A Behavioral Pharmacological Study of Mafoprazine, a New Phenylpiperazine Derivative

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Abstract—Behavioral pharmacological studies on mafoprazine, a new drug for the prevention of aggressive behavior, were performed to compare its effects with those of an existing drug, azaperone (Stresnil®). The acute toxicity of mafoprazine in mice was slightly stronger than that of azaperone. Mafoprazine showed the following effects (at 0.2 to 2.0 mg/kg, s.c.): a decrease in spontaneous motor activity, prolongation of the duration of pentobarbital anesthesia, inhibition of long-term isolation-induced aggressive behavior, inhibition of olfactory bulbectomy-induced hyperemotionality and muricide behavior in mice and rats, and a marked taming and tranquilizing effect on aggressive behavior in dogs. These effects of mafoprazine were qualitatively the same as those of azaperone. Mafoprazine showed cataleptogenicity in rats at 5 mg/kg, s.c. or more and motor incoordination in rats at 0.2 mg/kg, s.c. or more. In the experiment on operant behavior in rats, the effect of mafoprazine on differential reinforcement of the low rate (DRL) response was almost the same as those of azaperone and chlorpromazine. These results indicate that mafoprazine has substantially the same psychotropic effect as azaperone, while the former has a weaker action on the extrapyramidal system than the latter, suggesting that mafoprazine could be used as a unique aggression-inhibiting drug.

Mafoprazine, whose molecular formula is expressed as 4'·[[3-[4-(o-fluorophenyl)-1-piperazinyl]propyl]oxy]·3'-methoxyacetanilide methanesulfonate, is a compound with a chemical structure as shown in Fig. 1, which has been newly found in a series of phenylpiperazine derivatives synthesized in our Research Laboratory of Organic Chemistry. Mafoprazine shows apomorphine- and methamphetamine-antagonizing effects in mice, while it exhibits no typical catalep-
togenetic effect in monkeys (M. Yamamura, unpublished results). In addition, it is considered to be a unique neuroleptic drug, which biochemically has a moderate dopamine D2 receptor-blocking action, a relatively strong α1-adrenoceptor-blocking action and an α2-adrenoceptor-stimulating action (1). The purpose of the present study is to further clarify the properties of mafoprazine from the viewpoint of behavioral pharmacology, such as aggressive behavior in mice, hyperemotionally and muricide in olfactory bulbectomized rats, gross behavior in dogs and operant behavior in rats.

Materials and Methods

Materials

1. Experimental animals

Std:ddY male mice (weighing 26 to 28 g and 40 to 50 g), Slc:Wistar male rats
(weighing 60 to 80 g and 180 to 250 g) and beagles (weighing 12 to 16 kg) were used.

2. Housing

The animals were allocated cages as follows: Mice, 25 per one plastic cage (42×26×15 cm); rats, one rat to one compartment (15×25×14 cm) of stainless steel five-compartment wire-mesh cages (mesh: 6 mm, 75×25×14 cm); beagle dogs, each animal in an individual stainless steel cage (700×800×810 cm). All animals were housed in an animal room maintained at a temperature of 23±1°C and humidity of 55±5% and illuminated for 12 hr (from 6:30 a.m. to 6:30 p.m.).

The mice and rats were allowed to partake freely of a pellet food for mice and rats, CRF-1 produced by Oriental Yeast Industry Co., Ltd., and each beagle dog was given 300 g of a pellet food for dogs, DS produced by the same company, once a day at approx. 4:00 p.m. All animals were allowed to take tap water freely.

3. Drugs

Mafoprazine (Lot. No. 303020) is a slightly bitter, odorless, white crystalline powder, easily soluble in water, stable to heat and light and with no hygroscopicity or volatility. As for azaperone, Stresnil® (Sankyo) for animal use with a concentration of 40 mg/ml was used. Mafoprazine was, as a rule, dissolved in distilled water, while azaperone was, as a rule, dissolved in distilled water, while azaperone was diluted with distilled water as required, in most cases for subcutaneous administration. The dose volume were 10, 5 and 0.2 ml/kg in mice, rats and dogs, respectively.

