ABSTRACT—The effects of intravenous and intracerebroventricular administrations of certain H1-blockers on the active avoidance response in rats were studied. Among the classic H1-blockers used in this study: pyrilamine, diphenhydramine, promethazine and chlorpheniramine, promethazine was the most effective and chlorpheniramine the least in inhibiting the active avoidance response; namely, a variation of prolongation in the response latency of the avoidance response. Meanwhile, ketotifen most potently inhibited the active avoidance response when the drugs were administered intracerebroventricularly. Mequitazine, astemizole and oxatomide were weak depressants when administered by either route. Azelastine was less effective than the classic H1-blockers by intravenous injection, while by intracerebroventricular injection, the inhibition was almost identical to those induced by the classic H1-blockers. Intracerebroventricular injection of histamine was antagonized the prolonged latency in the avoidance response induced by pyrilamine or diphenhydramine. A similar effect was also produced by 2-methylhistamine, but 4-methylhistamine had no effect. Intracerebroventricular injection of acetylcholine was restored the retarded avoidance response induced by pyrilamine, but a dose 20 times greater than that of histamine was required. From these findings, it can be concluded that inhibition of the active avoidance response induced by H1-blockers may be exerted through interaction with H1-receptors in the brain.

It is well-known that the central cholinergic system is intimately involved in the modulation of learning acquisition and in memory retention in humans and animals (1). Recently, it has also been reported that in rats, histamine takes part not only in learning but also in memory retention (2, 3). However, it has long been emphasized that classic H1-blockers such as diphenhydramine, pyrilamine and promethazine provide potent depressant actions on the central nervous system (CNS) in many different situations (4, 5). We have previously reported that oral administration of classical H1-blockers inhibited the active avoidance response by prolonging the response latency, even with a single administration (6). Moreover, the chronic oral administration of these H1-blockers both remarkably retarded the acquisition of the active avoidance response and impaired the retention of acquired learning for as long as chronic administration was continued (6). These findings seem to support the data reported by de Almeida and Izquierdo (2). However, a series of new H1-blockers such as oxatomide, astemizole and mequitazine, which were developed exclusively for the treatment of allergic diseases, were much less effective in inhibiting
the response when administered orally than the classic H₁-blockers (6).

The present study was performed to clarify the effect of H₁-blockers on active avoidance when injected either intravenously or intracerebroventriculally, and also to determine whether H₁-blockers exert their inhibitory effect by competing with histamine for the same (H₁) receptor in the brain.

MATERIALS AND METHODS

Animals

Male Wistar rats weighing 200–300 g were used. All animals were kept in an air-conditioned room at a controlled temperature (24–25°C) and humidity (50–60%). The animals were given food and water ad libitum.

Surgery

Under sodium pentobarbital anesthesia (35 mg/kg, i.p.), the animals were placed on a stereotaxic apparatus (Narishige, Type SR-5). A guide cannula made of stainless steel tubing, 700 μm in outside diameter and 14 mm in length, was implanted in the right lateral ventricle (A:5.4, L:1.5, H:3.0) according to the atlas of de Groot (7) and fixed to the skull with dental cement. The animals were allowed at least 10 days to recover from the surgery (8).

Apparatus

The apparatus was divided into two compartments, a 19 × 15 × 14 cm lighted room and a 33 × 20.5 × 14 cm dark room, linked by a sliding door (5 × 5 cm). The lighted compartment was painted white, had a flat floor and was illuminated by a lamp (100 W). The floor of the dark compartment consisted of a series of copper rods (3 mm in outside diameter), arranged side by side, 1.0 cm apart, through which electroshock was delivered (40 V, 0.2 mA).

Experimental procedures

Immediately after the rats were placed in the dark room, the sliding door was opened, and unless the animals moved into the lighted compartment within 5 sec, the sliding door was closed and an electric shock was delivered for 5 sec. Acquisition training was repeated once a day for 10 days, and rats showing positive avoidance response within 2 sec (moving from the dark to the lighted room) were used for testing the drug effect. To evaluate the drug effects on the avoidance response, the latency (sec) before moving into the lighted side was measured. A group of eight to ten rats was used for each dose. When the drugs were administered both intravenously and intracerebroventriculally into the same animal, the drug was injected into the tail vein under the restraint conditions, and 10 min later, the other drugs were injected intracerebroventriculally via the implanted cannula under free movement conditions.

