chemical Co. St. Louis), zolantidine dimaleate (Smith-Kline Beecham Pharmaceuticals, London), and astemizole (a gift of Janssen Pharmaceutica, Belgium) were dissolved or suspended in saline. These drugs were administered IP in a volume of 0.1 ml/kg body weight. Doses of drugs are expressed as weights of free base.

Histamine, 2-thiazolylethylamine, or dimaprit was ICV administered 15 min before electroconvulsive shock or pentylenetetrazole administration. Control mice received the same volume of Ringer's solution (ICV). Pyrilamine (4 mg/kg), ketotifen (4 mg/kg), astemizole (4 mg/kg), zolantidine (8 mg/kg), or vehicle were IP administered 15 min before the ICV administration.

Statistics

The significance of differences in the durations of convulsive states was determined by analysis of variance (ANOVA) followed by Duncan's test. The significance of differences in the numbers of mice that exhibited clonic convulsions induced by pentylenetetrazole was determined by chi-squared test.

RESULTS

The Effects of ICV Administration of Histamine, 2-Thiazolylethylamine, and Dimaprit on Electrically Induced Convulsions in Mice

As shown in Fig. 1, the ICV administration of histamine significantly and dose-dependently decreased the duration of each convulsive phase, $F(4, 45) = 9.74$, $p < 0.01$; $F(4, 45) = 8.22$, $p < 0.01$; $F(4, 45) = 11.99$, $p < 0.01$ for tonic, clonic, and convulsive coma phases, respectively. Even at a dose of 30 ng (ICV) the changes were significant, $F(1, 18) = 15.10$, $p < 0.01$; $F(1, 18) = 11.11$, $p < 0.01$; $F(1, 18) = 21.10$, $p < 0.01$ for tonic, clonic, and convulsive coma phases, respectively. Figure 2 shows that the ICV administration of 2-thiazolylethylamine significantly and dose-dependently decreased the duration of each convulsive phase, $F(4, 45) = 9.30$, $p < 0.01$; $F(4, 45) = 10.03$, $p < 0.01$; $F(4, 45) = 9.54$, $p < 0.01$ for tonic, clonic, and convulsive coma phases, respectively. The ICV administration of dimaprit (100 and 1000 ng), a selective histamine H_2 agonist, did not affect any duration of the convulsive phases (data not shown).

The Effects of ICV Histamine and 2-Thiazolylethylamine on Electrically Induced Convulsions and Its Antagonism by Pyrilamine, Ketotifen, Astemizole, and Zolantidine in Mice

Figure 3 shows that the effect of ICV histamine on electrically induced convulsions was well antagonized by pretreatment with centrally acting histamine H_1 antagonists, pyrilamine, $F(1, 18) = 9.96$, $p < 0.01$; $F(1, 18) = 12.11$, $p <$

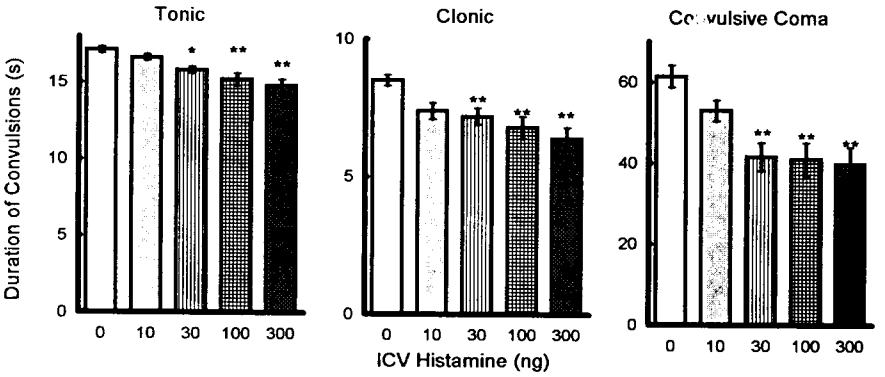

FIG. 1. Effects of intracerebroventricular (ICV) administration of histamine on electrically induced convulsions in mice. Fifteen minutes after ICV administration of histamine animals were subjected to electroshock and the durations of convulsions were measured. *$p < 0.05$, **$p < 0.01$; significance of difference between groups by ANOVA followed by Duncan's test.

