Pharmacology Biochemistry and Behavior, Vol. 46, pp 95–99, 1993
Printed in the U S A.

0091-3057/93 $6.00 + 00

Effects of (*S*)-α-Fluoromethylhistidine and (*R*)-α-Methylhistamine on Locomotion of *W/W*^{v} Mice

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Received 4 August 1992

SAKAI, N., S. YAMAZAKI, K. ONODERA, K. YANAI, K. MAEYAMA AND T. WATANABE. *Effects of (S)-α-fluoromethylhistidine and (R)-α-methylhistamine on locomotion of* W/W^v *mice.* PHARMACOL BIOCHEM BEHAV **46**(1) 95–99, 1993. — We studied the effects of inactivators of the central histaminergic neuron system, (*R*)-α-methylhistamine, a histamine H_3 receptor agonist, and (*S*)-α-fluoromethylhistidine, a histamine synthesis inhibitor, on locomotor activity and brain histamine content of mast cell-deficient *W/W*^{v} mice using a recently developed high-performance liquid chromatography system coupled with a fluorometric detector. IP injection of (*R*)-α-methylhistamine (6–50 mg/kg) increased brain histamine content after 1 h but caused no significant change in locomotor activity. IP injection of (*S*)-α-fluoromethylhistidine decreased brain histamine content at doses of 6–50 mg/kg and locomotor activity at doses of 12.5–50 mg/kg. However, locomotor activity was decreased significantly (in Student's *t*-test) by sequential administrations of (*S*)-α-fluoromethylhistidine (6 mg/kg) and (*R*)-α-methylhistamine (12.5 or 25 mg/kg), but not by (*S*)-α-fluoromethylhistidine (6 mg/kg) and other doses of (*R*)-α-methylhistamine (6 or 50 mg/kg). These results support the hypothesis that the central histaminergic neuron system is involved in the control of spontaneous locomotion or alertness.

Histamine Histamine H_3 receptor (*R*)-α-Methylhistamine (*S*)-α-Fluoromethylhistidine
Mast cell-deficient (*W/W*^{v}) mouse Locomotor activity

HISTAMINE functions as a neurotransmitter or neuromodulator and is involved in many physiological functions in the CNS such as the wakefulness-sleep cycle, food intake, drinking, body temperature, and endocrine regulation (10,21,26, 33,34). In addition to the classical H_1 and H_2 receptors, the existence of a presynaptic H_3 receptor has been suggested and confirmed by studies with specific ligands such as (*R*)-α-methylhistamine and thioperamide as an agonist and an antagonist, respectively (1,2,9,27,32). Thioperamide enhances and (*R*)-α-methylhistamine blocks histamine release from histaminergic neurons, and so these compounds cause decrease and increase, respectively, in brain histamine content (8,17). The H_3 receptors have also been shown to be located on peripheral and central cholinergic and serotonergic neurons (3,5,20,26, 31). The effects of histamine H_3 receptor ligands on CNS functions have been studied (4,14), but the relationship between H_3 receptor activation and behavior is still unclear.

The presence of mast cell in the brain has hampered studies on histamine in the CNS (10,27). However, the complication of the influence of mast cell-derived histamine on brain histamine receptors has been overcome by the development of *W/W*^{v} mutant mice (19,36,38) because these mice have no mast cells in either the CNS or peripheral systems (12). We reported previously that thioperamide (12.5 and 25 mg/kg, IP) increased locomotor activity of *W/W*^{v} mice with concomitant decrease in their whole-brain histamine content (23), suggesting that thioperamide activates the histaminergic neuron system and causes the hyperactivity via histamine released from the terminals. In the present study, we examined the effects of two inactivators of the histaminergic system, (*R*)-α-methylhistamine, an H_3 receptor agonist, and (*S*)-α-fluoromethylhistidine (FMH), a specific inhibitor of histidine decarboxylase (a histamine-forming enzyme) (13,34), on locomotor activity and brain histamine content of *W/W*^{v} mice.

METHOD

Animals

Male *W/W*^{v} mice of 5 weeks old were purchased from Funabashi Farm (Funabashi, Japan). Animals were housed at

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a constant temperature (22 ± 2°C) with lighting from 700–1900 h and allowed free access to food and water.

