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Effects of histidine, a precursor of histamine, on pentylenetetrazole-induced seizures in rats[1]

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KEY WORDS pentylenetetrazole; histamine; histidine; histamine H_1 receptors; histamine H_3 receptors

ABSTRACT

AIM: The effect of histidine on pentylenetetrazole-induced seizures was investigated in rats. **METHODS**: Chemical kindling was elicited by repeated ip injection a subconvulsant dose of pentylenetetrazole (35 mg/kg) once every 48 h until the occurrence of seizure stages 4-5, and seizure activity of kindling was recorded for 30 min. **RESULTS**: In the kindling development process, ip injection of histidine (200, 500 mg/kg), a precursor of histamine, prolonged latency for the onset of myoclonic jerks and the clonic generalized seizure, and inhibited seizure stage in a dose-dependent manner. In the kindling challenge process, histidine (500, 1000 mg/kg) and H_3 antagonist thioperamide (10, 20 μg) also showed a significant anticonvulsant effect. The inhibitory action of histidine was enhanced significantly by thioperamide (5 μg), however, was antagonized by both α-fluoromethylhistidine (20 μg), a selective histidine decarboxylase inhibitor and H_1 antagonist pyrilamine (2, 5 mg/kg), dose-dependently and significantly. In addition, H_2 antagonist zolantidine appeared no appreciable effect, even at a dose of 10 mg/kg. **CONCLUSION**: These results indicated that brain endogenous histamine may play certain important role in protect against generalized clonic seizures, its action may via presynaptic H_3-receptors and postsynaptic H_1-receptors.

INTRODUCTION

Kindling has been accepted as an experimental animal model for analyzing epilepsy and epileptogenesis, and estimating the effectiveness of antiepileptic drugs. The repeated application of initial subconvulsive electrical stimulation on different brain structures, or treatment with subconvulsive doses of different CNS stimulants, such as pentylenetetrazole (PTZ) could induce progressive seizure activity[1]. It has been demonstrated that PTZ creates proconflict and convulsant effects in rodents, which was considered as an adequate model of human absence epilepsy and myoclonic, generalized tonic-clonic seizure[2,3].

Histamine has been established to play an important role as a neurotransmitter or neuromodulator in the mammalian CNS[4,5]. Central histamine has been demonstrated to be involved in mechanisms regulating seizure susceptibility, and a possible seizure anticonvulsant action of histamine has been documented[6-8]. High doses of certain classic H_1-antagonists increased onset rate of heat seizure and decreased electrically induced maximal seizure thresholds[7,8]. Toyota *et al* has recently found a decreased histamine contents in the hippocampus and amygdala of the amygdaloid kindling rats[9]. On the other hand, an increase of brain histamine contents or activation of histaminergic H_1 receptor show anticonvulsant effect in maximal electrically seizure (MES) and amygdaloid kindling in rodents[9,10].

However, many of other studies yielded conflicting findings with regard to different substances, seizure test or animal species, for example biphasic action of *L*-histidine, a precursor of histamine is observed on electric amygdaloid kindled seizure in rats[11]. Thioperamide, one of representative H_3-antagonists, has been reported to create less effect on either PTZ kindled seizure threshold and electroconvulsion threshold in mice[12]. Therefore, there still existed considerable literature on the effect of histaminergic drugs with fully kindled seizure and less was known whether and how endogenous histamine is involved in PTZ kindled epilepsy in rats.

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We are hereby interested in establishing a possible relationship between appearance of seizures and activity of histaminergic neurons. Therefore, the present study was designed to clarify tie role of endogenous histamine on PTZ kindled seizure in rats.

MATERIALS AND METHODS

Animals The animals used in this study were Sprague-Dawley rats (♂, 220 – 300 g, $n = 126$, Grade Ⅱ, Certificate № 22-9601018, Experimental Animal Center, Zhejiang University), maintained in individual cages with a 12-h light-dark cycle (lights on from 8:00 – 20:00). Water was given *ad libitum*. Experiments were carried out each day between 09:00 – 17:00.

