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Correlation between Antiavoidance Activities of Antipsychotic Drugs in Rats and Daily Clinical Doses

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KURIBARA, H. AND S. TADOKORO. *Correlation between antiavoidance activities of antipsychotic drugs in rats and daily clinical doses.* PHARMAC. BIOCHEM. BEHAV. **14**(2) 181–192, 1981.—Effects of oral antipsychotic drugs, 12 phenothiazines, 3 thioxanthenes, 5 butyrophenones and 8 other derivatives on Sidman and discriminated avoidance responses in rats were investigated and compared to their clinical doses routinely used PO. Almost all drugs except sulpiride and clozapine suppressed the avoidance responses with a dose-dependent decrease in the response rate (lever-pressing) and increase in the shock rate in the Sidman avoidance performance or a decrease in both the response and avoidance rates in the discriminated one. Sulpiride (80–640 mg/kg) produced no marked change in the avoidance responses. Clozapine (2.5–10 mg/kg) increased the shock rate or decreased the avoidance rate without eliciting any change in the response rate. The avoidance-suppressing activities of the antipsychotic drugs were well correlated with their clinical daily doses. However, the avoidance-suppressing effects of carpipramine, clocapramine, thiothixene and sulpiride were relatively less potent, while that of clotiapine was more potent than in the clinical activities. The potencies of the avoidance-suppressing effects of each drug on the Sidman and the discriminated avoidance responses were almost identical except for triflupromazine, pimozide, thioridazine, spiclomazine and propericiazine. The former two drugs suppressed the Sidman avoidance response more than the discriminated avoidance response. However, the lattter three drugs suppressed the discriminated avoidance response more markedly than the Sidman avoidance response. The present results suggest that the avoidance response in rats is applicable in evaluating the clinical efficacies of antipsychotic drugs.

Avoidance-suppression Antipsychotic activity Sidman avoidance Discriminated avoidance Antipsychotic drugs Rats

ANTIPSYCHOTIC drugs have characteristic profiles of effects, such as suppression of many animal behaviors including avoidance responding and motor activity. They may produce ptosis and catalepsy effects which are antagonized by amphetamine and/or apomorphine [5, 6, 8, 17, 22, 23, 26, 28, 32, 35]. Cook and Catania [5], Fjalland [17], and Nakamura *et al.* [32] reported that the potencies of these behavioral effects of antipsychotic drugs were highly correlated with their clinical efficacies. Particularly, it has been considered that the antipsychotic drugs specifically suppress the avoidance response [5–8, 15, 18, 21, 23], and that this effect is stronger than the other behavioral effects [23]. Based on these findings, avoidance tests have been employed in the preclinical evaluation of the antipsychotic drugs.

Recently new antipsychotic drugs, which are different from the phenothiazines, thioxanthenes and butyrophenones in chemical structure, have been synthesized, and the number of antipsychotic drugs has increased. Therefore, it may be necessary to reexamine the correlation between the avoidance-suppressing effects of antipsychotic drugs and their clinical efficacies.

In this study, we examined the effects of 28 antipsychotic drugs on two types of avoidance responses in rats, i.e., the Sidman avoidance response [38] and the discriminated avoidance response [20, 25, 28]. The experimental results were compared with their clinical daily doses routinely used.

METHOD

Animals

The animals used were 120 adult male rats of the Wistar strain. This strain has been maintained by brother-sister mating for about 30 years in the breeding colony of Gunma University, Medical School. These rats were moved to our breeding room at 5 weeks of age. Therein, groups of 3–4 rats were housed in stainless steel wire mesh cages of 38 (D)×25(W)×20(H) cm, with free access to a solid diet of MF (Oriental Yeast Co., Tokyo) and tap water except during the experimental sessions. The breeding room was artificially illuminated with fluorescent lamps on a 12 hr light-dark cycle (light period: 6 a.m.-6 p.m., dark period: 6 p.m.-6 a.m.). The

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TABLE 1
DRUGS USED AND DOSAGES GIVEN