Measurements of Locomotor Activity and Motor Incoordination

Various doses (6, 12.5, 25, and 50 mg/kg) of (*R*)-α-methylhistamine dihydrochloride or FMH monohydrochloride hemihydrate were injected IP into *W/W*^{v} mice. In coadministration studies, various doses (6, 12.5, 25, and 50 mg/kg) of (*R*)-α-methylhistamine were injected IP into *W/W*^{v} mice 2 h after treatment with 6 mg/kg FMH. (*R*)-α-Methylhistamine and FMH were dissolved in saline, and control mice were given saline only. One and 3 h after injection of (*R*)-α-methylhistamine and FMH, respectively, locomotor activity of the *W/W*^{v} mice was measured with a photobeam system (BTA-1, Muromachi Kikai Co., Tokyo, Japan) for 3 min in the dark period (2100–2400 h) as described previously (23). With this method, the change in trajectory can be observed every 0.3 s. A rotarod test was employed for measurement of motor incoordination as previously described by Onodera and Ogura (18). Briefly, a wooden rod of 4 cm diameter (Tesco Co., Sendai, Japan) was rotated at a speed of 10 rpm and the number of mice that fell from the rod within 3 min was counted 1 h after injection of (*R*)-α-methylhistamine (25 and 50 mg/kg) or 3 h after injection of FMH (25 and 50 mg/kg).

Measurement of Brain Histamine Content of W/W^v *Mice*

Immediately after measurement of locomotor activity, mice were killed by decapitation and their brains quickly removed. Whole brains were homogenized in 2.6 ml cold 3% perchloric acid containing 5 mM EDTA-Na_2 in a Polytron homogenizer (Kinematica, Lucerne, Switzerland) at the maximum setting for two 10-s periods, the homogenate was centrifuged at 12,000 × *g* for 20 min, and the supernatant was collected. As histamine and (*R*)-α-methylhistamine were not separated by the high-performance liquid chromatography (HPLC) method described by Yamatodani et al. (37), we modified the HPLC system described by Fukuda et al. (6) using a mixture of 15% (v/v) methanol, 0.18 M imidazole, and 37.5 mM citric acid, pH 6.8, as a mobile phase and an ion exchanger resin CM-2SW (Tosoh, Tokyo, Japan) as a solid phase. Histamine and (*R*)-α-methylhistamine were postlabeled with *o*-phthalaldehyde (30) and detected with a fluoromonitor FS-8010 (Tosoh) using excitation and emission wavelengths of 360 and 450 nm, respectively. (*R*)-α-Methylhistamine and histamine were clearly separated from each other and other peaks as shown in Figs. 1A and 1B; their respective elution times were 24.0 and 28.8 min at a flow rate of 0.6 ml/min controlled with an L-6000 pump (Hitachi, Tokyo, Japan).

Chemicals

(*R*)-α-Methylhistamine dihydrochloride and FMH monohydrochloride semihydrate were kindly donated by Sumitomo Pharmaceutical Co. (Osaka, Japan) and Dr. J. Kollonitsch (Merck Sharp & Dohme, Rahway, NJ), respectively. Other chemicals were obtained from Wako Pure Chemical Co. (Tokyo, Japan).

Statistics

Data were analyzed by one-way analysis of variance (ANOVA) followed by a modified *t*-test. Data of Fig. 3 were also analyzed by Student's *t*-test. *P* values of less than 0.05 were considered significant.