Surgical procedure Rats were anesthetized with sodium pentobarbital (35 mg/kg, ip) and fixed on a stereotaxic apparatus (Narishige, SR-5, Tokyo, Japan), and a guide cannula made of stainless steel tubing 700 μm in outer diameter, was implanted into the right lateral ventricle according to the following coordinates measured from bregma; AP: – 1.0 mm, L: 1.5 mm, H: 3.8 mm from the skull. At least 10 d were allowed for recovery from the surgery.

Chemical kindling To induce kindling, PTZ 35 mg/kg was ip injected every 48 h, whereas control group was injected with vehicle. After each PTZ treatment, rats were then placed separately under glass funnels, and mortality as well as the appearance of clonic and tonic seizure was recorded during individual observation for 30 min. The 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. In addition, the latency for the onset of the myoclonic jerks and clonic generalized seizures was analyzed statistically. In the absence of seizures within 30 min, the latency was taken as 1800 s. When the rodents had a seizure score of 4 after three consecutive injections, it was defined as fully kindled. If they did not reach this criterion, the animals were not considered to be fully kindled, in which 7 of 126 rats were excluded in the following kindling challenge tests. Five days after fully kindled was completed, rodents were used for kindling challenge study. Studies for drug effect were carried out once a week, on Thursday or Friday. The same animals were repeatedly used for two months, and they experienced all doses of either drugs. Similar experimental process was carried out as above.

Drugs Pentylenetetrazole (Sigma, St Louis, USA), *L*-histidine monohydrochloride (Sigma, St Louis, USA), α-fluoromethylhistidine (Merck Sharp & Dohme Research Lab, Rahway, NJ), histamine H_3 antagonist thioperamide (Sigma, St Louis, USA), histamine H_1 antagonist pyrilamine maleate (Sigma, St Louis, USA), and histamine H_2 antagonist zolantidine dimaleate (SmithKline Beecham, London, UK). α-Fluoromethylhistidine and thioperamide were dissolved in saline and injected icv 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). The other drugs were dissolved in saline, and were injected ip. In the kindling challenge process, studies for drug effect were carried out once every 5 d. The same animals were repeatedly used, and they experienced all doses of each drugs administered in an ascending order.

Statistics One-way analysis of variance with Dunnett's test was used for calculating a significant difference. Values are shown as $\bar{x} \pm s$.

RESULTS

Effect of histidine on kindling development process induced by PTZ (35 mg/kg) in rats PTZ (35 mg/kg) produced fore- and hindlimbs myoclonic jerk (262 s ± 86 s, first day), and followed by a fall on one side or back with generalized clonic seizures (642 s ± 123 s). Ip injection of histidine prolonged the latency to clonic generalized seizures and decreased seizure stage. As shown in Tab 1, histidine at a dose of 200 mg/kg showed a tendency to ameliorate seizure induced by PTZ, prolonging the latency to seizure (451 s ± 101 s, 652 s ± 231 s) after its first injection, it significantly prolonged the latency for the clonic generalized seizure, and inhibited seizure stages after its fourth to fifth injection ($P < 0.05$). At a dose of 500 mg/kg, histidine significantly attenuated PTZ-induced seizure, the latencies for myoclonic jerks and latency for the clonic generalized seizure were both significantly delayed, and the seizure stage was also significantly decreased ($P < 0.05$).

Effect of histidine on kindling challenge induced by PTZ (35 mg/kg) in rats Histidine decreased seizure stage of PTZ-induced kindled seizure dose-dependently. As shown in Fig 1, at doses of 100 and 200 mg/kg histidine showed no marked effect, while at doses of 500 and 1000 mg/kg it caused a significant

Tab 1. Effect of histidine on the development process of PTZ (35 mg/kg)-induced epilepsy. LTMJ: latency for the onset of myoclonic jerks; LCGS: latency for the clonic generalized seizure; SS: seizure stage. $n = 16-18$ rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* LTMJ in the PTZ + saline group. $^cP < 0.05$ *vs* LCGS in the PTZ + saline group. $^hP < 0.05$ *vs* SS in the PTZ + saline group.