Drugs

The drugs used were astemizole (Janssen), azelastine hydrochloride (Eisai), d-chlorpheniramnine maleate (Yoshitomi), diphenhydramine hydrochloride (Wako), ketotifen fumarate (Sandoz), oxatomide (Janssen), promethazine hydrochloride (Yoshitomi), pyrilamine maleate (ICN Pharm), mequitazine (Nippon Shoji), histamine dihydrochloride (Wako), 2-methylhistamine dihydrochloride (SK&F), 4-methylhistamine dihydrochloride (SK&F) and acetylcholine chloride (Daiichi). The drugs were dissolved in saline. In the intracerebroventricular injection, the drug solutions were adjusted to pH 7.2, and 5 μl of drug solutions were injected into the lateral ventricle through the injection cannula at a constant speed of 60 sec.

Statistical analysis

One way analysis of variance with Dunnett’s test was used to determine statistical significance. ED₅₀ was calculated according to the method of Litchfield-Wilcoxon (9) using those among the eight to ten tested animals that displayed a latency more than twice as long as that of the pre-drug values (sec) for the active avoidance response.
RESULTS

Effects of intravenous administration of certain drugs on the active avoidance response

Figure 1 shows the effects of pyrilamine, chlorpheniramine, ketotifen, astemizole, oxatomi
dide and azelastine after intravenous administration. At a dose of 10 mg/kg, pyrilamine

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{Effects of intravenous injection of H1-blockers on the active avoidance response in rats. saline (○), 0.5 mg/kg (●), 1 mg/kg (∆), 2 mg/kg (▲), 5 mg/kg (□), 10 mg/kg (■), 20 mg/kg (▽). * * : Significantly different from the control group with P < 0.05 and P < 0.01, respectively (error bars = S.E.M.).}
\end{figure}

prolonged the response latency at 15 min and a significant effect was observed even 120 min after drug administration. At the same dosage, chlorpheniramine was less potent than pyrilame

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{Effects of intravenous injection of H1-blockers on the active avoidance response in rats. saline (○), 0.5 mg/kg (●), 1 mg/kg (∆), 2 mg/kg (▲), 5 mg/kg (□), 10 mg/kg (■), 20 mg/kg (▽). * * : Significantly different from the control group with P < 0.05 and P < 0.01, respectively (error bars = S.E.M.).}
\end{figure}

Ketotifen elicited a slight but significant prolongation of the latency even at a dose of 2 mg/kg. Because the LD50 of ketotifen by intravenous injection was 5.3 mg/kg (10), doses
higher than 2 mg/kg were not depicted. The effect of astemizole was almost negligible at a dose of 10 mg/kg, but at 20 mg/kg, the drug prolonged the response latency significantly. Both oxatomide and azelastine showed a significant effect at doses of 10 and 20 mg/kg. Table 1 summarizes the ED$_{50}$ values of H$_1$-blockers on the active avoidance response. Promethazine appeared to be the most potent drug, with an ED$_{50}$ of 2.50 (1.19–5.25) mg/kg. Both astemizole and mequitazine had low potencies; The ED$_{50}$s were 25.6 (23.7–28.1) mg/kg and 21.4 (18.9–25.2) mg/kg, respectively.

**Effects of intracerebroventricular administration of certain drugs on the active avoidance response**

Figure 2 shows the effects of the same group of drugs tested after intracerebroventricular administration. At doses of 20 and 50 µg, pyrilamine caused a significant retardation in the response latency. Chlorpheniramine elicited a significant prolongation at doses of