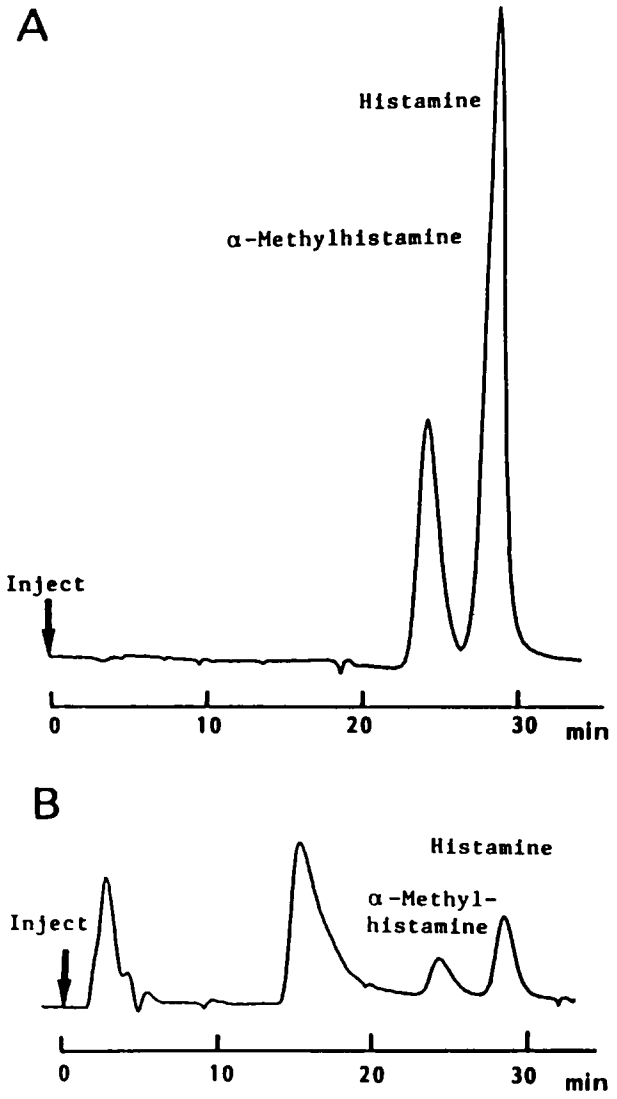

FIG. 1. Separation of histamine from (*R*)-α-methylhistamine in a newly developed high-performance liquid chromotography (HPLC) system. (A). Elution profiles of authentic (*R*)-α-methylhistamine and histamine (100 pmol each) with the HPLC system described in the Method section. (B). Typical elution profiles of an extract of the brain of a *W/W*^{v} mouse obtained 1 h after treatment with 20 mg/kg (*R*)-α-methylhistamine.

RESULTS

*Effects of (*R*)-α-Methylhistamine and FMH on Locomotor Activity and Motor Incoordination of* W/W^v *Mice*

As shown in Fig. 2, FMH alone decreased locomotor activity of *W/W*^{v} mice at higher doses (12.5, 25, and 50 mg/kg), but not at a lower dose (6 mg/kg), but as shown in Fig. 3 (*R*)-α-methylhistamine (6, 12.5, 25, and 50 mg/kg) did not affect locomotor activity of mice significantly, although it caused a much greater variance. Figure 3 also shows that administration of 12.5 mg/kg (*R*)-α-methylhistamine after injection of 6 mg/kg FMH significantly (in Student's *t*-test) decreased locomotor activity and that the same tendency was also seen by coadministration of 6 mg/kg FMH and 25 mg/

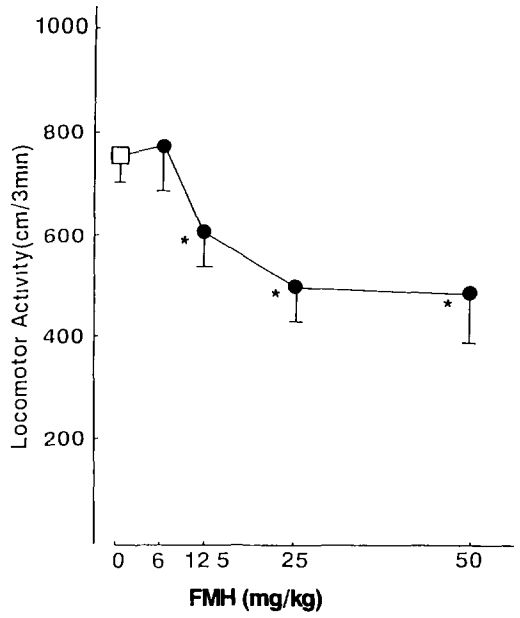

FIG. 2. Effect of (*S*)-α-fluoromethylhistidine (FMH) on locomotor activity of *W/W*^{v} mice. *W/W*^{v} mice were treated with FMH and 3 h later their locomotor activity was measured as described in the Method section. *$p < 0.05$, analysis of variance ($n = 6$).