The other drugs used in this study are as follows: pentobarbital sodium salt (Nakarai Chemicals), chlorpromazine hydrochloride (Shionogi) and chloriazepoxide (Yamanouchi).

Methods

1. Acute toxicity

Groups of 10 mice were used. After s.c. injection of mafoprazine or azaperone, gross behavior and the number of deaths were observed daily during 7 days. The LD50 values were calculated from the number of deaths within 7 days after administration of the drugs.

2. Effect on spontaneous motor activity

Mice were individually placed in an open plastic cage (25×40×15 cm) and spontaneous motor activity was measured by an Animex with a sensitivity of 10 µA in terms of counts/10 min before administration, and every 10 min for 60 min after s.c. administration of mafoprazine or azaperone. The ED50 values were calculated from the number of mice exhibiting less than 1/2 the mean total count of the control group in 60 min. The mice used in this experiment were preselected from among those which had demonstrated spontaneous motor activity equivalent to about 300 counts/10 min, divided into groups of 5 for the experiment.

3. Effect on anesthesia

The effect of mafoprazine and azaperone on pentobarbital-induced anesthesia was studied using groups of 10 mice. Thirty min after s.c. administration of the drugs, pentobarbital-Na was injected intraperitoneally at a dose of 40 mg/kg to measure the duration of anesthesia, represented by the loss of righting reflex. The ED50 values for the drugs were calculated from the number of mice which showed more than 2 times the mean duration of anesthesia observed in the control group.

4. Effect on aggressive behavior

1) Electroshock-induced fighting behavior: The effect of mafoprazine and azaperone on electroshock-induced fighting behavior was studied using mice divided into groups of 10 pairs per group, according to the method of Tedeschi et al. (2). At 0.5, 1 and 3 hr after each pair of mice were treated s.c. with the drugs, the paired mice were placed in a fighting box (13×13×17 cm) for application of 3-min electroshock (DC, 400 V, 2 mA, 2 msec, 0.25 Hz) to their plantar regions using an aggression-inducing apparatus that consisted of a transparent acrylic resin with an electrifiable metal grid floor (Kyoto Keisokuki) and the number of electroshock-induced fighting episodes was measured. The paired mice used in this experiment were preselected from among those that had demonstrated 10 or more fighting episodes by electroshock applied under the above conditions. The ED50 values for the drugs were calculated from the maximum number of pairs exhibiting less than 1/2 the mean number of fighting episodes observed in the control group at
each measuring time.

2) Long-term isolation-induced aggressive behavior: The effect of mafoprazine and azaperone on long-term isolation-induced aggressive behavior in mice was studied according to the method of Yen et al. (3, 4). The mice, placed in individual cages (12×14×16 cm) separated from each other by opaque PVC frames, were kept for more than 2 months isolated invisibly from each other. Thereafter, they were paired at random for the selection of pairs showing aggressive behavior, mainly involving biting, during a 5-min period, followed by division into groups of 8 pairs each for experimentation. At 0.5 and 3 hr after each pair of mice thus selected and grouped was treated s.c. with the drugs, the paired mice were allowed to be together for 5 min for observation of the presence/absence of fighting episodes. The ED50 values for the drugs were calculated from the number of pairs in which no fighting episode was observed. The mice were used repeatedly with not less than 7 days between administrations, during which time they were isolated from each other.

5. Effect on hyperemotionality and muricide in bilaterally olfactory bulbectomized rats

The effect of mafoprazine and azaperone on hyperemotionality and muricide in bilaterally olfactory bulbectomized rats was studied according to the method of Ueki et al. (5, 6). After bilateral olfactory bulbectomy by suction under pentobarbital-Na (35 mg/kg, i.p.) anesthesia, the rats were kept in individual wire-mesh cages for isolation throughout the experiment. Seven to 10 days after the operation, the rats showing specific aggressive behavior that exhibited hyperemotionality, represented by a total score of 8 points or more on the grading table formulated by King and Meyer (7), were selected and used in the experiment in groups of 10. Hyperemotionality was evaluated at 0.5, 1, 3 and 24 hr after administration of the drugs.

