Effects of Isofloxythepin on Central and Peripheral Histamine Systems

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Abstract—The effects of isofloxythepin, a dibenzo[b,f]thiepin derivative, on the central and peripheral histamine systems were compared with those of chlorpromazine and haloperidol. The three drugs examined all inhibited both the histamine-induced contraction of guinea pig ileum and the specific $[^3]$H$\text{-}$mepyramine binding to guinea pig brain membranes in a dose-dependent manner. The effectiveness in inhibiting these reactions was in the order of: chlorpromazine $>$ isofloxythepin $>$ haloperidol. The histamine-induced relaxation of rat uterus, which is mediated by $H_2$-receptors, was not affected by isofloxythepin. The effect of isofloxythepin on the pargyline-induced accumulation of $\text{N}$-methylhistamine in the mouse brain was indicative of a decrease in histamine turnover, whereas chlorpromazine and haloperidol were devoid of such effects. Isofloxythepin inhibited both the lethal effect of histamine injected i.v. in mice and histamine-induced edema in rat hind paws far more strongly than chlorpromazine or haloperidol did. These results show that isofloxythepin is a neuroleptic with $H_1$-antagonist properties, which are intermediate in potency between those of chlorpromazine and haloperidol, and also it may have an inhibitory action on histamine turnover in the brain. Protection against the lethal effect of histamine and the inhibition of histamine edema by isofloxythepin may largely be due to mechanisms other than the blocking of $H_1$-receptors.

Many of the neuroleptics have $H_1$-receptor antagonist activities which vary in potency. The phenothiazines, such as chlorpromazine and fluphenazine, potently inhibit the binding of $[^3]$H$\text{-}$mepyramine to the membrane fraction of guinea pig brain, but the potencies of haloperidol and spiperone are weak in this respect (1). The $H_1$-blocking activities of these drugs may contribute to their sedative properties (2). Studies of $H_1$-blocking activities and psychotropic properties of dihydrobenzo[b,f]thiepin derivatives have been performed in Czechoslovakia. Isofloxythepin, 3-fluoro-8-isopropyl-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodi-benzo[b,f]thiepin, was found to have properties as a neuroleptic drug (3–7), but its $H_1$-blocking activity has not been studied in detail. In the present study, the effects of isofloxythepin on the peripheral and central histamine systems were examined and compared with those of prototypical neuroleptics, chlorpromazine and haloperidol.

Materials and Methods

Animals: Male ddY mice (25–30 g), male Wistar rats (about 150 g) and female Hartley guinea pigs (about 300 g) were obtained from Seiwa Experimental Animals (Fukuoka). They were housed in a room controlled at 22±2°C. Standard food and tap water were provided ad libitum.

Chemicals: All chemicals used were at least of a guaranteed reagent grade and were obtained from Nakarai Chemicals (Kyoto), Sigma Chemical Co. (St. Louis, MO, U.S.A.) and Calbiochem-Behring Corp. (San Diego, CA, U.S.A.). $[^3]$H$\text{-}$Mepyramine (28 Ci/mmol) was obtained from NEN Research Products (Boston, MA, U.S.A.). The drugs used in the present study were: isofloxythepin methanesulfonate (Showa Denko, Tokyo),
chlorpromazine hydrochloride (Contomin injection, Yoshitomi Pharmaceutical Industries, Tokyo), haloperidol (Serenace injection, Dai-nippon Pharmaceutical Co., Osaka), pargyline hydrochloride (Sigma Chemical Co.) and ranitidine hydrochloride (Nippon Glaxo Corp., Tokyo). Neuroleptics were dissolved and diluted in distilled water and administered p.o.

Histamine-induced contraction of guinea pig ileum: Guinea pig ileal strips, about 2.5 cm in length, were suspended in a 10-ml Magnus bath containing Tyrode's solution maintained at 37°C and bubbled with air. The isotonic contractions induced by 9 x 10⁻⁶ M histamine were recorded on a kymogram at a loaded tension of 0.2 g. The drugs tested were added 3 min before the histamine. The IC₅₀ (concentration of the drug which produces 50% inhibition of the histamine-induced contraction) was estimated by plotting the % inhibition of the histamine-induced contraction by the drug against the log of the drug concentration.