| Table 1. ED$_{50}$ values of H$_1$-blockers for the prolongation of the response latency in the active avoidance response in rats |
|-----------------|-----------------|-----------------|
| Drugs       | ED$_{50}$ Values (95% confidence limits) |
|             | i.v.$^{a}$ (mg/kg) | i.vent.$^{a}$ (µg) |
| Pyrilamine  | 4.83 (4.31–5.42)  | 29.1 (27.1–31.5) | [72.8 (67.8–78.8)] |
| Diphenhydramine | 3.95 (2.26–6.91)  | 27.0 (23.2–32.4) | [91.8 (78.9–110.2)] |
| Promethazine | 2.50 (1.19–5.25)  | 19.8 (17.8–22.0) | [61.4 (55.2–68.2)] |
| Chlorpheniramine | 7.34 (6.94–7.80)  | 35.6 (31.3–41.9) | [92.6 (81.4–108.9)] |
| Mequitazine  | 21.4 (18.9–25.2)  | 177.2 (127.6–304.6) | [549.3 (395.6–944.3)] |
| Astemizole  | 25.6 (23.7–28.1)  | 134.7 (134.2–135.4) | [296.3 (295.2–297.9)] |
| Oxatomide   | 12.2 (11.9–12.5)  | 98.8 (86.2–117.4) | [227.2 (198.3–270.0)] |
| Azelastine  | 12.6 (11.1–14.7)  | 32.7 (30.9–34.7) | [78.5 (74.2–83.3)] |
| Ketotifen   | approximately 2$^{b}$ | 14.3 (14.0–14.5) | [34.3 (33.6–34.8)] |

$^{a}$i.v.: intravenous, i.vent.: intracerebroventricular. $^{b}$Since some toxic signs were observed at a dose of 5 mg/kg, ED$_{50}$ was not determined exactly. However, no such signs were observed in the case of intracerebroventricular administration. To make the comparison of the drug effect easier, ED$_{50}$s were described both in µg and in nmol.
20 and 50 μg. Ketotifen extended the response latency significantly at doses of 10 and 20 μg. However, astemizole elicited no significant effect even at a dose of 50 μg. Both oxatomide and azelastine showed significant effects at 50 or 100 μg and 10, 20 or 50 μg, respectively. The ED50 values determined after intracerebroventricular administration are also summarized in Table 1. Ketotifen and promethazine were effective in inhibiting the avoidance response (ED50 values of 14.3 (14.0–14.5) μg and 19.8 (17.8–22.0) μg, respectively). Mequitazine, astemizole and oxatomide were extremely weak compared with the classic H1-blocking agents.

Fig. 2. Effects of intracerebroventricular injection of H1-blockers on the active avoidance response in rats. saline (○), 5 μg (●), 10 μg (△), 20 μg (▲), 50 μg (■), 100 μg (▲). * * : Significantly different from the control group with P < 0.05 and P < 0.01, respectively (error bars = S.E.M.).
Effect of histamine administered intracerebroventricu-
larly on the active avoidance response inhibited by intravenous injection of pyrilamine or diphenhydramine.

Intracerebroventricular injections of histamine at doses of 0.1–1 μg dose-dependently suppressed the prolonged latency in the avoidance response produced by intravenous injec-

![Graphs showing effects of histamine, 2-methylhistamine, 4-methylhistamine, and acetylcholine on the active avoidance response.](image)

Fig. 3. Effects of intracerebroventricular injection of histamine, 2-methylhistamine, 4-methylhistamine and acetylcholine on the prolonged latency in the active avoidance response produced by pyrilamine or diphenhydramine or atropine. saline (○), 0.1 μg (●), 0.5 μg (△), 1 μg (▲), 2 μg (□), 5 μg (■), 10 μg (▽). Pyrilamine, diphenhydramine and atropine were injected intravenously at doses of 9.7 mg/kg, 7.9 mg/kg and 5.2 mg/kg, respectively. Arrows indicate the injection time of saline, histamine, 2-methylhistamine, 4-methylhistamine or acetylcholine (error bars = S.E.M.). *: **: Significantly different from the control group with P < 0.05 and P < 0.01, respectively.
tion of pyrilamine (9.7 mg/kg, double dose of ED₅₀) (Fig. 3). A significant effect appeared almost instantaneously after histamine injection at doses higher than 0.5 µg. The protracted latency in the avoidance response induced by diphenhydramine (7.9 mg/kg, double dose of ED₅₀) was also shortened after a brief period by intracerebroventricular administration of histamine as shown in Fig. 3. ID₅₀ values of histamine on pyrilamine- or diphenhydramine-induced inhibitions of active avoidance were 0.52 (0.22–2.99) µg and 0.79 (0.44–3.32) µg, respectively (Table 2). Histamine alone at a dose of 1 µg caused no significant effect on the active avoidance response (Table 3).

