PHARMACOLOGICAL STUDIES ON TRIAZINE DERIVATIVES V.
SEDATIVE AND NEUROLEPTIC ACTIONS OF 2-AMINO-4-[4-(2-HYDROXYETHYL)-PIPERAZIN-1-YL]-6-TRIFLUOROMETHYL-S-TRIAZINE (TR-10)

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Abstract—Pharmacological properties of 2-amino-4-[4-(2-hydroxyethyl)-piperazin-1-yl]-6-trifluoromethyl-s-triazine (TR-10) were investigated in mice and rats. Chlorpromazine served as a reference compound. TR-10 expressed in general the pharmacological profiles as neuroleptics ascertained by anti-methamphetamine activity, suppression of conditioned avoidance response, taming effects, decrease in exploratory behavior and cataleptogenic activity. Among these effects, anti-methamphetamine action was most potent. Different from chlorpromazine, TR-10 showed a similar pharmacological activity pattern in the intraperitoneal and oral routes of administration as depicted from ED50/LD50 values. Although the effects relevant to neuroleptics were less potent than chlorpromazine, such were seen with TR-10 at lower doses than those causing muscle relaxation. TR-10 significantly depressed the spontaneous motor activity but showed no anti-convulsant action in mice. Hypothermic action, potentiating effects of hypnotics and α-adrenergic blocking action, characteristic to chlorpromazine, were very weak for TR-10. TR-10 also showed low toxicity in mice (LD50 = 820 mg/kg p.o., 465 mg/kg i.p.) compared with that of chlorpromazine (LD50 = 370 mg/kg p.o., 228 mg/kg i.p.).

Since the discovery of chlorpromazine (1) or haloperidol (2), a large number of their derivatives has been synthesized and widely used for clinical treatment of schizophrenia.

Neuroleptics exhibit cataleptogenic, anti-methamphetamine (amphetamine), conditioned avoidance response depressant and other pharmacological actions in animals and these properties are often used for predicting neuroleptic actions of the compounds (3).

In the course of investigation with triazine derivatives which possessed central nervous system depressant action (4), 2-amino-4-[4-(2-hydroxyethyl)-piperazin-1-yl]-6-trifluoromethyl-s-triazine (TR-10) was considered to have a sedative action accompanied by cataleptogenic and anti-methamphetamine activities in mice.

Although there have been many reports concerning the pharmacological actions of triazine derivatives (5–7), little has been known about the neuroleptic actions of triazine derivatives.

The present study deals with the pharmacological actions of TR-10 and
such are compared with those of chlorpromazine. The chemical structure of TR-10 is shown in Fig. 1.

MATERIALS AND METHODS

Male mice of ddY-strain, weighing 20 to 23 g and male rats of Wistar-strain, weighing 200 to 250 g were used in the present experiments.

Acute toxicity in mice

Each group included 8 to 10 mice. Drugs were administered intraperitoneally (i.p.) and orally (p.o.). Lethality and gross behavior were observed for 72 hr. The LD50 and confidence limits were calculated according to the method of Litchfield and Wilcoxon (8).

Spontaneous motor activity in mice

Five mice were used per each dose level. Locomotor activity was measured for 10 min by ANIMEX activity meter (Ab Farad). Drugs were administered 30 min (i.p.) or 60 min (p.o.) before measurement and the ED50 was defined as the dose that reduced the locomotor activity to 50% of control value.

Exploratory behavior in rats (open-field test)

The open field is a square box (100 × 100 cm, 40 cm in height) the bottom and wall of which were painted black. The apparatus was placed in a dark room illuminated by a 100 W lamp situated 100 cm above the central part of the field. Seven rats were used per each dose level and drugs were administered i.p. 30 min before observation. The performance of the rats in the open field was observed for 3 min and the number of ambulations and rearings was calculated.

Cataleptogenic activity (9)

Cataleptogenic activity in mice: Each group included 7 mice and drugs were administered 30 min (i.p.) or 60 min (p.o.) before testing catalepsy. Forepaws were put on a horizontal steel bar, 5 cm in height, and mice were forced to maintain an abnormal position. When the mice could keep the same posture for over 30 sec, it was interpreted as drug effect (positive response). The ED50 was the dose that caused catalepsy in 50% of the mice treated.

Cataleptogenic activity in rats: Each group included 7 rats and the catalepsy was measured according to the method described in (9) until 6 hr after drugs (i.p.). The height of the horizontal bar was 8 cm.

