COMPARISON OF SUSCEPTIBILITIES TO THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON LEVER-PRESS AVOIDANCE RESPONSES BETWEEN MICE AND RATS

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Abstract—Effects of antipsychotic drugs, chlorpromazine, haloperidol and tetrabenazine, on lever-press avoidance responses under Sidman avoidance (response-shock interval=30 sec and shock-shock interval=5 sec) and discriminated avoidance (intertrial interval=25 sec and warning duration=5 sec) situations in male mice of the dd strain were investigated. The results were compared with those in male rats of the Wistar strain. All the drugs tested were administered s.c., and the avoidance responses of the mice and rats were observed for 1 hr after each administration. Chlorpromazine, haloperidol and tetrabenazine suppressed the avoidance responses of the mice and rats in a dose-dependent manner. The susceptibilities of the mice to these drugs were calculated to be 1/5-1/6 as low as those of the rats. However, the potencies of the avoidance-suppressing effects of chlorpromazine, haloperidol and tetrabenazine were estimated to be 1:20:1.3 and 1:18:1.4 by the Sidman avoidance responses in the mice and rats, respectively, and 1:18:1.1 by the discriminated avoidance responses in both the mice and rats. These results suggest that the conditioned lever-press avoidance responses in mice, as well as those in rats, are applicable for the evaluation of antipsychotic drugs.

Conditioned lever-press avoidance responses in Sidman and/or discriminated avoidance situations in rats have usually been utilized to study characteristics of central effects of drugs, in particular antipsychotic drugs (1). This is because antipsychotic drugs specifically suppress the avoidance responses, and the avoidance-suppressing activities correlate well with the clinical potencies and the daily doses in psychotic patients (2, 3). Although mice offer many advantages as experimental animals, there are few reports which have studied the effect of an antipsychotic drug, chlorpromazine, on the discriminated level-press avoidance response in mice (4).

Recently, we (5, 6) demonstrated that the dd strain male mice acquired well the conditioned lever-press avoidance responses in both Sidman and discriminated avoidance situations and that the avoidance responses established were stable for a long time. We (6) also reported that the change in the avoidance responses in mice after diazepam, an antianxiety drug, was almost identical with those in rats. However, it is unclear whether the changes in the lever-press avoidance responses in mice are similar or different to those of rats after antipsychotic drugs.

The purpose of this experiment was to compare susceptibilities to the effects of three different types of antipsychotic drugs, chlorpromazine, haloperidol and tetrabenazine, on conditioned lever-press avoidance responses in Sidman and discriminated avoidance situations.
situations between the dd strain mice and the Wistar strain rats.

Materials and Methods

Animals: The experimental animals were adult male mice of the dd strain and adult male rats of the Wistar strain. These animals were provided by the Institute of Experimental Animal Research, Gunma University School of Medicine. Groups of 8 mice each had been housed in aluminium cages of 30(W) × 20(D) × 10(H) cm with a wooden-flake floor mat. Groups of 4 rats each had been housed in stainless steel wire mesh cages of 45(W) × 25(D) × 20(H) cm. Solid diet (MF: Oriental Yeast Co., Tokyo) and tap water were freely available except during the times of the avoidance test. The breeding room was artificially illuminated by fluorescent lamps on a 12 hr light-dark schedule (light on at 6:00 and light off at 18:00), and the room temperature was regulated to 22±2°C. However, the humidity was not controlled.

When both the mice and rats were 10 weeks of the age, and weighed 30–32 g and 280–300 g, respectively, conditioning of the lever-press avoidance response in either Sidman or discriminated avoidance situation was started.

Apparatus: The operant chambers for mouse, 18(W) × 9(D) × 10(H) cm, and for rat, 25(W) × 20(D) × 19(H) cm, were made of acrylfiber and aluminium boards. A stainless steel lever was set in the right side wall of each chamber. A microswitch attached to the lever could be activated when the mouse and rat pressed the lever with forces of more than 1.5 g and 10 g, respectively. The avoidance-controlling and data-recording apparatus (GT 7705 and GT 7710, respectively; O'hara & Co. Ltd., Tokyo) used in the present experiments for both the mice and rats were the same as those used in our previous experiments (3, 5–7).

Avoidance schedules: The temporal factors of the Sidman avoidance schedule (8) were a response-shock interval=30 sec and a shock-shock interval=5 sec. The shock was an electric current of 100 V, 1 mA, 50 Hz AC, and was given to the animal through the stainless steel floor grid of the operant chamber for 0.3 sec. The indices of the Sidman avoidance response were response rate (lever-presses/min) and shock rate (shocks/min) during the avoidance session of 1 hr.