[³H] Mepyramine binding to the membrane fraction of guinea pig brain: [³H] Mepyramine binding was determined according to the method of Hill and Young (1). Guinea pigs were decapitated, and the whole brains were immediately dissected, washed in ice-cold 0.9% saline, and homogenized with 8 vol. of 50 mM phosphate buffer (Na₂HPO₄-KH₂PO₄, pH 7.7). The homogenates were centrifuged at 6,000 x g for 20 min, and the pellets were suspended in 10 ml of phosphate buffer. The suspensions were centrifuged at 8,700 x g for 1 min, and the resultant precipitates were resuspended in 10 ml each of phosphate buffer. A 50 μl aliquot of membrane suspension, [³H] mepyramine (a final concentration of 1 nM) and an appropriate concentration of the test drug dissolved in 50 mM phosphate buffer (pH 7.7) were mixed and incubated for 30 min at 30°C. Nonspecific binding was determined in the presence of 2 μM promethazine. The final volume of the incubation mixture was 2.3 ml. After incubation, the mixture was filtered through a Whatman GF/B glass filter by applying a vacuum and the membrane-bound [³H] mepyramine was recovered. The glass filter was soaked in a scintillation mixture, vortexed and allowed to stand overnight. The radioactivity was determined using a liquid scintillation counter. In all experiments, the effect of each concentration of the drugs was tested with four different samples. The data shown are the means of two separate experiments.

Relaxation by histamine of rat uterus contracted by potassium: The isolated rat uterine horn was suspended in a 10-ml Magnus bath containing normal Tyrode's solution at 25°C. While being bubbled with air, the preparation was left standing until the tone decreased to the base level. Then, the incubation medium was changed to Tyrode's solution containing 30 mM KCl. The isotonic contraction of the uterus in the high-potassium medium at a loaded tension of 0.2 g reached a maximum within 10 min. Histamine, 2.7 x 10⁻⁴ M, was added to the incubation medium 10 min after the change of the medium for high-potassium Tyrode. At the end of 10-min recording of the histamine-induced uterine relaxation, the incubation medium was replaced with normal Tyrode's solution, and the tissue was extensively washed. Isoflolxythepin (10⁻⁴ M) and ranitidine (10⁻⁴ M) were added 3 min before the addition of histamine. Within one set of experiments, the effects of these drugs on the histamine-induced relaxation were tested with the same uterine preparation.

Lethality in histamine-injected mice: Histamine dihydrochloride (600 mg/kg) was injected into the tail vein, and the lethality during a 30-min period after the injection was observed. Isoflolxythepin was administered p.o. 4 hr before the injection of histamine, and chlorpromazine and haloperidol were administered p.o. 1 hr before. Control mice were given distilled water p.o. in a volume of 0.1 ml/10 g at 1 hr before the histamine injection. The ED₅₀ value for each drug in protecting against the lethal effect of histamine was determined according to the method of Litchfield and Wilcoxon (8).

Histamine edema in rat hind paws: Histamine dihydrochloride (100 μg) dissolved in 0.1 ml of 0.9% saline was injected s.c. to the footpads of both hind paws. Isoflolxythepin was administered p.o. 3 hr before the injection of histamine, and chlorpromazine and haloperidol were given p.o. 1 hr before. Control mice were given distilled water p.o. in a volume of 0.1 ml/10 g at 1 hr before the
histamine injection. The intensity of edema was determined by measuring the volume of hind paws with a mercury plethysmometer, immediately before and 0.5, 1 and 2 hr after the injection of histamine, and calculating the difference from the preinjection volume.