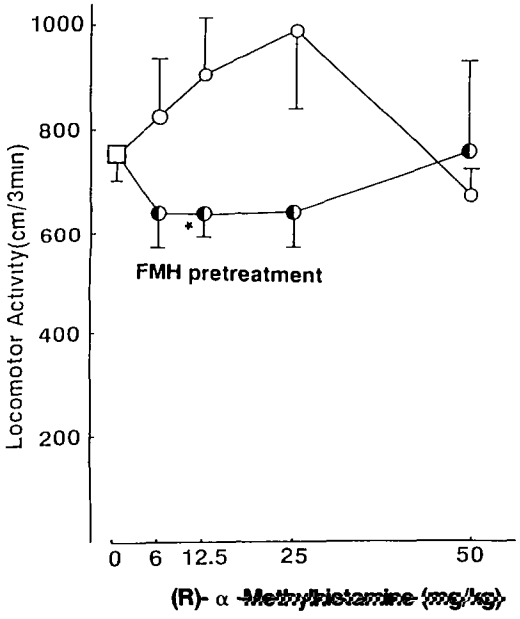

FIG. 3. Effect of (*R*)-α-methylhistamine without or with (*S*)-α-fluoromethylhistidine (FMH) on locomotor activity of *W/W*^{v} mice. (*R*)-α-Methylhistamine was injected IP into *W/W*^{v} mice and 1 h later locomotor activity was measured as described in the Method section. In coadministration studies, FMH (6 mg/kg) was injected IP into mice and 2 h later the indicated doses of (R)-α-methylhistamine (6–50 mg/kg) were injected IP and 1 h later locomotor activity was measured. *$p < 0.05$, Student's *t*-test ($n = 6$-8).

kg (*R*)-α-methylhistamine. No motor incoordination was observed with (*R*)-α-methylhistamine (25 and 50 mg/kg) or FMH (25 and 50 mg/kg).

Effects of (R)-α-Methylhistamine and FMH on Brain Histamine Content of W/W^v Mice

Brain histamine content of *W/W*^{v} mice was measured by a modification of the HPLC method of Fukuda et al. (6) as described in the Method section because with the original HPLC system (*R*)-α-methylhistamine was eluted in the same position as histamine (37). Figure 1A shows the elution profiles of authentic (*R*)-α-methylhistamine and histamine with the modified HPLC system and Fig. 1B shows a typical profile of a brain sample obtained 1 h after IP injection of 20 mg/kg (*R*)-α-methylhistamine. Brain histamine content of mice increased significantly ($p < 0.05$) after IP injection of (*R*)-α-methylhistamine (Fig. 4). Injection of FMH markedly decreased brain histamine levels, reducing the level to 20% of that of control at the highest dose tested (Fig. 4). Additional injection of 25 and 50 mg/kg (*R*)-α-methylhistamine 2 h after treatment with 6 mg/kg FMH significantly restored brain histamine content, but the level did not reach the control one as shown in Fig. 4.

DISCUSSION

There have been many reports on the effects of postsynaptic H_1 and H_2 receptors on the physiological functions (10,21,28,29,34) but only a few on the effects of H_3 ligands on CNS functions (4,14). Brain microdialysis studies showed that changes in histamine release are well controlled in vivo by H_3 receptors (11,16,22).

Previously, we examined the effect of IP thioperamide in-

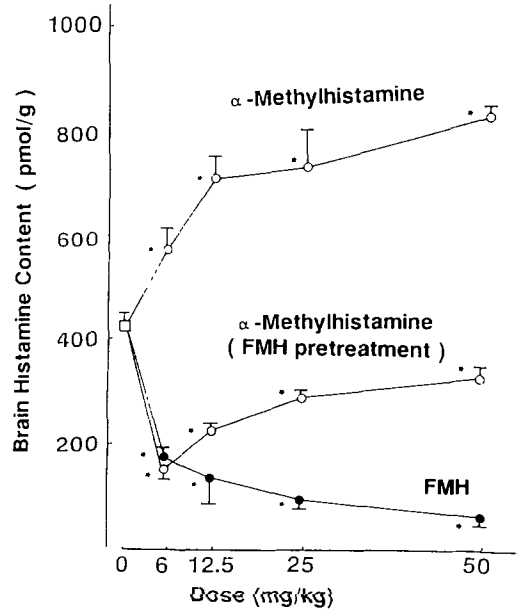

FIG. 4. Effects of (*R*)-α-methylhistamine, (*S*)-α-fluoromethylhistidine (FMH), and a combination of both on brain histamine contents of *W/W*^{v} mice. After measurements of locomotor activity as described in the legends of Figs. 2 and 3, mice were sacrificed by decapitation and their brain histamine contents measured as described in the Method section. *$p < 0.05$, analysis of variance ($n = 4$).

jection (12.5–75 mg/kg) on locomotor activity and brain histamine content (23). We found that brain histamine content decreased 1 h after thioperamide administration. At lower doses (12.5 and 25 mg/kg), thioperamide increased locomotor activity of W/W^v mice, possibly via H_1 and/or H_2 receptors, while at higher doses (50 mg/kg) it decreased their locomotor activity of mice, possibly by a motor incoordination effect of the drug.