Name of Drug	Doses (mg/kg PO) Sidman Avoidance Test	Discriminated Avoidance Test
1. Phenothiazine Derivatives		
Chlorpromazine (Contomin; Yoshitomi)	2.5 - 10	5 - 20
Triflupromazine (Vesprin; Squibb)	0.13- 1	1 - 4
Levomepromazine (Levotomin; Yoshitomi)	4 - 32	2 - 16
Thioridazine (Melleril; Sankyo)	10 - 80	5 - 40
Propericiazine (Neuleptil; Shionogi)	2 - 16	1 - 4
Perazine (Psytomin; Yoshitomi)	5 - 20	5 - 20
Prochlorperazine (Novamin; Shionogi)	1.3 - 5	1.3 - 10
Trifluoperazine (Trifluoperazine; Yoshitomi)	0.5 - 4	1 - 4
Thioproperazine (Cephalmin; Shionogi)	2 - 8	2 - 8
Perphenazine (PZC; Yoshitomi)	1 - 4	1 - 4
Fluphenazine (Anatensol; Squibb)	1 - 4	1 - 4
Spiclomazine (Diceplon; Yoshitomi)	2.5 - 10	1.3 - 10
2. Thioxanthene Derivatives		
Chlorprothixene (Traquilan; Eisai)	1.3 - 10	2.5 - 10
Thiothixene (Navane; Pfizer-Taito)	4 - 16	2 - 16
Flupenthixol (Metamin; Takeda)	2 - 8	2 - 8
3. Butyrophenone Derivatives		
Haloperidol (Cerenace; Dainippon)	0.25- 1	0.25- 1
Pipamperone (Propitan; Eisai)	5 - 20	5 - 20
Spiperone (Spiropitan; Eisai)	0.1 - 0.8	0.1 - 0.8
Moperone (Luvatoren; Yamanouchi)	1 - 8	1 - 4
Droperidol (Droleptan; Sankyo)	0.25- 2	0.13- 1
4. Other Derivatives		
Pimozide (Orap; Fujisawa)	0.25- 2	1 - 4
Clozapine (Bulk form)	2.5 - 10	2.5 - 10
Carpipramine (Defekton; Yoshitomi)	40 -640	160 -640
Clocapramine (Clofekton; Yoshitomi)	20 - 80	10 - 40
Clotiapine (Deliton; Dainippon)	0.25- 2	0.5 - 2
Sulpiride (Dogmatyl; Fujisawa)	80 -640	160 -640
Oxypertine (Forit; Daiichi)	2.5 - 10	2.5 - 20
Tetrabenazine (Bulk form)	2 - 8	2.5 - 10

room temperature was maintained at 23±2°C. However, the humidity was not controlled.

When the rats attained 10 weeks of age and weighed 200–230 g, they were divided at random into two groups of 60 each, and were trained in either the Sidman or the discriminated voidance situation.

Apparatus

Four operant chamber of the same type were used. They were made of acrylfiber and alminium boards with a size of 18 (D)×25(W)×19(H) cm. The floor of the chamber was a grid of stainless steel rods, which was electro-wired to pass an electric current. A lever and a pilot lamp were set in the right side wall of the chamber, at 4 cm and 8 cm, respectively, over the floor grid. The chamber was contained in a wooden sound-attenuating box. During the experimental sessions, the inside of the box was illuminated with a 10 W fluorescent lamp, and fresh air was circulated. The behavior-controlling and -recording apparatus for the Sidman and the discriminated avoidance responses were made of relays, timers and electromagnetic counters (MODEL GT 7705 and GT 7710, respectively, O'hara and Co. Ltd., Tokyo), and were placed in a room adjoined to the experimental room.