Determination of histamine and *tele*-methylhistamine and estimation of histamine turnover in mouse brain: Pargyline hydrochloride (80 mg/kg) was injected i.p. 1 hr after the p.o. administration of distilled water (control groups), chlorpromazine or haloperidol, but it was given i.p. 3 hr after the p.o. administration of isofloxythepin. Mice were decapitated immediately before or at 1 or 2 hr after the injection of pargyline. The brain excluding the cerebellum was immediately removed and homogenized in 5 ml of 0.4 N perchloric acid containing 40 ng of *pros*-methylhistamine as an internal standard. Histamine and *tele*-methylhistamine were simultaneously assayed by high-performance liquid chromatography with fluorescence detection, according to the method of Tsuruta et al. (9) with slight modifications (10). Histamine turnover was estimated from the pargyline-induced accumulation of *tele*-methylhistamine.

**Results**

Histamine-induced contraction of guinea pig ileum: Histamine (9.0×10⁻⁶ M; 10⁻⁶ g/ml) produced a marked contractile response of the guinea pig ileum. Isofloxythepin, chlorpromazine and haloperidol all inhibited the histamine-induced contraction in a dose-dependent manner (Fig. 1). The IC₅₀ values were (1.1±0.1)×10⁻⁶, (4.9±1.0)×10⁻⁷ and (3.3±0.7)×10⁻⁶ M (mean±S.E.M. of 4 experiments and calculated on the molecular weight of each drug) for isofloxythepin, chlorpromazine and haloperidol, respectively, which shows that the potency of isofloxythepin in antagonizing the histamine-induced contraction of guinea pig ileum is about one half and three times as high as those of chlorpromazine and haloperidol, respectively. In these experiments, it was observed that repeated washings of the tissue were required to remove the inhibitory effect of isofloxythepin. On the contrary, the effects of chlorpromazine and haloperidol were easily removed with only one or two washings.

![Fig. 1. Inhibition of the histamine-induced contraction of guinea pig ileum by isofloxythepin (IFT), chlorpromazine (CPZ) and haloperidol (HPD). The results are the means±S.E.M. of 4 experiments.](image-url)
Isofloxythepin is about one-sixth and fifteen times as potent as chlorpromazine and haloperidol, respectively.

Relaxation by histamine of rat uterus contracted by potassium: Histamine (2.7×10⁻⁴ M) produced a marked relaxation, which reached 80%, of the rat uterus contracted by K⁺ (30 mM) (Table 1). The H₂-antagonist ranitidine (10⁻⁴ M) completely blocked the relaxant effect of histamine. However, isofoxothyepin (10⁻⁴ M) had no significant influence on this relaxation.

Lethality in histamine-injected mice: Isofoxothyepin, chlorpromazine and haloperidol all produced a dose-dependent reduction in the lethality in histamine-injected mice (Table 2). The potency of isofoxothyepin in protecting the animals against the lethal action of histamine was about seven and sixteen times as high as those of chlorpromazine and haloperidol, respectively.

Histamine edema in rat hind paws: As shown in Fig. 3, histamine produced a marked edema that reached a peak 0.5–1 hr after injection. Isofoxothyepin produced a dose-dependent inhibition of the histamine-induced edema. The inhibitory effect was only slight at 0.3 mg/kg, but marked at 1 mg/kg, and a complete inhibition of the edema was observed at 3 mg/kg. Although both chlorpromazine and haloperidol inhibited the edema, the effects of these drugs were not dose-dependent and modest even at the highest doses tested (chlorpromazine at 10 mg/kg and haloperidol at 30 mg/kg).
Table 2. Effects of isofloxythepin (IFT), chlorpromazine (CPZ) and haloperidol (HPD) on lethality in histamine-injected mice

| Dose (mg/kg) | Number of mice surviving/Number of mice tested |
|-------------|-----------------------------------------------|
|             | IFT       | CPZ       | HPD       |
| 0.1         | 0/8       | 1/8       | 1/8       |
| 0.3         | 5/8       | 0/8       | 0/8       |
| 1.0         | 7/8       | 1/8       | 3/8       |
| 3.0         | 8/8       | 8/8       | 6/8       |
| 10.0        |           |           |           |
| 30.0        |           |           |           |
| 100.0       |           |           |           |