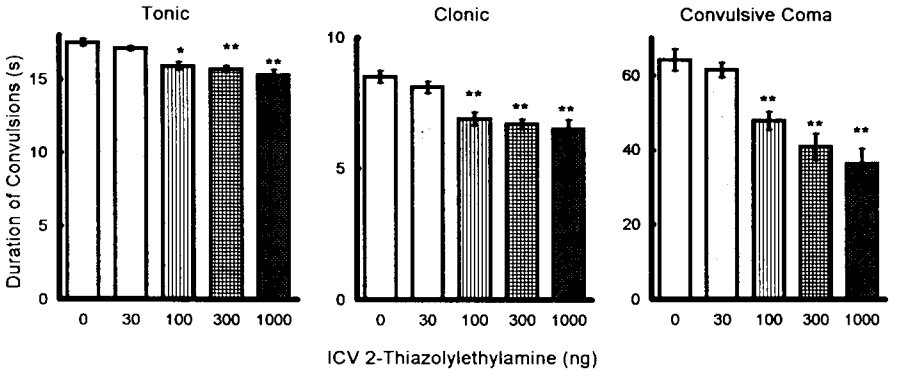

FIG. 2. Effects of intracerebroventricular (ICV) administration of 2-thiazolylethylamine on electrically induced convulsions in mice. Fifteen minutes after ICV administration of 2-thiazolylethylamine animals were subjected to electroshock and the durations of convulsions were measured. $*p < 0.05$, $**p < 0.01$; significance of difference between groups by ANOVA followed by Duncan's test.

0.01; $F(1, 18) = 11.40$, $p < 0.01$ for tonic, clonic, and convulsive coma phases, respectively, and ketotifen, $F(1, 18) = 8.87$, $p < 0.01$; $F(1, 18) = 9.26$, $p < 0.01$; $F(1, 18) = 6.49$, $p < 0.05$ for tonic, clonic, and convulsive coma phases, respectively. Pretreatment with astemizole, a peripherally acting histamine H_1 antagonist, did not block the effect of ICV histamine on electrically induced convulsions.

Figure 4 shows that the effect of ICV 2-thiazolylethylamine on electrically induced convulsions was well antagonized by pretreatment with pyrilamine, $F(1, 18) = 10.08$, $p < 0.01$; $F(1, 18) = 15.30$, $p < 0.01$; $F(1, 18) = 15.53$, $p < 0.01$ for tonic, clonic, and convulsive coma phases, respectively, and ketotifen, $F(1, 18) = 9.24$, $p < 0.01$; $F(1, 18) = 13.75$, $p < 0.01$; $F(1, 18) = 7.81$, $p < 0.05$ for tonic, clonic, and convulsive coma phases, respectively. Pretreatment with astemizole did not antagonize the effect of ICV 2-thyazolylethylamine on electrically induced convulsions. The pretreatment with zolantidine, a centrally acting H_2 antagonist, did not change the effects of ICV histamine or 2-thiazolylethylamine on electrically induced convulsions at all (data not shown). The IP administration of pyrilamine, ketotifen, astemizole, or zolantidine alone did not affect any duration of convulsive phases (data not shown).

