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Effects of drugs acting as histamine releasers or histamine receptor blockers on an experimental anxiety model in mice

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Abstract

Experimental anxiety in mice was evaluated using a light/dark test at 60 min after injection of various histaminergics. Thioperamide, a histamine H_3 receptor inhibitor (5–20 mg/kg, intraperitoneal [IP]), Compound 48/80, a mast cell degranulator (0.1–10 μg/2 μl, intracerebroventricularly [ICV]), mepyramine, a histamine H_1 receptor antagonist (0.1–10 μg/2 μl, ICV) or cimetidine, a histamine H_2 receptor antagonist (0.1–10 μg/2 μl, ICV) alone did not affect the locomotive activity, the time spent in the light zone, and number of shuttle crossings in the light/dark test. However, the time spent in the light zone and the number of shuttle crossings significantly decreased only when cimetidine (0.1–10 μg/2 μl, ICV) was co-treated with either thioperamide (10 mg/10 ml/kg, IP) or Compound 48/80 (1.0 μg/2 μl, ICV). The decrease in these behavioral parameters suggests induced experimental anxiety in mice. The experimental anxiety was antagonized by mepyramine (10 μg/2 μl, ICV). These results suggest that not only neuronal histamine release induced by thioperamide but also non-neuronal (mast cells) histamine release induced by Compound 48/80 play an important role in inducing experimental anxiety via post-synaptic H_1 and H_2 receptors. In addition, it is likely that the anxiety may be mediated by the stimulation of H_1 receptors, while H_2 receptors may inhibit the anxiety produced by the activation of H_1 receptors.

Keywords: Anxiety; Cimetidine; Compound 48/80; Histamine receptors; Light/dark test; Mepyramine; Thioperamide

1. Introduction

Histamine is widely distributed in the mammalian central nervous system [12,17,18,29,34]. The involvement of the histaminergic system in multifarious brain functions and various behaviors has been reviewed [27,34]. With regard to the relationship between cerebral histamine and anxiety, the clinically effective anxiolytic drugs, diazepam which is a benzodiazepine [5,26], and buspirone which is a serotonin (5-HT_{1A}) agonist [25], have been found to decrease the turnover rate of brain histamine in mice and rats. These findings suggest that cerebral histamine may play an important role in the regulation of anxiety. However, details of the neurochemical mechanism of histaminergic neurotransmission and its physiological role remain unclear.

Biochemical, pharmacological and anatomical evidence suggests a dual localization of histamine in mast cells and neurons of the central nervous system [4,10,24,30]. Compound 48/80 is well known as a selective histamine releaser or degranulator from mast cells. In the thalamus, the histamine level fell by 50% after mast cell degranulation by Compound 48/80 [4]. Russell et al. [30] showed that an intraperitoneal (IP) injection of Compound 48/80 increased the histamine levels in the extracellular fluid of both the hypothalamus and the striatum of rats as measured by microdialysis. On the other hand, in the histaminergic neurons, the presence of H_3 receptors regulating the release and synthesis of neuronal histamine as a presynaptic autoreceptor has been demonstrated [1,3,23]. Thioperamide, a selective antagonist of this receptor [1–3], increases histamine release by blocking presynaptic histamine H_3 autoreceptors [2,19,23].

The purpose of the present study is to elucidate the effects of cerebral histamine and its receptors on anxiety. In order to examine the effects of neuronal and non-

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neuronal cerebral histamine release on anxiety, thioperamide, which induces neuronal histamine release [2,19,23], and Compound 48/80, which induces non-neuronal histamine release [4,30], were used. The drug-induced increase in cerebral histamine release may in turn activate postsynaptic H_1 and H_2 receptors. The effects of H_1 and H_2 receptors on the experimental anxiety were evaluated using H_1 receptor antagonist, mepyramine, and H_2 receptor antagonist, cimetidine. The anxiolytic or anxiogenetic effects of drugs in mice were assessed using a light/dark test that has been shown appropriate for the evaluation of the experimental anxiety [6,16,35].