Anti-methamphetamine activity

Antagonism of methamphetamine-induced hypermotility in mice: Six mice were used per each dose level. Methamphetamine (5 mg/kg i.p.) was administered 30 min after drugs and 30 min thereafter, the locomotor activity was measured for 10 min using an ANIMEX activity meter. The ED50 was the dose that depressed the hypermotility of the control group to 50%.

Methamphetamine-induced stereotyped behavior in rats (10): Each group of 5–6 rats was given drugs (i.p. or p.o.) and 30 min later, the same rats were treated with 5 mg/kg s.c.
of methamphetamine. At least 30 min prior to experiments, rats were individually placed in the observation cages and allowed to adapt to the observation room. The cage was clear plastic (25 x 20 x 16 cm), open on top and with a wire mesh cover. Stereotyped behavior was observed at 30, 60, 120, 180 and 240 min after methamphetamine injection. Each animal was assigned a stereotyped score of 0 to 6, and the description of each rating score was given as follows:

Scoring system for methamphetamine-induced stereotyped behavior.

<table>
<thead>
<tr>
<th>Description of stereotyped behavior</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asleep, lying down, eyes closed.</td>
<td>0</td>
</tr>
<tr>
<td>Inactive, eyes open.</td>
<td>1</td>
</tr>
<tr>
<td>Grooming.</td>
<td>2</td>
</tr>
<tr>
<td>Moving around the cage.</td>
<td>3</td>
</tr>
<tr>
<td>Sniffing.</td>
<td>4</td>
</tr>
<tr>
<td>Licking or repetitive head and foreleg movement</td>
<td>5</td>
</tr>
<tr>
<td>Biting or gnawing</td>
<td>6</td>
</tr>
</tbody>
</table>

Conditioned avoidance response in rats

Five rats per each dose level were used. Each rat was trained in the two-compartment shuttle box for 30 trials a day. The training schedule was as follows: a light and buzzer (80 db) was used as conditioned stimulus (CS). Five sec after CS, the grid floor on the lighted compartment was electrified for an additional 5 sec as an unconditioned stimulus (US). When the rat avoided or escaped into another compartment during CS or US, CS was again delivered 25 sec after. After 10 days training, the rat which showed more than 80% conditioned avoidance response (CAR) was selected for the present experiments. CAR was tested 30, 60, 120, 180 and 240 min after drugs.

Long-term isolation-induced fighting in mice

Mice were isolated in individual cages (15 x 10 x 15 cm) for 6 to 7 weeks and pairs of mice which fought with each other during 1 min period of observation were selected for use. Mice were treated with drugs (6 pairs of mice per each dose level) and tested for fighting episodes 30, 60 and 120 min thereafter. Fighting behavior was considered to be depressed when a pair of mice had a fighting score below 2. The ED50 was the dose that depressed the fighting behavior in 50% of the pairs of mice treated. Fighting behavior was observed for at least 10 min. Scoring system for the estimation of fighting behavior was given as follows:

0: The animals showed no interest in each other.
1: Frequent nosing and tail rattling.
2: The animals showed a readiness to fight and occasionally attacked their partners.
3: Fighting behavior with biting.
4: Continued fighting with biting and squeaking.

Foot-shock-induced fighting in mice

Pairs of mice were placed within a large beaker (300 ml) and footshocked through the
grid floor with a current of 7 mA at 100 V. Prior to experiments, pairs of mice showing one or more episodes of fighting during the first 60 sec exposure to footshock were selected for drug treatment. Five pairs were used for each dose level and drugs were administered 60 min before exposure to footshock. Footshock was delivered for 2 min and the number of fighting incidences was calculated. The ED50 was taken as the dose which depressed the number of fighting incidences to 50% of the control values.

Muscle relaxant action (Traction test in mice) (11)
Each group included 8 mice. The forepaws were placed on a horizontal wire bar, 30 cm in height. A normal mouse grasped the wire with forepaws and when allowed to be free, placed hind feet on to the wire within 5 sec. Failure to place hind feet within 5 sec indicated that the drug administered had a muscle relaxant action. Drugs were administered 30 or 60 min before testing and the ED50 was defined as the dose which caused muscle relaxation in 50% of the mice tested.

Hypothermic action in mice
Change in rectal temperature was measured at 30 min intervals for 4 hr after the i.p. administration of drugs in a room conditioned to 23°C. Six mice were used per each dose level and the rectal temperature was calculated by an electronic thermister (Nihon Kohden, MG III-A).