The olfactory bulbectomized rats were judged to be positive for muricide when they bit to death a mouse put in their cage within 3 min. Rats were given a non-treatment period of at least 6 days before repetitive use.

6. Effect on gross behavior in dogs

The effect of mafoprazine and azaperone on dog behavior was studied using 3 violent beagle dogs with markedly aggressive and defensive behavior involving the assumption of a strongly defensive posture, biting, barking and assuming an offensive posture. The gross behavior was observed for 3 hr after administration of the drugs. The dogs were used repeatedly after a non-treatment period of 7 days or more.

7. Effect on differential reinforcement of low rate (DRL) response

In the DRL response schedule (8), only rats which gave a lever pushing interval or inter-response time (IRT) of 20 sec or more but less than 80 sec were given reinforcement of about 50 mg food pellets, and the number of responses, mean IRT, number of reinforcements, response efficiency [defined as F(t)·(40-t)], where F(t) indicates IRT frequency for t sec] and IRT distribution were determined.

The DRL response schedule was controlled with a BRS/LVE conditional behavior programming device, while the response measurement and computational processing were carried out using a PC-9801E personal computer (NEC). During the experiment, the body weights of the rats were controlled by limited feeding so that their weights were maintained at about 80% of those with free access to food. The rats were kept in a Skinner box housed in a soundproof box with a forced ventilator and given a 60-min session of training once a day except on holidays so that their DRL response became almost constant in number before being subjected to experimentation. Operant behavior was observed for 60 min. Mafoprazine, azaperone or chlorpromazine was subcutaneously administered to rats 30 min before the observation. The rats were divided into groups of 5 and used repeatedly with not less than a week between administrations in increasing doses. The day before administration of the drugs, water was administered subcutaneously to the rats for observation of its effect, which was used as a control.

8. Cataleptogenic activity

The cataleptogenic activity of mafoprazine and azaperone was studied in groups of 5 rats, according to the method of Janssen et al. (9). One hr after s.c. injection with the
drugs, one foreleg of the rat was forcedly placed in a rubber stopper 9 cm in height. Rats sustaining the forced posture for more than 30 sec were judged to be cataleptic. The ED50 values for the drugs were calculated from the number of rats which developed catalepsy after administration. The rats were repeatedly used after a non-treatment period of 7 days or more.

9. Effect on motor coordination

The effect of mafoprazine and azaperone on motor coordination was studied in mice and rats, divided into groups of 10, according to the method of Dunham and Miya (10); animals chosen for this test were those who when placed on a wooden rod (diameter: mice, 3.5 cm; rats, 8.5 cm) rotating at 7.5 r.p.m., did not fall from it once within 3 min. At 0.5 and 1 hr after s.c. administration of the drugs, the animal was again placed on the rotating rod for 2 min. If the mouse or rat fell from the rod twice or more within this period of time, it was judged to be positive for motor incoordination. The ED50 values of the drugs were calculated from the number of rats which developed motor incoordination after administration.

Statistical analyses

The LD50 and ED50 values for the drugs and their 95% confidence limits were determined by the probit method. A test for significant difference from the control was made for hyperemotionality and muricide in olfactory bullectomized rats by the Dunnett type multiple comparison test after the Kruskal-Wallis test and Fisher's exact probability test, respectively, and for the other items by Student's t-test with the level of significance taken to be less than 5%.

Results

1. Acute toxicity

Mafoprazine caused death in mice at 300 mg/kg, s.c., or more. The symptoms which developed included decreased spontaneous motor activity within 5 min after administration, followed by a prone posture and ptosis, decreased body temperature, loss of righting reflex and inhibited respiration, before eventual death caused by respiratory paralysis within 24 hr after administration. The rats which survived after s.c. administration of 200, 300 and 500 mg/kg showed almost the same symptoms as the dead mice, but they regained a normal state on the 2nd to 3rd days at 200 mg/kg, on the 3rd to 4th days at 300 mg/kg, and on the 4th day at 500 mg/kg. The LD50 value of the drug, calculated from the number of deaths within 7 days after administration, was 480.1 (292.9–612.3) mg/kg, s.c.