It is evident from previous studies that FMH can inhibit HDC activity and reduce histamine in the brain (7,15,24,35) whereas (*R*)-α-methylhistamine decreases the release of intrinsic histamine (1). In this study, we found that the effects of these two inactivators of the histaminergic neuron system, FMH and (*R*)-α-methylhistamine, on locomotor activity were different. FMH decreased locomotor activity at doses of 12.5, 25, and 50 mg/kg and decreased brain histamine content appreciably at all doses tested. On the other hand, (*R*)-α-methylhistamine alone did not affect locomotor activity although it had a great variance effect on locomotor activity, with its marked effect on histamine stores as shown in Figs. 3 and 4. The dose of 25 mg/kg (*R*)-α-methylhistamine may affect some other neurotransmitter system(s), but it is difficult to detect them with our method. Anyhow, to confirm these effects of the drugs on behavior we carried out experiments of coadministration of 6 mg/kg FMH and 6, 12.5, 25, and 50 mg/kg (*R*)-α-methylhistamine. Coadministration of FMH (6 mg/kg) and (*R*)-α-methylhistamine (6 mg/kg) showed no change in histamine content compared with that caused by 6 mg/kg FMH only. In accordance with this, locomotor activity was not influenced by FMH (6 mg/kg) with or without 6 mg/kg (*R*)-α-methylhistamine. But, administration of (*R*)-α-methylhistamine (12.5, 25, and 50 mg/kg) after FMH treatment increased brain histamine content, which was decreased by FMH, and this storage effect of (*R*)-α-methylhistamine increased the reduced brain histamine content dose-dependently. Locomotor activity was decreased by coadministration of FMH (6 mg/kg) and (*R*)-α-methylhistamine (12.5 mg/kg) significantly (in Student's *t*-test). The same tendency was seen in the combination of FMH (6 mg/kg) and (*R*)-α-methylhistamine (25 mg/kg), although not significantly. Administration of 25 mg/kg (*R*)-α-methylhistamine did not affect the decrease in locomotor activity induced by 25 mg/kg FMH only (data not shown). In all these studies, we monitored the spontaneous locomotor activity of mice including exploratory behavior and ambulation for only 3 min without taming in a sensor box. In the next 3-min trial, the distances of migration were greatly reduced and there were little differences between animals treated with drugs and ones with saline (data not shown). The reason for this discrepancy between behavioral and biochemical effects is not known, but there are several possible explanations. One is that even after treatment with (*R*)-α-methylhistamine histaminergic terminals contained so much histamine that they still release a small, but sufficient amount of histamine to activate locomotion, whereas upon treatment with FMH the terminals are depleted of releasable histamine. In support of this idea, the brain HDC activity was not decreased by (*R*)-α-methylhistamine treatment in vivo whereas it was increased by thioperamide (25). Another possibility is that (*R*)-α-methylhistamine may act on other kinds of neuronal receptors or histamine receptors, that is, H_1 and/or H_2, besides the H_3 receptor, particularly at its higher doses. Our findings suggest that (*R*)-α-methylhistamine actually affects the regulation of histamine release and spontaneous locomotion via histaminergic neurons. There is no discrepancy between the previous findings obtained with thioperamide (23) and the present ones; thioperamide increases and (*R*)-α-methylhistamine with FMH decreases locomotor activity. In view of the possibility described above, it would be interesting to test the effect of (*R*)-α-methylhistamine on the release of histamine or other neuromodulators in vivo by the brain microdialysis technique because there are no reports in articles on brain microdialysis experiments on the effect of (*R*)-α-methylhistamine on histamine release (11,16,22). Our pharmacokinetic studies showed that (*R*)-α-methylhistamine is poor in penetration into the brain (Yamazaki et al., to be published).

ACKNOWLEDGEMENTS

The authors thank Sumitomo Pharmaceutical Co. (Osaka, Japan) and Dr. J. Kollonitsch (Merck Sharp & Dohme, Rahway, NJ) for generous gifts of (*R*)-α-methylhistamine and FMH, respectively. They also thank A. Sakurai for help in experiments. This work was partially supported by Grants-in-Aid from the Japanese Ministry of Education, Science and Culture (63065004), the Kowa Research Foundation, CIBA-GEIGY Foundation (Japan), and Suzuken Life Science Foundation.

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