Pentobarbital sleeping time prolongation effect
Mice (8 mice per each dose level) were given pentobarbital (45 mg/kg i.p.) 30 min after drugs (i.p.). The time interval between the loss of righting reflex and the recovery of reflex was recorded for each mouse. The average sleeping time was determined and significance of the difference between the drug treated and the control group was determined.

Maximal electroshock convulsion in mice
Maximal electroshock was induced by shocking mice (8 mice per each dose level) via a pair of ear electrodes with a current intensity of 30 mA and shock duration of 0.2 sec. The electroshock was given 30 min after administration of the drugs. The ED50 was taken as the dose which prevented tonic hind limb extension in 50% of the mice tested.

Acetic acid-induced writhing in mice (12)
Eight mice per each dose level were used. Thirty min after drug dosing, 0.6% acetic acid was given i.p. (0.1 ml/10 g) and the number of writhings was measured for 20 min. The ED50 was taken as the dose that depressed the number of writhings to 50% of the control value in all mice.

α-Adrenergic blocking action in isolated vas deferens of guinea pig
Isolated vas deferens was mounted in a 10 ml organ bath and contraction was registered with a strain gauge transducer (Nihon Kohden, SB-1T). Adrenaline $10^{-5}$ g/ml was used as the agonist. The results were expressed as the concentration (ED50) reducing the induced contraction by 50%. Drugs were introduced 5 min before adrenaline.

Drugs
TR-10 (2-amino-4-[4-(2-hydroxyethyl)-piperazin-1-yl]-6-trifluoromethyl-s-triazine),
chlorpromazine (Shionogi), methamphetamine (Dainippon), pentobarbital (Dainippon), aminopyrine (Sanko), adrenaline (Sankyo), phentolamine (Tokyo Kasei) were used.

RESULTS

Acute toxicity and gross behavior in mice

As shown in Table 1, acute toxicity of TR-10 was significantly lower than that of chlorpromazine. TR-10 showed marked neurological defects such as ataxia, prostration, catalepsy and muscle relaxation without loss of righting reflex at 300 mg/kg i.p. and 600 mg/kg p.o.. At lethal doses, salivation, twitch, tremor and death due to clonic convulsion occurred. At low doses ranging from 10 to 30 mg/kg i.p. or p.o., TR-10 exhibited sedation with mild catalepsy and decrease in locomotor activity but palpebral ptosis, hypothermia and muscle relaxation were not observed. On the other hand, with chlorpromazine administration, strong sedation accompanied by ataxia, catalepsy, muscle relaxation, palpebral ptosis, hypothermia and dullness at 5 to 10 mg/kg i.p. were evident.

<table>
<thead>
<tr>
<th>Pharmacological profiles</th>
<th>TR-10</th>
<th>Chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p.o.</td>
<td>i.p.</td>
</tr>
<tr>
<td>Acute toxicity</td>
<td>820(766-880)*</td>
<td>465(408-530)</td>
</tr>
<tr>
<td>Spontaneous motor activity</td>
<td>13.5(7.8-13.2)</td>
<td>12.0(7.5-19.2)</td>
</tr>
<tr>
<td>Traction test</td>
<td>82(51-133)</td>
<td>40(27-66)</td>
</tr>
<tr>
<td>Catalepsy</td>
<td>27(16-46)</td>
<td>14(6-34)</td>
</tr>
<tr>
<td>Methamphetamine antagonism</td>
<td>24(15-38)</td>
<td>8.8(5.1-15.8)</td>
</tr>
<tr>
<td>Isolation mice fighting</td>
<td>18(10-31)</td>
<td>9.0(4.5-18)</td>
</tr>
<tr>
<td>Foot-shock fighting</td>
<td>26(16-42)</td>
<td>16(8-34)</td>
</tr>
</tbody>
</table>

* Each value indicates 50% effective dose (ED50) and figures in parentheses represent 95% confidence limits.

Spontaneous motor activity in mice

TR-10 depressed spontaneous motor activity at doses ranging from 5 to 30 mg/kg either given p.o. or i.p.. The ED50 for TR-10 was 12 mg/kg i.p. and 13.5 mg/kg p.o.. Compared with the ED50 for chlorpromazine, the potency of TR-10 was about 1/2 (p.o.) and 1/6 (i.p.) that of chlorpromazine (Table 1). When spontaneous motor activity was measured for 4 hr, TR-10 showed the peak depressant effect at 60 min and then gradually recovered to the control level. In contrast, with chlorpromazine, the peak effect was seen at 30 min and depressant action continued longer than that of TR-10 (Fig. 2).