The temporal factors of the discriminated avoidance schedule (7, 9, 10) were an intertrial interval=25 sec and a warning duration=5 sec. The warning signal was an 800 Hz pure tone from a speaker. The shock was the same intensity and duration with that presented in the Sidman avoidance situation. However, during the conditioning sessions, an escape contingency was inserted in the schedule to enable the animals to rapidly acquire the discriminated avoidance response as mentioned above (7). The indices of the discriminated avoidance response were response rate and avoidance rate (number of correct responses/number of avoidance trials) during the avoidance session of 1 hr.

Each avoidance session consisted of 1 hr per day, and it was held every other day during the conditioning period and every day during the drug testing period. The procedures for the conditioning of the avoidance responses in mice and rats were the same and have been reported in the previous papers (5–7, 10, 11). After a conditioning of 15 sessions, the mice and rats which achieved a shock rate of less than 0.5/min in the Sidman avoidance situation and an avoidance rate of higher than 75% in the discriminated avoidance situation, with a stable response rate, were selected. The drug tests were carried out by using these animals.

All the avoidance tests were held between 9:00–18:00.
Drugs: The drugs tested were chlorpromazine HCl (Contomin Inj.; Yoshitomi Pharm. Co., Osaka), haloperidol (Serenace Inj.; Dainippon Pharm. Co., Osaka) and tetrabenazine HCl (powder; Pfizer-Taito Co., Tokyo). The commercial preparations of chlorpromazine and haloperidol were diluted by a physiological saline vehicle, and tetrabenazine powder was dissolved in the saline vehicle. All the drugs were administered s.c. immediately before the start of the avoidance session, and the avoidance response was observed for 1 hr thereafter. Each administration volume was fixed to 1 ml/100 g body weight for the mouse and 1 ml/kg body weight for the rat. The doses tested (shown in Figs. 1 and 2) were expressed in the salt forms. The drug testing sessions were held once a week, and on the days before, the saline vehicle was administered as the control sessions. On the other days except Sunday, the avoidance response was monitored without administration of the drug or the saline vehicle to check stability of the avoidance response. The order of the drugs tested was chlorpromazine, haloperidol and tetrabenazine, and the doses administered were changed from the lower ones to the higher ones.

Data analysis: The data obtained were statistically analyzed by Student's t-test within the same species. When P values were equal or less than 0.05, they were considered to be significant differences.

In order to compare the susceptibilities of the mice to the avoidance-suppressing effect of the drugs with those of the rats, the doses which increased the shock rate to 1/min in the Sidman avoidance situation and decreased the avoidance rate to 50% in the discriminated avoidance situation were graphically estimated from the dose-effect relation curves for these measurements as mentioned above (3). These doses were considered to be effective doses for suppression of the Sidman and discriminated avoidance responses.

Results

After 15 sessions of conditioning, about 60% and 80% of the mice subjected achieved the critical levels of shock rate of less than 0.5/min in the Sidman avoidance situation and avoidance rate of higher than 75% in the discriminated avoidance situation, respectively. About 90% of the rats subjected achieved the critical levels after the conditioning on both the schedules.

Chlorpromazine, haloperidol and tetrabenazine suppressed the Sidman avoidance response of both the mice and rats, and induced dose-dependent decrease in the response rate and increase in the shock rate (Fig. 1). The response rate was significantly lower as compared with the saline vehicle administered control value when doses of more than 1 mg/kg of chlorpromazine, 0.1 mg/kg of haloperidol and 2 mg/kg of tetrabenazine were administered to the mice and when doses of more than 0.5 mg/kg, 0.025 mg/kg and 0.5 mg/kg, respectively, were administered to the rats. The shock rate was significantly higher as compared with the control value when doses of more than 1 mg/kg of chlorpromazine, 0.1 mg/kg of haloperidol and 1 mg/kg of tetrabenazine were administered to the mice and when doses of more than 0.25 mg/kg, 0.018 mg/kg and 0.25 mg/kg, respectively, were administered to the rats.

Chlorpromazine, haloperidol and tetrabenazine suppressed the discriminated avoidance response of both the mice and rats and induced dose-dependent decrease in the response rate and avoidance rates (Fig. 2). The response rate was significantly lower as compared with the saline vehicle administered control value when doses of more than 2 mg/kg of chlorpromazine, 0.2 mg/kg of haloperidol and 4 mg/kg of tetrabenazine were administered to the mice and when
Fig. 1. Dose-effect relation curves of chlorpromazine (CPZ), haloperidol (HPD) and tetrabenazine (TBZ) for the lever-press Sidman avoidance response in mice (○) and rats (○—○). The mean±S.E.M. of response rate (upper panel) and shock rate (lower panel) of 15–20 animals are plotted. *: Statistically significant difference (P<0.05) as compared with the respective controls (saline, dose=0).

Doses (mg/kg s.c.)