Azaperone caused death in mice at 500 mg/kg, s.c., or more. The symptoms which developed, in addition to those observed in the case of mafoprazine, included clonic convolution, which appeared about 10 min after administration and lasted for approximately 1 to 2 hr before eventual death caused by respiratory paralysis within 24 hr after administration. The rats which survived

| Table 1. Effect of mafoprazine and azaperone on spontaneous motor activity in mice |
|-------------------------------------------------|
| Drugs/ | Doses  | Spontaneous motor activitya (counts/10 min, mean±S.E.) |
|        | mg/kg, s.c. |  | before | 10 | 20 | 30 | 40 | 50 | 60 minb |
|-------|-----------|----|--------|----|----|----|----|----|-------|
| Control | — | 269±12 | 98±12 | 71±12 | 61±18 | 41±24 | 30±24 | 19±11 |
| Mafoprazine | 0.1 | 266±18 | 75±10 | 42±22 | 36±20 | 37±17 | 39±19 | 16±3 |
| | 0.5 | 266±17 | 37±7** | 11±7** | 21±10 | 20±9 | 25±15 | 6±5 |
| | 1 | 278±10 | 49±15* | 1±1*** | 9±7* | 24±11 | 17±7 | 5±5 |
| Azaperone | 0.1 | 259±17 | 87±13 | 31±15 | 11±6* | 18±7 | 38±20 | 26±17 |
| | 0.5 | 260±10 | 42±13* | 3±2*** | 2±1* | 3±2 | 10±10 | 8±7 |
| | 1 | 262±18 | 34±7** | 1±1*** | 0±0* | 1±1 | 0±0 | 2±2 |

aThe spontaneous motor activity was individually measured by Animex for 10 min at each time. bTime after administration of the drugs. Groups of 5 mice were used. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control.
at 200, 500 and 600 mg/kg, s.c., developed almost the same symptoms as the dead rats, but they regained an almost normal state on the 2nd to 3rd day at 200 mg/kg and on the 3rd to 4th day at 500 and 600 mg/kg. The LD50 value for the drug, calculated from the number of deaths within 7 days after administration, was 547.7 (494.8–606.3) mg/kg, s.c.

2. Effect on spontaneous motor activity
Both mafoprazine and azaperone dose-dependently decreased the spontaneous motor activity in mice at 0.5 mg/kg, s.c., or more and 0.1 mg/kg, s.c., or more, respectively, with ED50 values of 0.39 (0.25–0.70) mg/kg, s.c., and 0.22 (0.11–0.48) mg/kg, s.c., respectively. There were no remarkable differences between the two in their effects (Table 1).

3. Effect on anesthesia
Both mafoprazine and azaperone dose-dependently prolonged the duration of pentobarbital-induced anesthesia in mice at 0.2 mg/kg, s.c., or more, with ED50 values of 0.40 (0.30–0.55) mg/kg, s.c., and 0.32 (0.26–0.42) mg/kg, s.c., respectively. There were no remarkable differences between the two in their effects (Table 2).

4. Effect on aggressive behavior

| Drugs   | Doses (mg/kg, s.c.) | Sleeping time (min) mean±S.E. | ED50 (95% C.L.) mg/kg, s.c. |
|---------|---------------------|-------------------------------|-----------------------------|
| Control | —                   | 29±1.4                       |                             |
| Mafoprazine | 0.1               | 33±2.4                       |                             |
|          | 0.2                 | 41±1.9***                    | 0.40                        |
|          | 0.5                 | 51±2.2***                    | (0.30–0.55)                 |
|          | 1                   | 56±3.1***                    |                             |
| Control | —                   | 30±1.5                       |                             |
| Azaperone | 0.1               | 33±2.2                       |                             |
|          | 0.2                 | 45±2.6***                    | 0.32                        |
|          | 0.5                 | 53±3.8***                    | (0.26–0.42)                 |
|          | 1                   | 66±4.1***                    |                             |