Injections	PTZ + saline			PTZ + histidine (200 mg/kg)			PTZ + histidine (500 mg/kg)		
	LTMJ/s	LCGS/s	SS	LTMJ/s	LCGS/s	SS	LTMJ/s	LCGS/s	SS
1	262 ± 86	642 ± 123	1.8 ± 0.6	451 ± 101	652 ± 231	1.1 ± 0.4	808 ± 132^b	1459 ± 608^c	1.0 ± 0.4
2	147 ± 54	421 ± 138	2.1 ± 0.4	205 ± 69	486 ± 206	1.5 ± 0.6	1132 ± 296^b	1347 ± 520^c	1.2 ± 0.6
3	110 ± 33	226 ± 94	3.4 ± 0.6	253 ± 67^b	433 ± 135^c	2.2 ± 0.7	650 ± 222^b	1162 ± 431^c	1.6 ± 0.6^h
4	85 ± 16	180 ± 59	3.5 ± 0.5	189 ± 53	466 ± 233^c	2.0 ± 0.5^h	453 ± 162	872 ± 257^c	1.8 ± 0.4^h
5	86 ± 21	256 ± 92	3.3 ± 0.5	136 ± 40	428 ± 162^c	2.1 ± 0.4^h	467 ± 141^b	799 ± 340^c	2.1 ± 0.5^h
6	80 ± 15	192 ± 68	3.7 ± 0.7	96 ± 27	253 ± 77	2.8 ± 0.5	307 ± 108^b	756 ± 312^c	2.1 ± 0.4^h
7	74 ± 15	176 ± 35	3.5 ± 0.5	103 ± 16	229 ± 60	3.2 ± 0.6	361 ± 213	558 ± 266^c	2.4 ± 0.6^h
8	71 ± 10	224 ± 95	3.9 ± 0.6	121 ± 35	218 ± 105	3.3 ± 0.6	300 ± 224	802 ± 327^c	2.3 ± 0.5^h
9	73 ± 20	301 ± 88	4.2 ± 0.5	89 ± 20	192 ± 59	3.2 ± 0.5	264 ± 98	666 ± 286^c	2.5 ± 0.3^h
10	68 ± 12	255 ± 49	4.3 ± 0.4	75 ± 29	171 ± 86	3.3 ± 0.5	174 ± 30^b	966 ± 305^c	2.4 ± 0.4^h
11	68 ± 9	253 ± 64	4.4 ± 0.6	92 ± 23	169 ± 62	3.2 ± 0.4	139 ± 26^b	670 ± 248^c	2.2 ± 0.2^h
12	82 ± 29	230 ± 59	4.6 ± 0.5	92 ± 18	176 ± 56	3.7 ± 0.6	100 ± 32	438 ± 193	2.3 ± 0.3^h

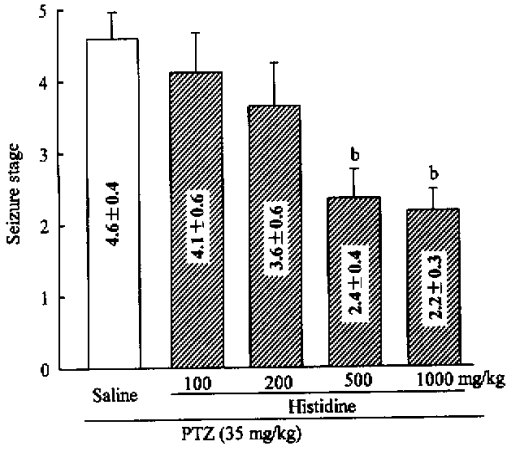

Fig 1. Effect of histidine on kindling challenge induced by PTZ (35 mg/kg) in rats. $n = 13-15$ rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* PTZ + saline-treated group.

decrease of seizure stage ($P < 0.05$).

Effect of thioperamide on kindling challenge induced by PTZ (35 mg/kg) in rats As shown in Tab 2, thioperamide, a representative H_3-antagonist, reversed PTZ-induced kindled seizure, in a dose-dependent manner. At doses of 2 and 5 μg thioperamide created no significant effect, while at doses of 10 and 20 μg it caused a marked decrease of seizure stage ($P < 0.05$). In addition, in combined treatment with thioperamide (2, 5 μg) and histidine (100, 200 mg/kg) significantly potentiated the effects of histidine by inhibiting PTZ-induced kindled seizure ($P < 0.05$), at the doses which caused no appreciable change when given alone.