Influence of intracerebroventricular administration of 2-methylhistamine and 4-methylhistamine on the inhibition induced by intravenous injection of pyrilamine

As shown in Fig. 3, intracerebroventricular injection of 2-methylhistamine, an H₁ agonist, antagonized the pyrilamine-induced inhibition of the active avoidance response in the same way as histamine; significant shortening of the response latency was observed at doses greater than 1 µg. In contrast, 4-methylhistamine, an H₂ agonist, did not affect the response latency, even at a dose of 5 µg (Fig. 3, Table 2). When these two agonists were injected separately, without being combined with H₁-blockers, neither of them had any effect at doses of 2 and 5 µg, respectively (Table 3).

**Table 2.** ID₅₀ values of histamine, 2-methylhistamine, 4-methylhistamine or acetylcholine administered intracerebroventricularly on the response latency in the active avoidance response induced by H₁-blockers and atropine

| Drugs (i.v.) | Drugs (i.vent.) | ID₅₀ (µg) [nmol] |
|-------------|----------------|-----------------|
| Pyrilamine  + Histamine | 0.52 (0.22–2.99) [2.8 (1.2–16.1)] |
| Diphenhydramine + Histamine | 0.79 (0.44–3.32) [4.3 (2.4–17.9)] |
| Pyrilamine  + 2-Methylhistamine | 1.40 (1.03–2.53) [7.0 (5.2–12.7)] |
| Pyrilamine  + 4-Methylhistamine | > 5.00 [≥ 25.0] |
| Pyrilamine  + Acetylcholine | 11.6 (5.11–75.4) [63.8 (28.1–414.7)] |
| Atropine    + Acetylcholine | 1.23 (0.75–4.48) [6.8 (4.1–24.6)] |

Pyrilamine, diphenhydramine and atropine were injected intravenously at doses of 9.7 mg/kg, 7.9 mg/kg and 5.2 mg/kg, respectively. To make the comparison of the effects of these agonists easier, ID₅₀ values of agonists were described both in µg and in nmol.
avoidance response induced by pyrilamine. At the dose of 10 μg, however, acetylcholine produced a transient, contradictory effect; a significant shortening was observed 2–10 min after acetylcholine administration (Fig. 3). In contrast, the inhibition of active avoidance induced by atropine (5.2 mg/kg, twice of ED50 value) (11) was strongly antagonized by acetylcholine injection; a significant suppression was observed at 1 μg of acetylcholine. ID50 values for acetylcholine on pyrilamine and atropine-induced inhibitions of the avoidance response were 11.6 (5.1–75.4) μg and 1.23 (0.75–4.48) μg, respectively (Table 2). No influence on the response latency was found following a single injection of acetylcholine at a dose of 10 μg (Table 3).

**DISCUSSION**

These studies demonstrated that newly developed H1-blockers which are used as anti-allergic agents (such as oxatomide, astemizole and mequitazine) were less potent than classic H1-blockers (pyrilamine, diphenhydramine, promethazine, chlorpheniramine) in inhibiting the active avoidance response when the drugs were administered either intravenously or intracerebroventricularly. We found that while ketotifen caused a relatively potent inhibition of the avoidance response in the present experiment, it exerted only a weak influence on this response after oral administration when the ED50 values were compared (6). Therefore, it seems likely that either 1) ketotifen may not be easily absorbed from the gastrointestinal tract or 2) the drug may go through the first-pass effect. Martin and Romer (12) reported that an inhibition of passive cutaneous anaphylaxis (PCA) in rats induced by intravenous injection of ketotifen was 17 times more potent than that induced by oral administrations (ED50: 0.3 mg/kg, i.v.; 5.1 mg/kg, p.o.). The discrepancy due to the difference in administration routes was also found in the other drugs used in the present study. The potency of azelastine exerted by intracerebroventricular injection was slightly stronger than that of chlorpheniramine, while in intravenous injections, azelastine was evidently less effective than chlorpheniramine. This suggests that the penetrating amount of azelastine into the CNS may be much less to compare with that of chlorpheniramine. Actually, Tatsumi et al. (13) reported that the radioactivity derived from azelastine was extremely low in the brain when the drug was intravenously administered in rats, and the