Sidman Avoidance Schedule

The schedule consisted of a 30 sec Response-Shock interval and a 5 sec Shock-Shock interval. The shock was an electric current of 150 V, 0.3 mA, 50 Hz AC, and was passed for 0.3 sec through the floor grid. The response was a downward lever-pressing with a force of more than 10 g. During the conditioning period, one session consisted of 1 hr training per day, and was held every other day until the establishment of the behavioral baselines for both the response and shock rates, that is, stable levels of these rates being maintained for more than 5 consecutive sessions. Thereafter, however, the session was lengthened from 1 hr to 2 hr, and

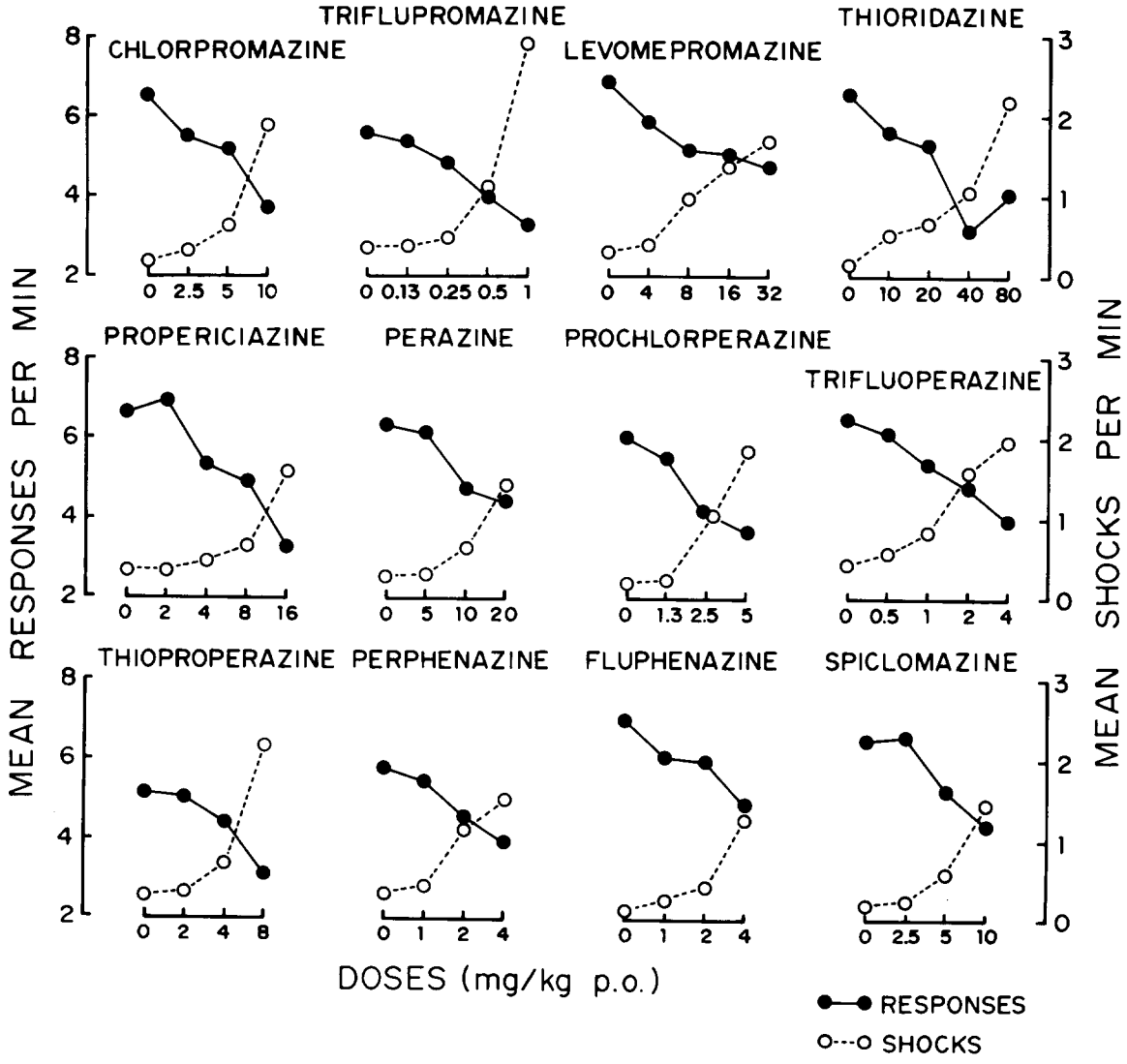

FIG. 1. Dose-effect relation curves of 12 phenothiazine derivatives; chlorpromazine, trifluprom azine, levomepromazine, thioridazine, propericiazine, perazine, prochlorperazine, trifluoperazine, thioproperazine, perphanazine, fluphenazine and spiclomazine, for the Sidman avoidance response in rats. The drugs were given PO immediately before the start of the experiment, and then the rat's avoidance response was observed for 2 hr. The average response (lever-pressing) and shock rates are plotted. Five to eight animals were subjected to each drug test. A dose of zero indicates the saline or carboxymethyl cellulose-Na administration.

was held every day. After the reconfirmation of the baseline stability, the drug tests were started.