Exploratory behavior in rats (open field test)

As shown in Fig. 3., TR-10 significantly depressed exploratory behavior at the dose of
Fig. 2. Depressant action of TR-10 and chlorpromazine on the spontaneous motor activity in mice. Spontaneous motor activity was observed each time for 10 min.

\[ \text{FIG. 3. Effect of TR-10 and chlorpromazine on exploratory behavior in rats. Vertical bars indicate S.E. } \text{.* Significantly different from control (P<0.05), ** P<0.01.} \]

10 to 20 mg/kg i.p.. Ambulation was somewhat more strongly depressed than rearing. Chlorpromazine almost equally depressed ambulation and rearing at 2.5 to 5 mg/kg i.p..

**Cataleptogenic activity**

*Cataleptogenic activity in mice:* As shown in Table 1, moderate catalepsy in mice was evident after TR-10 and the ED50 was 14 mg/kg i.p. and 27 mg/kg p.o.. At this dose level of TR-10, there was no muscle relaxation while the cataleptogenic activity of chlorpromazine was accompanied by significant muscle relaxation.

*Cataleptogenic activity in rats:* As illustrated in Table 2, TR-10 revealed a weak and delayed onset of cataleptogenic activity compared with that of chlorpromazine. The peak

**TABLE 2.** Cataleptogenic activity of TR-10 and chlorpromazine in rats

<table>
<thead>
<tr>
<th>Compounds</th>
<th>ED50 (mg/kg i.p.) at each time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>TR-10</td>
<td>( \geq 45 ) (1/7)**</td>
</tr>
<tr>
<td></td>
<td>32 (23-45)*</td>
</tr>
<tr>
<td></td>
<td>27 (17-43)</td>
</tr>
<tr>
<td></td>
<td>24 (18-31)</td>
</tr>
<tr>
<td></td>
<td>32 (23-45)</td>
</tr>
<tr>
<td></td>
<td>( \geq 45 ) (2/7)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>7.1 (3.9-12.8)</td>
</tr>
<tr>
<td></td>
<td>6.7 (4.3-10.4)</td>
</tr>
<tr>
<td></td>
<td>6.7 (4.3-12.8)</td>
</tr>
<tr>
<td></td>
<td>7.1 (3.9-12.8)</td>
</tr>
<tr>
<td></td>
<td>5.8 (4.1-8.1)</td>
</tr>
<tr>
<td></td>
<td>8.0 (4.9-10.3)</td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate 95% confidence limits.
** Number of rats with catalepsy/number of rats used.
effect of TR-10 was observed at 3 hr after the injection. Six hr after TR-10, moderate catalepsy occurred only with high doses (45 mg/kg i.p.) and control levels were reverted to after 8 hr. With chlorpromazine, the peak effect was seen at 4 hr after administration and the effect continued longer than that of TR-10.

Anti-methamphetamine activity

Antagonism of methamphetamine-induced hypermotility in mice: As described in Table 1, TR-10 revealed significant anti-methamphetamine activity by both intraperitoneal and oral routes below the dose level that caused muscle relaxation. The ratio of ED50-traction test to ED50-anti-methamphetamine effect was 4.5 (i.p.), 3.4 (p.o.) for TR-10 and 0.57 (i.p.), 1.5 (p.o.) for chlorpromazine. Anti-methamphetamine activity of TR-10 was about 0.6 to 0.7 times that of chlorpromazine.

Methamphetamine-induced stereotyped behavior in rats: Depressant effect of TR-10 and chlorpromazine on the methamphetamine-induced stereotyped behavior is illustrated in Fig. 4. The peak depressant effect of TR-10 was observed at 120 min after methamphetamine by both intraperitoneal and oral routes of administration. In contrast to TR-10, chlorpromazine expressed the peak depressant effect at 90 min (i.p.) and 60 min (p.o.) after methamphetamine. 50% inhibitory dose (ED50) at the peak time was 8.0 mg/kg i.p. (4.0—15.8 mg/kg) for TR-10 and 3.4 mg/kg i.p. (1.4—8.2) for chlorpromazine respectively.