Groups of 10 mice were used. ED50 values were calculated from the number of mice which slept more than 2 times as long as the mean sleeping time of the control. The drugs were administration 30 min before pentobarbital-Na (40 mg/kg, i.p.). ***P<0.001, significantly different from the control.

| Drugs   | Doses (mg/kg, s.c.) | No. of fighting episodes (mean±S.E.) before | 0.5 | 1 | 3 hr^a |
|---------|---------------------|---------------------------------------------|-----|---|-------|
| Control | —                   | 11.5±0.6                                    | 10.8±0.7 | 10.5±0.8 | 10.1±0.9 |
| Mafoprazine | 0.5               | 11.9±0.5                                    | 8.5±0.6* | 8.4±0.8 | 10.6±0.6 |
|          | 1                   | 11.6±0.8                                    | 9.1±1.0 | 7.5±0.9* | 10.3±0.6 |
|          | 2                   | 11.7±0.6                                    | 7.0±1.2* | 6.6±0.9* | 9.9±1.1 |
|          | 5                   | 11.6±0.4                                    | 4.9±0.7*** | 4.1±0.9*** | 9.5±0.6 |
| Azaperone | 0.2               | 11.6±0.6                                    | 9.7±0.7 | 10.1±0.8 | 10.4±0.1 |
|          | 0.5                 | 11.9±0.6                                    | 5.4±0.8** | 7.2±0.9* | 11.3±0.5 |
|          | 1                   | 11.7±0.6                                    | 5.7±0.9** | 6.8±0.7** | 10.2±1.1 |
|          | 2                   | 11.6±0.5                                    | 4.5±0.9*** | 7.3±1.0* | 9.9±0.9 |

^aTime after administration of the drugs. Groups of 10 paired mice were used. The paired mice were given electroshock (DC, 400V, 2 mA, 2 msec, 0.25 Hz) via an electrifiable grid floor for 3 min. The pairs which exhibited at least 10 fighting episodes were selected for the test. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control.
1) Electroshock-induced fighting behavior: Mafoprazine and azaperone dose-dependently inhibited the electroshock-induced fighting behavior in mice at 1 mg/kg, s.c., or more and 0.5 mg/kg, s.c., or more, respectively, with ED50 values of 1.99 (1.39–3.11) mg/kg, s.c., and 0.88 (0.56–1.53) mg/kg, s.c., respectively. The activity of the former was about 1/2 that of the latter (Table 3).

2) Long-term isolation-induced aggressive behavior: Mafoprazine and azaperone, when administered to mice at 0.1 mg/kg or more, dose-dependently inhibited their long-term isolation-induced aggressive behavior. The effect developed 0.5 hr after administration, but disappeared 3 hr after administration in both cases. The ED50 values calculated from the number of mice which showed inhibition of their aggressive behavior at 1 hr after administration were 0.28 (0.16–0.46) mg/kg, s.c., for mafoprazine and 0.14 (0.06–0.21) mg/kg, s.c., for azaperone. Thus, a comparison between the activities of the two drugs in terms of ED50 indicated that the activity of the former was about 1/2 that of the latter.

5. Effect on hyperemotionality and muricide in bilaterally olfactory bulbectomized rats

Mafoprazine and azaperone dose-dependently inhibited the hyperemotionality in bilaterally olfactory bulbectomized rats at 2 mg/kg, s.c., or more and 1 mg/kg, s.c., or more, respectively. Mafoprazine and azaperone dose-dependently inhibited the muricide at 2 mg/kg, s.c., and 1 mg/kg, s.c., or more, respectively. Both drugs demonstrated their maximum effects on hyperemotionality and muricide at 0.5 to 1 hr after administration, respectively. Azaperone showed a tendency to have a slightly stronger effect on hyperemotionality and muricide than mafoprazine (Figs. 2 and 3).