The Effects of ICV Histamine and 2-Thiazolylethylamine on Pentylenetetrazole-Induced Convulsions and Its Antagonism by Pyrilamine, Ketotifen, and Astemizole in Mice

Table 1 shows the effect of ICV histamine and 2-thiazolylethylamine on pentylenetetrazole-induced convulsions and its antagonism by pyrilamine, ketotifen, and astemizole in mice. Histamine and 2-thiazolylethylamine significantly and dose-dependently decrease frequency of pentylenetetrazole-induced convulsions. The effect of ICV histamine and 2-thiazolylethylamine was well antagonized by pyrilamine and ketotifen, but not by astemizole. Pyrilamine, ketotifen, and astemizole alone

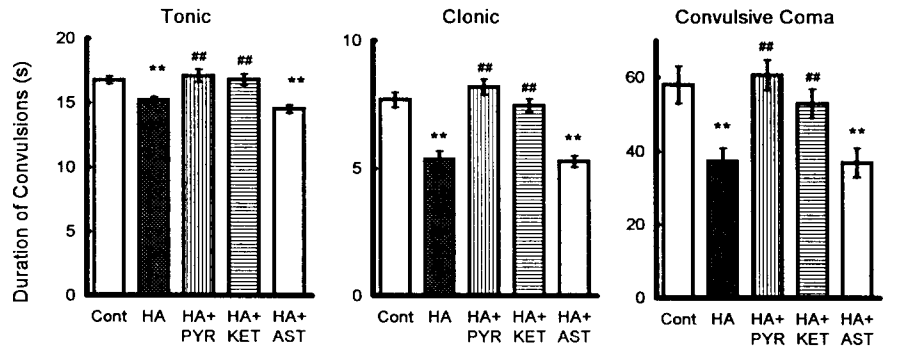

FIG. 3. Effects of intracerebroventricular (ICV) administration of histamine (HA) on electrically induced convulsions in mice, and its antagonism by histamine H_1 antagonists. Fifteen minutes after ICV administration of histamine animals were subjected to electroshock and the durations of convulsions were measured. Animals were pretreated with histamine H_1 antagonists 30 min before ICV administration of histamine. PYR = pyrilamine, KET = ketotifen, AST = astemizole. $*p < 0.05$, $**p < 0.01$ vs. control group, $\#p < 0.05$, $\#\#p < 0.01$ vs. histamine-treated group; significance of difference between groups by ANOVA followed by Duncan's test.

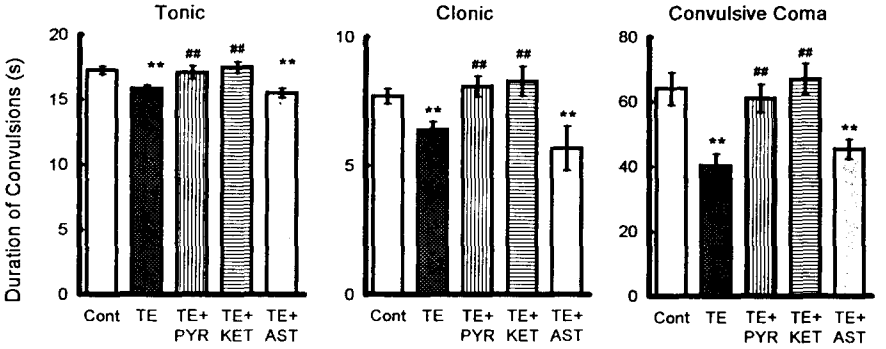

FIG. 4. Effects of intracerebroventricular (ICV) administration of 2-thiazolylethylamine (TE) on electrically induced convulsions in mice, and its antagonism by histamine H_1 antagonists. Fifteen minutes after ICV administration of TE animals were subjected to electroshock and the durations of convulsions were measured. Animals were pretreated with histamine H_1 antagonists 30 min before ICV administration of histamine. PYR = pyrilamine, KET = ketotifen, AST = astemizole. $*p < 0.05$, $**p < 0.01$, $\#p < 0.05$, $\#\#p < 0.01$ vs. TE-treated group; significance of difference between groups by ANOVA followed by Duncan's test.