Conditioned avoidance response in rats

As shown in Fig. 5, TR-10 inhibited conditioned avoidance response at the dose of 15

![Fig. 4. Anti-methamphetamine activity of TR-10 and chlorpromazine in rats. Each point represents the mean stereotyped score in 5 animals.](image-url)
FIG. 5. Effect of TR-10 and chlorpromazine on the conditioned-avoidance response in trained rats. Each point represents the mean of 5 animals. Vertical axis indicates inhibition % of conditioned avoidance response.

to 20 mg/kg i.p. and 20 to 40 mg/kg p.o.. TR-10 given i.p., revealed the peak depressant effect at 120 min. In case of oral administration, the 20 mg/kg p.o. dose showed the peak depressant effect at 120 min, while with the 30 and 40 mg/kg p.o. doses, the most potent depressant effect was seen at 4 hr although a plateau was not reached during this experimental period. Chlorpromazine depressed conditioned avoidance response at low doses and almost complete inhibition was observed at 5 mg/kg i.p. and 15 mg/kg p.o..

Long-term isolation-induced fighting in mice

As shown in Table 3, the ED50 values were determined at 30, 60 and 120 min after drugs. TR-10 expressed the lowest ED50 value at 120 min (7.0 mg/kg i.p., 16 mg/kg p.o.), while chlorpromazine showed the peak depressant effect at 60 min. The depressant activity of chlorpromazine was considered to be 4 to 5 times more potent than that of TR-10.

Footshock-induced fighting in mice

Depressant effect of TR-10 for footshock-induce fighting was to some extent weak

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Route</th>
<th>LD50 (mg/kg) at each time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30 min</td>
</tr>
<tr>
<td>TR-10</td>
<td>i.p.</td>
<td>16(10-26)*</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>32(15-70)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>i.p.</td>
<td>2.4(1.3-4.6)</td>
</tr>
<tr>
<td></td>
<td>p.o.</td>
<td>5.0(2.3-11)</td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate 95% confidence limits.
compared with the taming effect for isolation-induced fighting. The potency of TR-10 was about 1/8 (i.p.) and 1/3 (p.o.) that of chlorpromazine (Table 1).

Muscle relaxant action (Traction test in mice)

As shown in Table 1, TR-10 expressed considerably weak muscle relaxant action with the traction test. The ED50 of TR-10 was 40 mg/kg i.p. and 82 mg/kg p.o., respectively. Chlorpromazine, however, had 10 (i.p.) and 4 (p.o.) times a more potent relaxant activity than that of TR-10.

Hypothermic action in mice

Fig. 6 shows the effect of TR-10 and chlorpromazine on the normal body temperature in mice. Slight hypothermic effects of TR-10 were seen at doses of 20 to 40 mg/kg i.p. while chlorpromazine revealed strong hypothermic action at 5 to 10 mg/kg i.p.

Pentobarbital sleeping time prolongation effect

As shown in Table 4, with TR-10 there was a less potentiating effect of pentobarbital than with chlorpromazine. Chlorpromazine had a significant potentiating effect at 2.5 to 5 mg/kg i.p., while with TR-10, doses of 30 mg/kg or over were required to obtain the same effects.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Dose (mg/kg)a</th>
<th>Loss of righting reflex (sec)</th>
<th>Sleeping time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>153±19.3b</td>
<td>30.1±3.73</td>
</tr>
<tr>
<td>TR-10</td>
<td>15</td>
<td>153±15.7</td>
<td>47.0±3.59**</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>103±10.6*</td>
<td>71.0±6.57**</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2.5</td>
<td>122±7.7</td>
<td>106.2±3.15**</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>93.6±14.9*</td>
<td>134.7±14.7**</td>
</tr>
</tbody>
</table>

* Significantly different from control (P<0.05), **P<0.01.
a Drugs were administered intraperitoneally.
b Standard errors of mean (S.E.)
Maximal electroshock convulsion in mice

Neither TR-10 nor chlorpromazine had a protective effect against maximal electroshock convulsion at 50 to 100 mg/kg p.o.

Acetic acid-induced writhing in mice

TR-10 depressed the writhing syndrome at comparatively low doses as described in Table 5. Chlorpromazine also had a potent depressant effect and the potency was about 4 times that of TR-10.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>ED50 (mg/kg i.p.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR-10</td>
<td>4.5 (3.0-6.7)*</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>Aminopyrine</td>
<td>24 (17-34)</td>
</tr>
</tbody>
</table>

* Figures in parentheses indicate 95% confidence limits.