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**Table 3. Effect of intracerebroventricular injection of histamine, 2-methylhistamine, 4-methylhistamine and acetylcholine on active avoidance response**

| Drugs          | Dose (μg) | N  | 0    | 2    | 5    | 10   | 15   | 20   | 50   | 170 min |
|----------------|-----------|----|------|------|------|------|------|------|------|--------|
| Saline         |           | 8  | 1.3±0.1 | 1.4±0.2 | 1.4±0.2 | 1.3±0.3 | 1.4±0.1 | 1.2±0.1 | 1.4±0.1 | 1.3±0.1 |
| Histamine      | 8         | 1  | 1.4±0.2 | 1.6±0.3 | 1.6±0.3 | 1.5±0.2 | 1.4±0.3 | 1.4±0.2 | 1.2±0.1 | 1.3±0.1 |
| 2-Methylhistamine | 2         | 8  | 1.2±0.1 | 1.3±0.2 | 1.3±0.2 | 1.2±0.1 | 1.3±0.1 | 1.2±0.1 | 1.2±0.2 | 1.2±0.2 |
| 4-Methylhistamine | 5         | 8  | 1.3±0.2 | 1.4±0.2 | 1.5±0.2 | 1.2±0.3 | 1.3±0.3 | 1.3±0.2 | 1.3±0.1 | 1.3±0.2 |
| Acetylcholine  |           | 10 | 1.2±0.1 | 1.4±0.2 | 1.6±0.2 | 1.4±0.2 | 1.4±0.1 | 1.5±0.2 | 1.4±0.1 | 1.4±0.2 |
concentrations of the drug in the brain tissue were lower than the concentration in the blood. Ohmori et al. (14) found that azelastine gave rise to a marked inhibition of \[^{3}H\]-pyrilamine binding to guinea pig cerebellum, indicating that the drug is able to bind the CNS efficiently. Therefore, it is reasonable to assume that the relatively weak depressant effect on the active avoidance response caused by intravenous injection of azelastine may not be due to its feeble CNS activity but simply to its low capacity for penetrating the CNS.

In the cases of mequitazine, oxatomide and astemizole, relatively high ED\(_{50}\)s were obtained compared with those of classical H\(_{1}\)-blockers when administered intravenously or intracerebroventricularly. It has been reported that the concentration of mequitazine in the brain after intravenous administration was not lower than that determined in the blood (15). Similar results were obtained in the case of oxatomide after oral administration (16). Therefore, it was assumed that mequitazine may have almost negligible affinity for the brain. Uzan et al. (17) reported that mequitazine is \(15-20\) times less potent than chlorpheniramine and promethazine in preventing \[^{3}H\]-pyrilamine binding to guinea pig brains. Ahn and Barnett (18) reported that astemizole has a larger \(K_{i}\) value than mequitazine in the \[^{3}H\]-pyrilamine binding test. Oxatomide also caused an inhibition of \[^{3}H\]-pyrilamine binding, although the effect was weaker than that of mequitazine (14). From these findings, it seems likely that the depressant effects of mequitazine, astemizole and oxatomide on the avoidance response were less potent compared with that of classical H\(_{1}\)-blockers, and this may be attributable to their poor affinities for brain tissues rather than difficulty in penetrating the brain.

In the present experiment, it was also found that the inhibition of the avoidance response (indicated by prolongation of the response latency) induced by an intravenous injection of pyrilamine or diphenhydramine was depressed dramatically by intracerebroventricular application of histamine (Table 2). Since these two drugs are typical H\(_{1}\)-blockers and the drugs showed a marked prolongation of response latency, pyrilamine and diphenhydramine were selected in this experiment. In similar experiments, 2-methylhistamine, an H\(_{1}\) agonist, produced the same effect as histamine, whereas 4-methylhistamine, an H\(_{2}\) agonist, was totally ineffective. This may indicate that the inhibitory effect of H\(_{1}\)-blockers on the avoidance response may be exerted through the H\(_{1}\)-receptor. In accordance with this, acetylcholine administered at a dose \(20\) times greater than that of histamine was required to suppress the prolongation of the response latency in the avoidance response induced by the same dose of pyrilamine. However, the inhibitory effect of atropine on active avoidance was blocked by intracerebroventricular administration of acetylcholine at a dose of \(1.23 \mu g\), which is one-tenth of the dose used to compete with the pyrilamine effect. From these findings, it can be assumed that an inhibition of active avoidance due to H\(_{1}\)-blockers may be exerted via H\(_{1}\)-receptors in the brain.

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