ED50 (mg/kg) | 0.9 (0.3–2.3) | 6.4 (3.4–12.2) | 14.4 (5.0–41.6)

IFT, CPZ and HPD were administered p.o. and histamine dihydrochloride (600 mg/kg) was injected i.v. 4 hr (IFT groups) or 1 hr (CPZ and HPD groups) later. The lethality was observed for 30 min after histamine injection. The 95% confidence limit of ED50 is shown in parentheses. The dose of drugs used is expressed as the base.

and histamine turnover in the mouse brain:

Isofloxythepin at 3 mg/kg significantly increased the steady-state level of tele-methylhistamine, but not that of histamine 3 hr after injection. In the control mice, pargyline produced accumulations of 68.3 and 108.3 ng/g of tele-methylhistamine for 1- and 2-hr periods after the administration, respectively (Table 3). In the mice treated with isofloxythepin, the pargyline-induced accumulation of tele-methylhistamine was smaller than that in the control mice. On the other hand, in the mice treated with chlorpromazine (10 mg/kg) or haloperidol (1 mg/kg), the extents of tele-methylhistamine accumulations induced by pargyline were similar to those observed in the control mice. No concentrations of isofloxythepin, chlorpromazine or haloperidol had any influence on the histamine level, except for a significant rise in the histamine level 1 hr after the injection of pargyline to the isofloxythepin (3 mg/kg)-
Table 3. Effects of isofloxythepin (IFT), chlorpromazine (CPZ) and haloperidol (HPD) on the histamine and tele-methylhistamine contents and the pargyline-induced accumulation of tele-methylhistamine in the mouse brain

| Drugs          | Time after pargyline (hr) | Histamine (ng/g) | tele-Methylhistamine (ng/g) |
|---------------|---------------------------|------------------|-----------------------------|
| Control       | 0                         | 35.3±2.5         | 95.3±6.4                    |
|               | 1                         | 35.8±2.0         | 163.6±7.4 (68.3)            |
|               | 2                         | 44.5±2.4         | 203.6±7.2 (108.3)           |
| IFT, 1 mg/kg  | 0                         | 36.5±4.7         | 116.6±8.9                   |
|               | 1                         | 39.3±2.2         | 172.1±10.1 (55.5)           |
|               | 2                         | 43.8±5.9         | 198.7±8.4 (82.1)            |
| IFT, 3 mg/kg  | 0                         | 40.7±2.7         | 122.5±6.1*                  |
|               | 1                         | 48.4±2.0**       | 168.8±9.8 (46.3)            |
|               | 2                         | 49.5±5.4         | 187.8±11.3 (65.3)           |
| CPZ, 10 mg/kg | 0                         | 37.4±2.6         | 105.4±4.5                   |
|               | 1                         | 39.2±2.0         | 166.9±12.5 (61.5)           |
|               | 2                         | 45.7±5.1         | 200.4±9.8 (95.0)            |
| HPD, 1 mg/kg  | 0                         | 38.8±3.6         | 96.1±10.0                   |
|               | 1                         | 49.8±4.7         | 158.2±21.1 (62.1)           |
|               | 2                         | 50.5±6.0         | 195.8±6.6 (99.7)            |

Mice were given p.o. water, IFT, CPZ or HPD. They were injected with pargyline hydrochloride (80 mg/kg, i.p.) 3 hr (IFT groups) or 1 hr (control, CPZ and HPD groups) later. The brain histamine and tele-methylhistamine contents of mice killed immediately before pargyline injection were used as 0-time values. The results represent the means±S.E.M. of 6–9 mice. Figures in parentheses represent the tele-methylhistamine accumulation. *P<0.01, **P<0.001, as compared with the corresponding values in the control groups (Student's t-test). The dose of drugs used is expressed as the base.

treated mice.