6. Effect on gross behavior in dogs

The three beagle dogs used had all shown aggressive or defensive behavior involving the assumption of a strongly defensive posture against observers, biting, barking and assuming an offensive posture. When administered to these violent dogs at 0.2 mg/kg, s.c., mafoprazine demonstrated an inhibitory effect on their behavior, which developed within 30 min after administration and lasted for about 3 hr. At a dose of 1 mg/kg, s.c., mafoprazine caused sedation within 15 to 30 min after administration and made the dogs draw their noses close to an introduced object such as a hand or a bar, held out at an opened door in their cages for sniffing with no defensive or offensive posture assumed, which allowed them to be touched. At 3 hr after treatment, the effect still remained, although the dogs showed a slight increase in behavior. During this period of time, the dogs sometimes assumed a prone posture, but showed no catalepsy. During the first 3 hr
after administration, the dogs occasionally showed slight vomiting. Azaperone at 0.2 and 1 mg/kg, s.c., caused them to behave in almost the same manner as in the case of mafoprazine in the corresponding doses, except that, unlike the latter, the former induced mild catalepsy at both doses and frequent vomiting over more than 3 hr at 1 mg/kg, s.c.

7. Effect on DRL response

Mafoprazine, azaperone and chlorpromazine all dose-dependently caused changes in the DRL response parameters such as the number of responses, number of reinforcements, mean IRT and response efficiency. Each of the drugs resulted in a decreased number of responses, decreased number of reinforcements, prolonged mean IRT and lowered response efficiency at maximum dose (Fig. 4). The IRT distribution at the maximum dose of each of the drugs was flat and shifted to the right.

8. Cataleptogenic activity

Mafoprazine and azaperone, when administered to rats at 5 mg/kg, s.c., or more and 1 mg/kg, s.c., or more, respectively, dose-dependently showed cataleptogenic activities 1 hr after administration, giving respective ED50 values of 9.1 (5.8–15.8) and 2.4 (1.3–8.8) mg/kg, s.c.

9. Effect on motor coordination

Both mafoprazine and azaperone, when administered to mice at 2 mg/kg, s.c., or more, dose-dependently produced the motor incoordination at 0.5 hr after administration, giving respective ED50 values of 4.9 (3.7–7.0) mg/kg, s.c., and 3.7 (2.6–5.0) mg/kg, s.c. Mafoprazine at the maximum dose of 10 mg/kg, s.c., no longer showed the motor incoordination at 1 hr after administration, while azaperone still had such an effect in 6 out of 10 mice at 1 hr after administration at 5 or 10 mg/kg, s.c.

Both mafoprazine and azaperone, when administered to rats at 0.5 mg/kg, s.c., or more, dose-dependently produced the motor incoordination at 0.5 hr after administration, giving respective ED50 values of 2.3 (1.5–3.5) mg/kg, s.c., and 1.8 (1.2–2.8) mg/kg, s.c.

Discussion

The effect of mafoprazine was studied from the viewpoint of behavioral pharmacology, and the results obtained were compared with those for azaperone.

In the acute toxicity study using mice, death from mafoprazine was observed at 300 mg/kg, s.c., or more. Such mice developed almost the same symptoms as azaperone-treated mice, showing decreased spontaneous motor activity, ptosis, decreased body temperature, lost of righting reflex and inhibited respiration, before eventual death caused by respiratory paralysis within 24 hr.
after administration. The symptoms developed in mafoprazine-treated mice, however, were mainly characterized by lowered muscular tonus, while those of azaperone-treated mice showed increased muscular tonus and clonic convulsion. A comparison of the LD50 values between the two drugs suggests that the acute toxicity of mafoprazine in mice is slightly stronger than that of azaperone.

Mafoprazine inhibited spontaneous motor activities in mice at 0.5 mg/kg, s.c., or more and prolonged the duration of pentobarbital anesthesia in mice at 0.2 mg/kg, s.c. These effects of the drug were not considered to be a secondary action resulting from its behavioral toxicity because such effects were produced by low doses compared to those which produced motor incoordination in mice (the difference of which was equivalent to about 1/13 in terms of their ED50 ratio).