α-adrenergic blocking activity in isolated vas deferens of guinea pig.

TR-10 showed no antagonism against adrenaline-induced contraction of the vas deferens at $10^{-5}$ to $10^{-4}$ g/ml. Chlorpromazine depressed the adrenaline-induced contraction from $10^{-5}$ g/ml and the 50% inhibitory concentration (ED50) was $2.2 \times 10^{-8}$ g/ml.

DISCUSSION

Pharmacological properties of TR-10, a new compound not chemically related to existing classes of psychoactive drugs, were investigated in comparison with those of chlorpromazine.

As shown in Fig. 7, pharmacological activity pattern (ED50/LD50) of TR-10 was characterized by weak muscle relaxant action and close resemblance of the pattern between oral and intraperitoneal routes of administration, while in the case of chlorpromazine, there were considerable differences and pharmacological activity with intraperitoneal admin-

![Fig. 7. Pharmacological activity pattern of TR-10 and chlorpromazine in mice.](image)
istration was many times more potent than with oral administration. These results indicate that TR-10 is more readily absorbed by the oral route.

Anti-methamphetamine action (anti-amphetamine action) is one of the notable characteristics of neuroleptics and the stereotyped behavior induced by methamphetamine or amphetamine is considered to be closely related to the dopaminergic mechanism (13) in the central nervous system. TR-10 showed a pronounced depressant action against methamphetamine-induced hypermotility in mice and stereotyped behavior in rats. While the activity in mice was 0.6 to 0.7 times that of chlorpromazine, TR-10 exhibited anti-methamphetamine action with considerably lower dose levels than that causing muscle relaxation. The ratio of ED50-traction test to ED50-anti-methamphetamine action was 4.5 for TR-10 and 0.57 for chlorpromazine by the intraperitoneal route, 3.4 for TR-10 and 1.5 for chlorpromazine by the oral route, respectively.

Most neuroleptics induced catalepsy in animals and this property is frequently used for evaluating the neuroleptic action (14). TR-10 resulted in catalepsy in mice and the potency was 0.7 (p.o., 60 min) and 0.3 (i.p., 30 min) times that of chlorpromazine.

In contrast to the results in mice, TR-10 had a weak and delayed onset of cataleptogenic effect in rats. Since catalepsy in rats more than in mice is considered to be closely related to clinical effects (15) and potent cataleptogenic action often reflects severe extrapyramidal side effects (16), TR-10 appears to have better properties as a neuroleptic.

Chlorpromazine depressed the conditioned avoidance response and the exploratory behavior at lower doses than those which depressed methamphetamine-induced stereotyped behavior. Conditioned avoidance response and exploratory behavior were also depressed by TR-10 but higher doses were required in comparison with the effective doses of anti-methamphetamine action. Although conditioned avoidance response depressant action is considered specific for neuroleptics (17), newly synthesized compounds exhibited weak or little depressant action against conditioned avoidance response in spite of possessing anti-schizophrenic clinical effects. One such case is Sch 12679 (18), and the other is clozapine (19). Sch 12679 is actually devoid of depressant action and clozapine is effective only at the doses causing muscle relaxation. Although the type of action of TR-10 is considered to be different from that of chlorpromazine or other new compounds, the aforementioned reports indicate that a mild conditioned avoidance response depressant action of TR-10 does not always mean a weak anti-psychotic effect.

TR-10 also depressed fighting in isolated mice and the foot-shock-induced fighting in mice. Inhibitory effect of TR-10 for foot-shock-induced fighting was to some extent weak compared with the marked taming effect seen in isolated mice. These properties which coincide with spontaneous motor activity depressant effects, indicate that TR-10 has a mild anti-anxiety or sedative action.

Other pharmacological properties characteristic to chlorpromazine are potent muscle relaxant, hypothermic, hypnotic potentiating and α-adrenergic blocking actions. Chlorpromazine strongly revealed these effects at the dose level which expressed neuroleptic action. On the other hand, TR-10 showed weak actions as a muscle relaxant and also had
weak hypnotic potentiating effects. Hypothermic action was only slightly observed at 40 mg/kg i.p. and α-adrenergic blocking action was not observed. The LD50 value of TR-10 was about twice that of chlorpromazine. In view of the present results, TR-10 is considered to be a neuroleptic with moderate sedative effect and weak side effects.

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REFERENCES