Effect of α-fluoromethylhistidine, pyrilamine, and zolantidine on histidine-induced anticonvulsant effect in rats Icv treatment with α-fluoromethylhistidine (α-FMH), a selective histidine decarboxylase inhibitor, dose-dependently antagonized histidine's action. As shown in Tab 3, α-FMH at a dose of 20 μg, significantly reversed the anticonvulsive effect of histidine ($P < 0.05$). H_1-antagonist pyrilamine inhibited the effect of histidine dose-dependently, and a significant effect was observed at doses of 2 and 5 mg/kg ($P < 0.05$) (Tab 3). In contrast to pyrilamine, H_2-antagonist zolantidine created no appreciable effect against histidine action, even at a dose of 10 mg/kg. In addition, no significant changes were observed when α-FMH (10, 20 μg), pyrilamine (5 mg/kg), or zolantidine (10 mg/kg) were given alone (data not shown).

DISCUSSION

In the present study, it was found that histidine significantly protected against PTZ kindled seizures in a dose-dependent manner. Furthermore, the inhibitory action of histidine was completely prevented by α-FMH, a selective histidine decarboxylase inhibitor which is indicated to markedly decrease endogenous histamine

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Tab 2. Effect of thioperamide on kindling challenge induced by PTZ (35 mg/kg) in rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* PTZ + saline group. $^cP < 0.05$ *vs* PTZ + histidine (100 mg/kg) + saline group. $^bP < 0.05$ *vs* PTZ + histidine (200 mg/kg) + saline.

Drugs	Doses	*n*	Seizure stage
PTZ + saline	–	15	4.5 ± 0.5
PTZ + thioperamide	2 μg, icv	13	3.9 ± 0.8
	5 μg, icv	13	3.4 ± 0.6
	10 μg, icv	13	2.8 ± 0.6[b]
	20 μg, icv	13	2.1 ± 0.5[b]
PTZ + histidine (100 mg/kg) + saline	–	13	4.1 ± 0.6
PTZ + histidine (100 mg/kg) + thioperamide	2 μg, icv	12	3.2 ± 0.6
	5 μg, icv	12	2.5 ± 0.6[c]
PTZ + histidine (200 mg/kg) + saline	–	15	3.7 ± 0.6
PTZ + histidine (200 mg/kg) + thioperamide	2 μg, icv	13	2.8 ± 0.7
	5 μg, icv	13	2.3 ± 0.4[b]

Tab 3. Effect of histidine (500 mg/kg) on kindling challenge induced by PTZ (35 mg/kg) in rats. $\bar{x} \pm s$. $^bP < 0.05$ *vs* PTZ + saline group. $^cP < 0.05$ *vs* PTZ + histidine + saline group.

Drugs	Doses	*n*	Seizure stage
PTZ + saline	–	18	4.6 ± 0.6
PTZ + histidine + saline	–	18	2.3 ± 0.6[b]
PTZ + histidine + α-fluoromethylhistidine	5 μg, icv	15	2.5 ± 0.7
	10 μg, icv	15	3.3 ± 0.7
	20 μg, icv	16	3.9 ± 0.6[c]
PTZ + histidine + pyrilamine	1 mg/kg, ip	14	3.2 ± 0.6
	2 mg/kg, ip	16	4.0 ± 0.7[c]
	5 mg/kg, ip	15	4.4 ± 0.5[c]
PTZ + histidine + zolantidine	2 mg/kg, ip	14	2.3 ± 0.6
	5 mg/kg, ip	14	2.6 ± 0.5
	10 mg/kg, ip	13	2.5 ± 0.8

content from the nerve terminals without affecting the levels of other neurotransmitters[5]. We have previously reported histidine (500 mg/kg) caused a marked increase of histamine contents in the cortex, hippocampus, and amygdala in rats, and the pretreatment of α-FMH could antagonize these increases of brain histamine contents[5]. There exist some more evidences of good correlation between epileptogenic activity and brain histamine levels. For example, Yokoyama *et al* reported that a decrease in the brain histamine contents increased the duration of clonic convulsions induced by MES in mice[11]. Recent studies is also demonstrated that amygdaloid kindling resulted in a significant decrease of histamine contents in the hippocampus and amygdala[9,13]. It is likely to presume that the observed effect of histidine was due to an increase of synthesis of histamine.