2. Method

2.1. Animals

Six-week-old male ddY mice weighing 30–35 g obtained from SLC (Hamamatsu, Japan) were used in this study. Five animals were housed in a cage and allowed ad lib access to water and standard laboratory food (MF, Oriental Yeast, Tokyo, Japan). The facility maintained a temperature of 24 ± 1°C, relative humidity of 55 ± 5%, and had controlled lighting with light on from 7:00 to 19:00 daily. All tests were carried out between 13:00 and 17:00.

Experimental protocols met the "Guidelines for Animal Experimentation" approved by the Japanese Association of Laboratory Animal Science and the Japanese Pharmacological Society.

2.2. Drugs

Compound 48/80, mepyramine (or pyrilamine) maleate and cimetidine were purchased from Sigma (St. Louis, MO, USA). Thioperamide maleate was purchased from Research Biochemicals International (Natick, MA, USA).

Compound 48/80, mepyramine and thioperamide were dissolved in saline. Cimetidine was dissolved in 0.1 N HCl, and subsequently adjusted to the pH at 7.0 with 0.1 N NaOH.

2.3. Apparatus for a light/dark test and experimental procedure

Compound 48/80, mepyramine and cimetidine (each dose in 2 μl/animal) were intracerebroventricularly (ICV)-administered following the procedure described by Klemm [20]: in brief, 2 μl of drug or vehicle solution was injected into the right lateral ventricle (coordinates: posterior to bregma, 2 mm; right lateral, 2 mm; ventral, 3 mm from the outer surface of the cranium) through a 26-gauge needle using a microinjection pump (CMA/100, Carnegie Medicine, Stockholm, Sweden). Thioperamide (each dose in 10 ml/kg) was IP-administered. Sixty minutes after the administration of these drugs, their anxiogenic or anxiolytic effects were assessed using a light/dark test [16,35].

The apparatus (model 111, Tsumura, Tokyo, Japan) for a light/dark test consisted of two compartments: one light zone (30 L × 27 W × 27 H cm, 1000 lx) illuminated by fluorescent light, and the other dark zone (15 L × 27 W × 27 H cm, 5 lx) illuminated by dim red light. The two compart-

Table 1
Effect of compound 48/80, mepyramine, cimetidine or thioperamide alone on each parameter of the light/dark test

Group	Dose	Locomotion (counts/5 min)	Time spent in the light zone (s/5 min)	Shuttle crossings (times/5 min)
Compound 48/80[a]	0 (control)	273.4 ± 16.9	56.0 ± 4.4	15.9 ± 2.4
(mast cell degranulator)	0.1	260.7 ± 10.6	48.3 ± 5.1	11.9 ± 1.8
	1.0	292.2 ± 15.6	48.1 ± 5.3	9.8 ± 0.6
	10.0	273.9 ± 17.0	43.8 ± 7.3	13.3 ± 1.5
Mepyramine[a]	0 (control)	290.6 ± 10.0	58.3 ± 3.8	15.0 ± 1.4
(H_1 receptor inhibitor)	0.1	317.2 ± 8.7	56.0 ± 4.5	11.6 ± 1.1
	1.0	314.5 ± 21.4	59.3 ± 4.3	13.2 ± 1.4
	10.0	290.7 ± 16.7	61.3 ± 5.1	14.6 ± 1.9
Cimetidine[a]	0 (control)	303.8 ± 11.5	49.6 ± 3.2	11.5 ± 1.4
(H_2 receptor inhibitor)	0.1	302.3 ± 11.8	50.1 ± 2.7	12.0 ± 1.0
	1.0	278.1 ± 14.6	51.0 ± 4.6	10.4 ± 1.5
	10.0	289.4 ± 16.8	53.9 ± 5.3	11.0 ± 1.5
Thioperamide[b]	0 (control)	338.2 ± 10.6	55.4 ± 3.0	14.0 ± 0.8
(H_3 receptor inhibitor)	5.0	320.0 ± 9.5	50.5 ± 4.1	12.4 ± 1.2
	10.0	333.0 ± 17.1	50.5 ± 5.2	13.1 ± 1.9
	20.0	305.2 ± 14.2	48.5 ± 3.0	13.0 ± 1.6

Two microliters of various concentrations of Compound 48/80, mepyramine or cimetidine was ICV-injected. Various concentrations of thioperamide (10 ml/kg) were IP-injected. Control in each group was injected with the same volume of the corresponding vehicle. The light/dark test was carried out 60 min after each drug injection. Each value is expressed as mean ± SE (n = 10). No significant differences were observed in all groups.