The susceptibilities of the mice to the avoidance-suppressing effects of the drugs tested were calculated to be 1/5.5–1/5.8 and 1/4.7–1/4.9 as low as those of the rats by the Sidman and discriminated avoidance tests, respectively (Table 1). The effective doses for avoidance-suppression of chlorpromazine, haloperidol and tetrabenazine were slightly lower in the Sidman avoidance situation than in the discriminated avoidance situation. However, the ratios for the avoidance-suppressing potencies of chlorpromazine, haloperidol and tetrabenazine were almost the same in the mice and rats in both the Sidman and discriminated avoidance situations, i.e., chlorpromazine: haloperidol : tetrabenazine=1 : 17–20 : 1.1–1.4. The ratios inversely correlated with the daily clinical doses in psychotic patients (12) as shown in Table 1.

Discussion

The main purposes of a behavioral study of a drug are to predict clinical effects such
Fig. 2. Dose-effect relation curves of chlorpromazine (CPZ), haloperidol (HPD) and tetrabenazine (TBZ) for the lever-press discriminated avoidance response in mice (●—●) and rats (○—○). The mean±S.E.M. of response rate (upper panel) and avoidance rate (lower panel) of 15–40 animals are plotted. *: Statistically significant difference (P<0.05) as compared with the respective controls (saline, dose=0).

Table 1. The effective doses for suppression of avoidance responses in mice and rats estimated graphically by dose-effect relation curves for the shock rate and avoidance rate shown in Figs. 1 and 2, respectively.

| Species          | Chlorpromazine | Haloperidol | Tetrabenazine |
|------------------|----------------|-------------|---------------|
| Mice (Sidman)    | 2.4 mg/kg*     | 0.12 mg/kg* | 1.8 mg/kg*    |
|                  | (1)            | (20)        | (1.3)         |
| Rats (Sidman)    | 0.42*          | 0.022*      | 0.31*         |
|                  | (1)            | (18)        | (1.4)         |
| Mice (Discriminated) | 2.9**         | 0.16**      | 2.7**         |
|                  | (1)            | (18)        | (1.1)         |
| Rats (Discriminated) | 0.61**        | 0.034**     | 0.55**        |
|                  | (1)            | (18)        | (1.1)         |

Daily clinical doses: 225–300 mg/man, 5–10 mg/man, 150 mg/man

*: Doses increased the shock rate to 1/min in the Sidman avoidance situation. **: Doses decreased the avoidance rate to 50% in the discriminated avoidance situation. The figures in the parentheses indicate the relative potencies of the avoidance-suppressing effects as an unit of chlorpromazine's effect. Daily clinical doses are taken from ref. (12).
as property, potency, persistence, etc. and to establish appropriate schedules of administration to patients.

It has been well known that the avoidance-suppressing effect of antipsychotic drugs in rats correlate well with the clinical antipsychotic potencies and the daily doses in the patients (2, 3). However, no systematic investigation about the effects of antipsychotic drugs on conditioned avoidance response in mice has been carried out.

The present experiment demonstrates that even though both the mice and rats show almost the same levels of shock rate and avoidance rate, the mice emit a higher baseline response rate than the rats in both the Sidman and discriminated avoidance situations. This result is probably due to a difference in the characteristics between mice and rats, i.e., mice show a higher locomotor activity than rats in general. A gross observation also revealed that the mice emit higher rates of after shock burst response and intertrial response.

However, the present experiment demonstrates that three different types of antipsychotic drugs, chlorpromazine, haloperidol and tetrabenazine, i.e., phenothiazine, butyrophenone and benzoquinolizine derivatives, respectively, suppress both the Sidman and discriminated avoidance responses in the mice as well as in the rats in a dose-dependent manner. These results are consistent with those reported in rats by many investigators (1, 3, 13, 14).

In addition, the dose-effect relation curves of chlorpromazine, haloperidol and tetrabenazine for the shock rate and avoidance rate and the effective doses for suppression of the avoidance responses reveal that the susceptibility of mice to the avoidance-suppressing effects of these drugs is 1/6 as low as those of rats. The species difference in the susceptibility to drugs as well as in the baseline behavior are considered to be due to the difference in the drug metabolizing rates, neural activities etc. A further study is required to elucidate the species difference in the susceptibility to drug effects.

However, the dose-effect relation curves for the shock rate and avoidance rate in mice are almost identical with parallel shifted curves in rats. Moreover, the ratios for the potencies of the avoidance-suppressing effects of chlorpromazine, haloperidol and tetrabenazine estimated by the effective doses for avoidance suppression are almost the same between mice and rats in both the Sidman and discriminated avoidance situations. These ratios also inversely correlated fairly well with the daily doses in psychotic patients (12).

In these respects, it can be concluded that the conditioned lever-press avoidance responses in the Sidman and discriminated avoidance situations in mice, as well as those in rats, are applicable for the preclinical evaluation of antipsychotic drugs.

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