Discussion

The three neuroleptics examined in the present study all inhibited the histamine-induced contraction of the guinea pig ileum. The order of the inhibitory potencies was: chlorpromazine>isofloxythepin>haloperidol. These drugs also showed the same order of relative potencies in inhibiting [3H]mepyramine binding to the membranes from guinea pig brains. The IC50 values, obtained in the present experiment, for chlorpromazine and haloperidol in inhibiting [3H]mepyramine binding are in good agreement with those reported by Hill and Young (1). These results suggest that isofloxythepin is an H1-receptor blocker with an intermediate potency between those of chlorpromazine and haloperidol.

The histamine-induced relaxation of the rat uterine smooth muscle is mediated by H2-receptors (11, 12). In the present study, ranitidine, an H2-antagonist (13), completely inhibited the histamine-induced relaxation of the rat uterus from potassium contracture. However, isofloxythepin had no significant influence, suggesting that it has no blocking activity at H2-receptors.

Chlorpromazine and haloperidol had no influence on the steady-state levels of histamine or tele-methylhistamine in the brain. They had no effect on the pargyline-induced accumulation of tele-methylhistamine, either. However, isofloxythepin decreased the pargyline-induced accumulation of tele-methylhistamine by 24 and 40% at the doses of 1 and 3 mg/kg, respectively. Because the steady-state tele-methylhistamine level was significantly increased by a dose of 3 mg/kg of isofloxythepin, further studies are necessary to confirm the inhibitory effect of isofloxythepin on histamine turnover in the brain.

The presence of histaminergic systems in the brain has recently been proved immunohistochemically (14, 15), and these systems have been suggested to function in the regulation of arousal level, body temperature, sympathetic activity, hormone secretion and
so forth (16–18). The decreased histaminergic transmission by isofloxythepin (postsynaptically and possibly presynaptically as well) may be associated with its sedative effect.

Isofloxythepin gave mice much stronger protection against the lethal effect of histamine than chlorpromazine or haloperidol. The order in ranking the potencies of these drugs in reducing lethality in the histamine-injected mice was clearly different from the potency ranking order in inhibiting the histamine-induced contraction of guinea pig ileum or \([^{3}\text{H}]\)mepyramine binding to the membranes of guinea pig brains. Fujimura et al. (19) determined the ED50 values for mequitazine and clemastine fumarate, administered p.o., in protecting mice against the lethal effect of 700 mg base/kg of histamine injected i.v. 30 min later. They obtained approximately the same ED50 values (2.25 mg/kg) for mequitazine and clemastine fumarate. Mequitazine is about equipotent to promethazine in inhibiting \([^{3}\text{H}]\)mepyramine binding to the membranes from guinea pig lungs or mouse brains (20). Promethazine is 6–80 times as potent as chlorpromazine in blocking \(H_1\)-receptors, e.g., see Rocha e Silva and Antonio (21). Therefore, the potency of isofloxythepin in inhibiting the lethal effect of histamine seems to be relatively high, considering its rather low potency as an \(H_1\)-antagonist. It is likely that isofloxythepin protects animals against the lethal effect of histamine not only by blocking \(H_1\)-receptors, but also by other unknown mechanisms.

Isofloxythepin markedly and dose-dependently inhibited the edema induced by histamine in rat hind paws. It is noteworthy that 1 and 3 mg/kg of isofloxythepin inhibited the edema almost completely. However, inhibition by chlorpromazine or haloperidol was not dose-dependent and was partial even at the high doses. Fujimura et al. (19) reported that \(H_1\)-antagonists, mequitazine and clemastine fumarate inhibited only by about 50% the histamine-induced leakage of pontamine sky blue injected i.v., even at a high oral dose of 50 mg/kg. This suggests that orally administered \(H_1\)-antagonists do not have very strong inhibitory effects on the increase in vascular permeability induced by histamine injected locally. The strong inhibitory effect of isofloxythepin on histamine edema may not be largely due to the blocking of \(H_1\)-receptors, but rather due to other mechanisms; e.g., possible stabilization of the microvascular endothelium and the inhibition of calmodulin. Many neuroleptics inhibit calmodulin (22). Since chlorpromazine and haloperidol had only partial inhibitory effects on the edema, this isofloxythepin action does not seem to be a common property among neuroleptics.

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