[a] μg/2 μl, ICV.

[b] mg/10 ml/kg, IP.

Table 2
Effect of mepyramine or cimetidine co-injected with Compound 48/80, mast cell degranulator (1.0 μg/2 μl, ICV) on each parameter of the light/dark test

Group	Dose (μg/2 μl, ICV)	Locomotion (counts/5 min)	Time spent in the light zone (s/5 min)	Shuttle crossings (times/5 min)
Mepyramine (H_1 receptor inhibitor)	0 (control)	305.6 ± 15.5	51.4 ± 2.8	15.1 ± 2.2
	0.1	316.5 ± 18.9	54.3 ± 4.7	13.9 ± 1.8
	1.0	277.1 ± 27.9	46.2 ± 5.7	10.5 ± 1.4
	10.0	271.5 ± 19.2	49.6 ± 4.8	15.0 ± 2.3
Cimetidine (H_2 receptor inhibitor)	0 (control)	306.1 ± 15.5	60.6 ± 3.9	13.5 ± 1.5
	0.1	323.5 ± 13.4	41.2 ± 2.6*	12.2 ± 1.1
	1.0	284.6 ± 28.7	35.6 ± 5.6*	10.9 ± 2.9
	10.0	274.8 ± 20.6	22.8 ± 3.7**	6.8 ± 1.1**

Two microliters of a mixture of various concentrations of mepyramine (or cimetidine) and Compound 48/80 (1.0 μg) was ICV-injected. Control in each group was injected with the same volume of Compound 48/80 (1.0 μg). The light/dark test was carried out 60 min after each drug injection. Each value is expressed as mean ± SE (n=10).

* $p < 0.05$ vs. the corresponding control group.

** $p < 0.01$ vs. the corresponding control group.

ments were separated by a partition with an opening (7.5 × 7.5 cm). The mice were not habituated to the apparatus and the measurement began immediately after the animals were placed in the center of the light zone. Three parameters — locomotion, time spent in the light zone and the number of shuttle crossing between light and dark zones — were measured for each animal for a period of 5 min; locomotion was counted using Animex (model MK-110, Muromachi Kikai, Tokyo, Japan) while the other two behavioral parameters were analyzed from video recording.

2.4. Statistics

Data were expressed as mean ± standard error (SE). Statistical significance was measured by a one-way analysis of variance (ANOVA) followed by Dunnet least significant difference procedure. Significance was accepted at $p < 0.05$.

3. Results

The effect of individual drugs on each parameter of the light/dark test is shown in Table 1. Compared with the corresponding control in each group, all drugs, Compound 48/80 (0.1–10.0 μg/2 μl, ICV), thioperamide (5.0–20.0 mg/10 ml/kg, IP), mepyramine (0.1–10 μg/2 μl, ICV) and cimetidine (0.1–10.0 μg/2 μl, ICV), did not affect the locomotion, time spent in the light zone and the number of shuttle crossings during the light/dark test.

The effect of mepyramine or cimetidine co-injected with Compound 48/80 (1.0 μg/2 μl, ICV) or thioperamide (10 mg/10 ml/kg, IP) on each parameter of the light/dark test is shown in Tables 2 and 3, respectively. No effects of mepyramine on each parameter of the light/dark test were observed by co-administration with Compound 48/80 or thioperamide. However, cimetidine co-administered with Compound 48/80 or thioperamide induced significant decrease in the time spent in the light zone and the number of shuttle crossings without significantly altering the locomotion.