It is generally known that H_3-receptors regulate the release and synthesis of neuronal histamine, and thioperamide which is considered as a potent and selective histamine H_3-receptor antagonist can activate the central histaminergic system increasing histamine release from nerve terminals[14]. The treatment of thioperamide resulted in an inhibitory effect on PTZ-induced kindled seizure. The release of histamine by thioperamide might be, at least in part, contributing to the observed anticonvulsant effect. In addition, we found that thioperamide, at a dose that showed no appreciable effect on PTZ-kindling when given alone, potentiated the histidine-induced inhibition of PTZ kindling. It is indicated that thioperamide could potentiate histamine release induced by histidine in the hypothalamus[15]. These findings provided more evidences that endogenous histamine

participated the inhibitory effect against PTZ, and its action might be mediated by presynaptic H_3-receptors.

Histamine has been demonstrated to increase learning and memory in rats, differing from clinically used antiepileptic drugs, which commonly cause sleepiness and impairment in cognition as untoward effects[16,17]. Therefore, if histaminergic substance would show an anticonvulsant effect, it might become a useful antiepileptic drug. So far, there are several reports concerning with histaminergic effect against convulsant[3,6-10]. In the present studies, the treatment of histidine not only inhibited seizure stage, but also prolonged the latency for the myoclonic jerks and the clonic generalized seizure in both kindled development and challenge processes, indicating that activating histaminergic neurons might play a certain role in preventing and treating PTZ kindled seizure in rats.

In addition, clinical studies have showed that histamine H_1-antagonists increase the onset rate of convulsions in epileptic patients and healthy children[11]. It is found that the effect of histidine was also reversed by H_1-antagonist pyrilamine, but not by H_2-antagonist zolantidine. H_1-antagonist including diphenhydramine, pyrilamine, and ketotifen show an acceleration in the rate of electrical stimulation to develop fully amygdaloid kindled seizure in rats[7,18], and promote convulsive effects on acute electroconvulsive seizure in mice[11]. In addition, it is indicated that 2-thiazolylethylamine, a selective histamine H_1-agonist, decreased seizure susceptibility in mice[8]. The present study was consistent with the previous findings. Therefore, these findings confirm that histaminergic H_1-receptors are involved in mechanisms of convulsant processes.

In conclusion, endogenous histamine could provide adequate protection of clonic convulsions induced by PTZ in rats, and its action is mediated by presynaptic H_3-receptors and postsynaptic H_1-receptors.

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组氨酸，一种组胺的前体对戊四唑诱发大鼠癫痫的作用[1]

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关键词 戊四唑；组胺；组氨酸；组胺 H_1 受体；组胺 H_3 受体

目的：研究和阐明中枢组胺对戊四唑(PTZ)诱发大鼠点燃癫痫的作用机制． **方法**：隔日腹腔内注射亚惊厥剂量的 PTZ 35 mg/kg 诱发化学点燃癫痫，直至癫痫发作级别为 4－5 级． 观察每次 PTZ 注射后 30 分钟内大鼠的行为变化． **结果**：在癫痫形成过程中，腹腔内注射组氨酸(200，500 mg/kg)，一种组胺的前体，剂量依赖性地延缓出现肌性痉挛和阵挛性癫痫全身性发作的反应潜时和抑制癫痫发作的级别． 在癫痫模型形成后点燃激发过程中，组氨酸(500，1000 mg/kg)和组胺 H_3 受体阻断剂 4-[4′-(环己氨基硫代甲酰基哌啶)]-4*H*-咪唑(10，20 μg)也分别表现出了明显的抗癫痫作用(2.6 ± 0.4，2.2 ± 0.3)，(2.8 ± 0.6，2.1 ± 0.5)． 组氨酸的作用可被 4-[4′-(环己氨基硫代甲酰基哌啶)]-4*H*-咪唑(5 μg)显著性增强，却被选择性组氨酸脱羧酶抑制剂 α-氟甲基组胺酸(20 μg)和 H_1 受体拮抗剂美吡拉敏(2，5 mg/kg)剂量依赖性、显著性地抑制． 另外，H_2 受体拮抗剂卓兰替丁即使在 10 mg/kg 剂量下也无明显的对抗作用． **结论**：内源性组胺在对抗阵挛性癫痫全身性发作中起到了较重要的作用，其作用主要与突触前膜 H_3 受体与突触后膜 H_1 受体相关．

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