Mafoprazine and azaperone inhibited the fighting behavior in mice caused by electrical stimulation of plantar regions at 1 mg/kg, s.c., or more and 0.5 mg/kg, s.c., or more, respectively. The fact that mafoprazine produced

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**Fig. 4.** Effect of mafoprazine, azaperone and chlorpromazine on DRL response in rats. Each index is expressed as the average ratio of the value of the 1 hr post-administration period to that of the 1 hr pre-administration period. Abbreviations: MPZ, mafoprazine; APR, azaperone; CPZ, chlorpromazine. *P<0.05, **P<0.01, ***P<0.001, significantly different from the control [Student's t-test].
motor incoordination in mice at 2 mg/kg, s.c., suggests that the electroshock-induced fighting behavior-inhibiting effects of mafoprazine are probably based on its motor activity disordering action. However, since there is also a report pointing out the inadequacy of the method mentioned above as an indicator for evaluating the taming effect of drugs in rats (11–13), the results obtained for mafoprazine may not satisfactorily reflect this drug's taming effect. Neuroleptic and anti-anxiogenic drugs exhibit relatively selective inhibition of aggressive behavior in long-term isolated mice (14, 15), although anti-depressants are lacking in the specificity of their action on such behavior (16). Mafoprazine inhibited the long-term isolation-induced aggressive behavior in mice at 0.1 mg/kg, s.c., or more. Since this effect was produced at doses well below those causing motor incoordination (the difference of which was equivalent to about 1/18 in terms of the ED50 ratio), it was not considered to a secondary action resulting from its behavioral toxicity.

Both mafoprazine and azaperone inhibited hyperemotionality and muricide in bilaterally olfactory bulbectomized rats. Neuroleptic and anti-anxiogenic drugs inhibited both hyperemotionality and muricide developed in bilaterally olfactory bulbectomized rats (17), although requiring such large doses as to cause ataxia or catalepsy, especially for sufficient inhibition of muricide (5), while anti-depressants are assumed to have little effect in hyperemotionality (18), selectively inhibiting muricide (6, 11, 12). Mafoprazine showed the same action as neuroleptic and anti-anxiogenic drugs.

Both mafoprazine and azaperone at 0.2 and 1 mg/kg showed marked taming and tranquilizing effects in violent dogs which showed marked defensive and offensive behavior involving the assumption of a very defensive posture, biting, barking and assuming an offensive posture. The above results suggested that mafoprazine had the same tranquilizing and taming effects as azaperone both qualitatively and quantitatively.

The experiment involving operant behavior in rats reported that their DRL responses were accelerated by chloridiazepoxide when applied at low doses, developing excitatory symptoms in them, with an increased number of responses, shortened mean IRT and left-shifted IRT distribution; and these responses were inhibited by the same drug when applied at high doses, with a decreased number of responses, prolonged mean IRT and right-shifted IRT distribution (19, 20). On the other hand, chlorpromazine, displayed a dose-dependent operant behavior-inhibiting effect with a decreased number of DRL responses, prolonged mean IRT and right-shifted IRT distribution (21, 22). In comparison with the above two drugs, the action of mafoprazine and azaperone on operant behavior in rats was almost similar to that of chlorpromazine which showed a non-specific DRL response inhibiting effect. The above results indicate that the effect of mafoprazine on operant behavior in rats is similar to those of neuroleptic drugs. On the other hand, the cataleptogenic activity of mafoprazine, considered to reflect a side effect of neuroleptic drugs, developed in rats only very weakly at an intensity of about 1/4 that caused by azaperone. This suggests that azaperone causes the development of extrapyramidal symptoms at a higher rate and more intensively than mafoprazine when applied in doses sufficient to develop their respective medicinal effects. In addition, the fact that azaperone showed little difference between its ED50 values for cataleptogenicity and motor incoordinating action suggests that the cataleptogenicity of this drug reflects its motor incoordinating action. On the other hand, mafoprazine caused the catalepsy at about four times higher dose than that producing the motor incoordination, suggesting a possible qualitative difference between extrapyramidal symptoms caused by azaperone and mafoprazine.

The results obtain in this study suggest that mafoprazine has aggressive behavior-inhibiting, taming and tranquilizing effects. The present study also suggests that mafoprazine has almost the same effect on operant behavior as existing neuroleptics, allowing this drug to be considered as an aggressive behavior-inhibiting drug.
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