Cimetidine (10 μg/2 μl, ICV) co-injected with Compound 48/80 (1 μg/2 μl, ICV) or thioperamide (10 mg/10 ml/kg, IP) reduced the time spent in the light zone and the number of shuttle crossings were antagonized by mepyramine (10 μg/2 μl, ICV) as shown in Table 4. In this experiment, reduction of the locomotion was observed in

Table 3
Effect of mepyramine or cimetidine co-injected with thioperamide, H_3 receptor inhibitor (10 mg/10 ml/kg, IP) on each parameter of the light/dark test

Group	Dose (μg/2 μl, ICV)	Locomotion (counts/5 min)	Time spent in the light zone (s/5 min)	Shuttle crossings (times/5 min)
Mepyramine (H_1 receptor inhibitor)	0 (control)	319.4 ± 15.3	53.0 ± 5.0	13.1 ± 1.8
	0.1	312.5 ± 14.7	52.7 ± 3.6	12.2 ± 1.2
	1.0	304.5 ± 13.2	53.1 ± 3.9	11.8 ± 1.5
	10.0	310.9 ± 9.8	56.8 ± 3.9	11.6 ± 1.2
Cimetidine (H_2 receptor inhibitor)	0 (control)	315.5 ± 15.4	56.1 ± 4.1	13.7 ± 2.0
	0.1	313.2 ± 18.5	51.6 ± 3.7	12.2 ± 1.1
	1.0	294.0 ± 13.3	43.8 ± 2.3	9.2 ± 0.9
	10.0	266.9 ± 10.1	33.9 ± 3.2**	6.4 ± 1.1**

Two microliters of various concentrations of mepyramine or cimetidine was ICV-injected, immediately followed by thioperamide (10 mg/10 ml/kg) IP-injection. Control in each group was IP administered with the same dose of thioperamide after the same volume of each vehicle was ICV-injected. The light/dark test was carried out 60 min after thioperamide injection. Each value is expressed as mean ± SE (n = 10).

** $p < 0.01$ vs. the corresponding control group.

Table 4
Antagonization of mepyramine (10 μg/2 μl, ICV) on each parameter induced by co-administration of cimetidine (10 μg/2 μl, ICV) with Compound 48/80 (1 μg/2 μl, ICV) or thioperamide (10 mg/10 ml/kg, IP) in the light/dark test

Group	Locomotion (counts/5 min)	Time spent in the light zone (s/5 min)	Shuttle crossings (times/5 min)
Compound 48/80 (control)	349.5 ± 8.5	60.2 ± 3.7	14.2 ± 1.4
Compound 48/80 + cimetidine	308.0 ± 11.8	38.5 ± 3.5**	8.5 ± 2.4**
Compound 48/80 + cimetidine + mepyramine	325.6 ± 7.5	50.5 ± 2.5†	12.2 ± 2.4
Thioperamide (control)	323.8 ± 9.8	57.2 ± 3.9	14.2 ± 1.3
Thioperamide + cimetidine	270.0 ± 10.9 *	34.8 ± 2.1**	7.6 ± 0.7**
Thioperamide + cimetidine + mepyramine	294.6 ± 11.0	52.1 ± 2.2†	11.2 ± 1.2

In the experiment involving Compound 48/80, 2 μl of a mixture containing Compound 48/80 (1 μg) and cimetidine (10 μg), a mixture containing Compound 48/80 (1 μg), cimetidine (10 μg) and mepyramine (10 μg), or a solution of Compound 48/80 alone (1 μg) as control was ICV-injected. In the experiment involving thioperamide, 2 μl of a solution of cimetidine (10 μg) or a mixture containing cimetidine (10 μg) and mepyramine (10 μg) was ICV-injected, immediately followed by thioperamide (10 mg/10 ml/kg) IP-injection. In the control, the same dose of thioperamide was IP-injected after the same volume of vehicle was ICV-injected. The light/dark test was carried out 60 min after last drug injection. Each value is expressed as mean ± SE (n = 10).

* $p < 0.05$ vs. the corresponding control group.

** $p < 0.01$ vs. the corresponding control group.

† $p < 0.01$ vs. compound 48/80 + cimetidine group or thioperamide + cimetidine group.

thioperamide–cimetidine group, although no significant difference was observed in the same group in the other set of experiments shown in Table 3. The reduction of the locomotion was also antagonized by mepyramine.