TABLE 1

THE EFFECTS OF HISTAMINE (HA) AND 2-THIAZOLYLETHYLAMINE (TE) ON PENTYLENETETRAZOLE-INDUCED CONVULSIONS IN MICE AND THEIR ANTAGONISM

Drug	Convulsions (+)	Convulsion (−)
Histamine		
0 ng	20	0
30 ng	18	2
100 ng	16	4*
300 ng	12	8†
2-Thiazolylethylamine		
0 ng	20	0
100 ng	17	3
300 ng	15	5†
1000 ng	13	7†
Histamine (100 ng ICV) with antagonists		
Control	20	0
HA	15	5†
HA + Pyrilamine	19	1
HA + Ketotifen	20	0‡
HA + Astemizole	15	5†
2-Thiazolylethylamine (300 ng ICV) with antagonists		
Control	20	0
TE	16	4*
TE + Pyrilamine	20	0§
TE + Ketotifen	20	0§
TE + Astemizole	15	5†

The figures show the number of mice with or without clonic convulsions induced by pentylenetetrazole after treatments with agents. The doses of pyrilamine, ketotifen, and astemizol are 4 mg/kg (IP). Each group consists of 20 mice. $*p < 0.05$, $\dagger p < 0.01$ vs. control group, $\ddagger p < 0.01$, $\S p < 0.05$ vs. histamine or TE treated group, significance of difference between groups by chi-squared test.

did not affect any seizure frequency on pentylenetetrazole-induced convulsions (data not shown).

DISCUSSION

This study clearly demonstrated that ICV histamine and 2-thiazolylethylamine decreased seizure susceptibility on both electrically and pentylenetetrazole-induced convulsions in mice. 2-Thiazolylethylamine is a more selective and potent histamine H_1 agonist than other agents (3). The effects of histamine and 2-thiazolylethylamine on seizure susceptibility were well antagonized by pyrilamine and ketotifen, but not by astemizole. The difference among these antagonists is that pyrilamine and ketotifen can enter the brain easily, whereas astemizole hardly enters (15). Thus, ICV administration of histamine and 2-thiazolylethylamine decreased seizure susceptibility through central histamine H_1 receptors. However, dimaprit, a selective histamine H_2 agonist, and zolantidine, a selective histamine H_2 antagonist, did not affect both electrically and pentylenetetrazole-induced convulsions at all. These findings indicate that exogeneously administered histamine and histamine H_1 agonist decrease seizure susceptibility through histamine H_1 receptors in the brains of mice.

Moreover, it has been established that endogenous histamine is an inhibitory transmitter against convulsions in rodents (2,13,16,19,24–26). Brain histamine levels in epilepsy-prone Krushinsky-Molodkina rats were significantly lower than in the epilepsy-resistant Wistar rats (13). Metoprine, which raised brain histamine levels by inhibition of histamine *N*-methyltransferase, decreased seizure susceptibility to electrically induced seizure in rats (19) and also in mice (1,16,26). L-Histidine, a precursor of histamine, decreased seizure susceptibility through the central histamine H_1 receptors (26). Conversely, α-fluoromethylhistidine, which decreased brain histamine levels by inhibition of histamine synthesis, showed a potent proconvulsant effect on clonic and convulsive coma phases in mice (26). More recently, we found that thioperamide, a histamine H_3 antagonist which increased endogenous histamine release (1,10), decreased seizure susceptibility on electrically induced convulsions in mice (24). These experimental studies demonstrate that the central histaminergic neu-

ron system is involved in inhibition of seizures through histamine H_1 receptors in rodents. Furthermore, clinical reports showed that histamine H_1 antagonists occasionally produced convulsions in epileptic patients (21,23). Histamine H_1 antagonists increased epileptic discharges on the electroencephalograph in epileptic patients (9,23). Histamine H_1 receptor binding increased at epileptic foci and their surroundings in patients with complex partial seizures, as found using positron emission tomography (5).

From all these findings, it is most probable that the central histaminergic neuron system plays an inhibitory role in convulsions through histamine H_1 receptors.

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