4. Discussion

In the light/dark test, experimental anxiety is measured using the rodent's propensity for exploratory behavior and preference for a dark location. Anxiolytics have been found to increase the time spent in the light zone and the number of shuttle crossings between the dark and light zones, while anxiogenics decrease these parameters [6,16]. In addition to these parameters, Imaizumi and Onodera [15] report that a decrease in locomotor activity in the light zone is also a behavioral parameter of experimental anxiety, because the aversion of or anxiety in the light zone induce the decrease in locomotor activity as well as the time spent in the light zone. In the present study, both behavioral parameters (the time spent in the light zone and the number of shuttle crossings) showed significant decrease only when cimetidine, H_2 antagonist, was co-injected with histamine releaser, Compound 48/80 or thioperamide. No significant changes in locomotor activity were observed in all groups except for the thioperamide–cimetidine group. With regard to the thioperamide–cimetidine group shown in Tables 3 and 4, in spite of treatment with the same drug a significant reduction of locomotor activity was observed in the group shown in Table 4 but not in the group shown in Table 3. As locomotor activity in the present study was measured as the total motor activity in both zones of the light/dark task, it is unclear whether the changes in total locomotion are due to the reduction of activity in the light zone. However, the reduction or reduction tendency observed in the combination group differed from behavioral toxicity such as motor incoordination or general suppression of motor behavior induced by chlorpromadine [15,35]. Therefore, we concluded that the decreased two parameters were not due to the behavioral toxicity, and that the experimental anxiety was induced only when the animal was co-treated with H_2 antagonist and a cerebral histamine inducer (thioperamide or Compound 48/80).

It has been established that mast cells exist in the mammalian central nervous system [4,10,24,30]. Although the physiological functions of mast cells in the brain have not been thoroughly investigated, their role in defensive inflammatory responses and tissue repair, myelination and the metabolism of sulphate and lipid have been suggested [7,8,13]. In addition, it has been suggested that the biogenic amines, histamine and serotonin (5-HT), which are stored and released by brain mast cells, may serve a physiological role as neuromodulators or regulators [8,13]. It has been demonstrated that a mast cell degranulator, Compound 48/80, increases the histamine levels in the extracellular fluid in rat brain [30]. Lewis et al. [21] have reported that the 10 μg/10 μl, ICV, dose of Compound 48/80 in the rats, which effectively reduces the regional brain histamine content, does not modify the concentration of either 5-HT or the metabolite 5-HIAA. Recently, Bugajski et al. [4] also reported that Compound 48/80 (1 and 5 μg/10 μl, ICV) injected into the rats reduces the histamine content of the hypothalamus in a dose-dependent manner, but it does not substantially alter the 5-HT and 5-HIAA levels. These results suggest that the dose range from 1 to 10 μg of Compound 48/80 selectively liberates histamine from brain mast cells, although in the present study, histamine, 5-HT and 5-HIAA contents in the brain were not measured after ICV injection of Compound 48/80.

Lewis et al. [22] demonstrate that acute ICV injection of Compound 48/80 produces a marked behavioral syndrome in rats, in particular sedation and catalepsy observed in higher concentrations (15 and 25 μg/kg) are maintained for 90–120 min. The authors suggest that some of the beha-

vioral effects of ICV Compound 48/80 may arise from action other than mast cell degranulation, such as the modulation of cholinergic and opioid neurotransmission and the accumulation of cAMP. Onodera and Shinoda [28] have reported that catalepsy induced by high dose (100 μg) of ICV histamine in mice can be evoked not only by the activation of the histamine receptor, but also indirectly through cholinergic and dopaminergic imbalance. In the present study, video recording did not reveal any abnormal behaviors in Compound 48/80-treated mice, suggesting that higher doses than the doses (0.1–10 μg) used in this study may induce indirect actions such as the modulation of cholinergic, opioid or dopaminergic neurotransmission.

Histamine in mast cells is also thought to be an important mediator of itchiness. For example, subcutaneous or intradermal injection of Compound 48/80 has been reported to cause scratching behavior or itching in mice [32]. It is believed that the scratching behavior induced by Compound 48/80 is attributable to the release of histamine from the skin mast cells. In fact, it has been reported that intradermal injection of histamine produces an itching sensation in humans [11]. Sugiura et al. [33] suggest that the mast cells' invasion of dermal nerves with edematous changes of the nerve fiber bundles might be related to provocation or aggravation of itchiness of atopic dermatitis. Thus, the aversion induced by itching may affect the anxietic behavior. However, a marked scratching behavior was not observed during the experimental period followed by ICV injection of Compound 48/80 in the present study, suggesting that there is no relationship between itching and experimental anxiety.

In the present study, a light/dark test for 5 min was carried out at 60 min after IP or ICV injection of drugs. The time interval was selected on the basis of the following findings; Ito et al. [19] have reported that IP injection of thioperamide (5 mg/kg) caused an approximately twofold increase in rat hypothalamic histamine output at 30–60 min after the injection and the increased histamine levels were maintained for at least 4 h. Bugajski et al. [4] have reported that ICV injection of Compound 48/80 caused significant increases in the number of degranulated mast cells and histamine content in the rat thalamus at 1 h after the injection. The effects of ICV-injected histamine antagonists have also been evaluated at 75 min after each drug-injection on Compound 48/80-induced pituitary–adrenocortical activity [9]. These findings suggest that it is possible to evaluate these drug effects at 60 min after either IP or ICV injection.

Regarding the mechanism inducing experimental anxiety in the present study, we hypothesize as follows; both Compound 48/80 and thioperamide enhance endogenous cerebral histamine release via different mechanisms: degranulation from non-neuronal mast cells in the case of Compound 48/80 [31] and inhibition of H_3 autoreceptors inhibitory-regulating neuronal histamine release in the case of thioperamide [23]. Released histamine induced by Compound 48/80 or thioperamide is likely to stimulate both postsynaptic H_1 and H_2 receptors. It seems that H_1 receptors have an anxiogenic effect, while H_2 receptors have anxiolytic effect. Since the experimental definite anxiety was induced by co-injection of H_2 blocker and each histamine releaser; it is believed that the inhibition of anxiolytic effect by H_2 blocker may also enhance the anxiogenetic effect of postsynaptic H_1 receptors. Therefore, this combined treatment-induced experimental anxiety was antagonized by H_1 antagonist, mepyramine. The H_1 and H_2 blockers did not affect the behaviors in normal mice, suggesting that the antagonistic mechanism with both receptors may be activated at the levels of histamine release higher than normal. Thus, the imbalance of activities between postsynaptic H_1 and H_2 receptors in cooperation with increased histamine release in the brain may affect the induction of the experimental anxiety. Imaizumi et al. [14] demonstrated that betahistine, a histamine H_1 agonist and H_3 antagonist, significantly decreased the number of shuttle crossings and the time spent in the light zone during the light/dark test, suggesting the importance of histamine release and postsynaptic activity for the experimental anxiety. The present result concerning thioperamide is in agreement with the results and conclusion reported by Imaizumi and Onodera [15], although the present study used cimetidine instead of zolantidine as H_2 antagonist and ICV route was used rather than IP route. The present study suggests that non-neuronal histamine release induced by Compound 48/80 as well as neuronal histamine release induced by thioperamide causes the induction of the experimental anxiety.

In conclusion, experimental anxiety was induced by co-injection of the H_2 receptor antagonist, cimetidine, and histamine release enhancer, Compound 48/80 for enhancing non-neuronal histamine release, or thioperamide for enhancing neuronal histamine release. The results suggest that non-neuronal as well as neuronal histamine release cause the induction of the experimental anxiety; however, the physiological relevance of the findings remains to be demonstrated. Our findings also suggest that the experimental anxiety is closely related to the activities of postsynaptic H_1 and H_2 receptors. It is likely that the activation of histamine H_1 receptors has an anxiogenic effect and that activation of histamine H_2 receptors has a negative modulating effect on experimental anxiety. Our findings lay the foundation for further investigations to assess the role of the cerebral histaminergic system including neuronal and non-neuronal histamine in anxiety.

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