Discriminated Avoidance Schedule

The discriminated avoidance schedule used in the present drug tests was a midification of the original procedure of Hoffman *et al.* [20]. Details of this schedule have been described in previous papers [25,28]. The schedule consisted of a 25 sec intertrial interval and a 5 sec warning duration. The warning signals were visual and auditory stimuli generated by the lighting of a pilot lamp and the sounding of an 800 Hz pure tone from a small speaker. The shock was the same intensity and duration as that used in the Sidman avoidance situation. The response was a downward lever-pressing with a force of more than 10 g.

When the rats were trained from the beginning under the present discriminated avoidance situation, however, a long period of training of more than 20 sessions was required for the establishment of the behavioral baselines for the response and avoidance rates, and drop-out cases, which failed to show a high level of the avoidance rate, were sometimes observed [27,28]. In the training sessions, therefore, the maximum duration of the shock presentation was 5 sec, but an excape contingency was considered in the schedule. One session consisted of 1 hr training per day, and was held every other day during the conditioning period. When rats attained a critical level of the avoidance rate (85%), the schedule

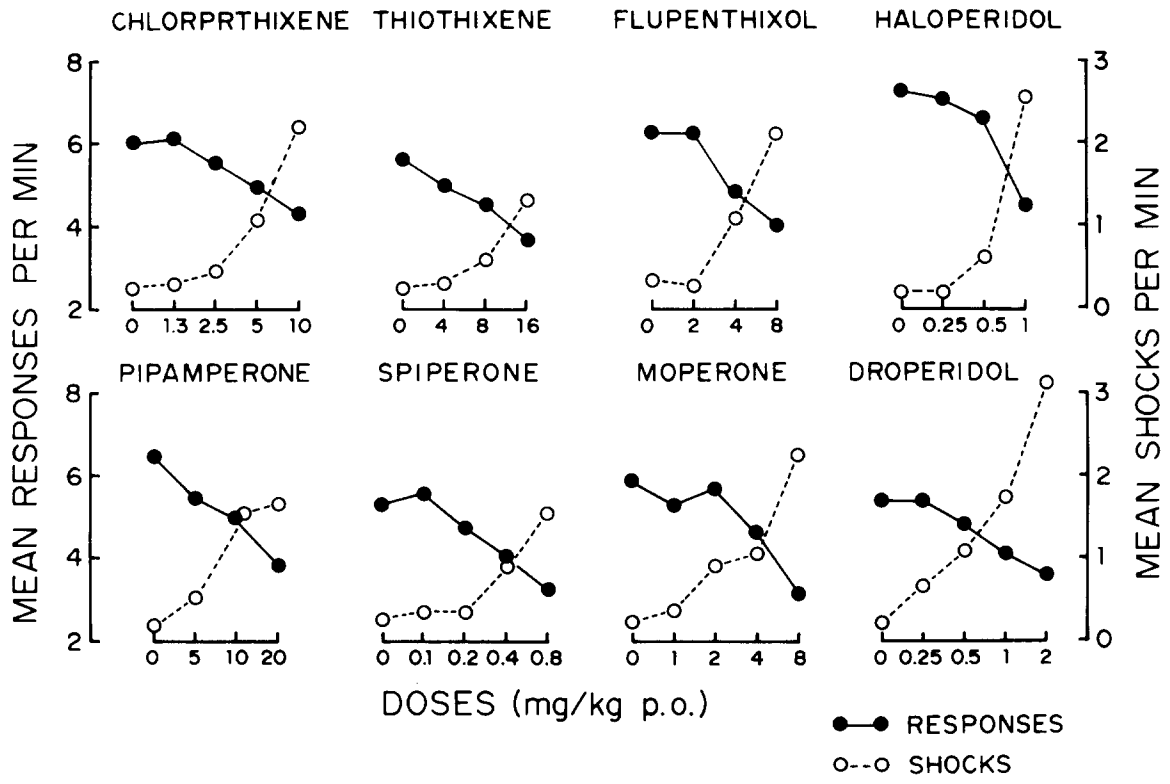

FIG. 2. Dose-effect relation curves of 3 thioxanthene derivatives; chlorprothixene, thiothixene and flupenthixol, and 5 butyrophenone derivatives; haloperidol, pipamperone, spiperone, moperone and droperidol, for the Sidman avoidance response in rats. The data shown as in Fig. 1.

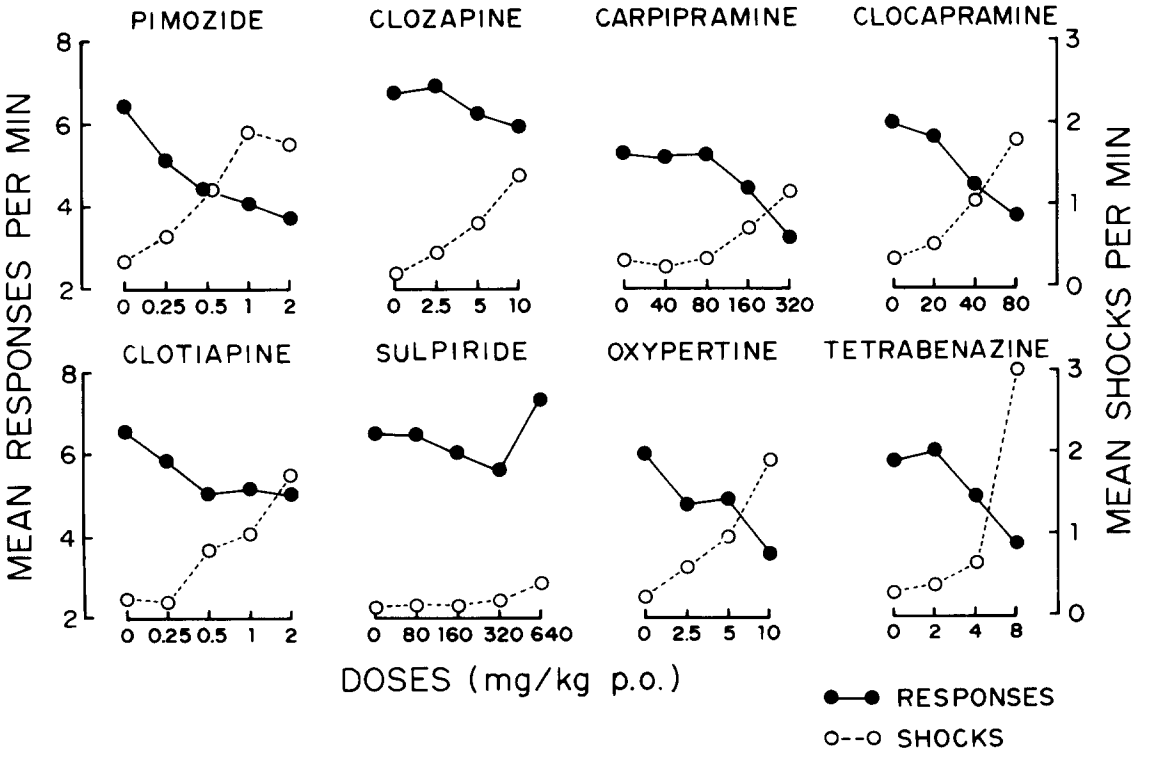

FIG. 3. Dose-effect relation curves of 8 antipsychotic drugs; pimozide, clozapine, carpipramine, clocapramine, clotiapine, sulpiride, oxypertine and tetrabenazine, for the Sidman avoidance response in rats. The data shown as in Figs. 1 and 2.

program was changed to eliminate the escape contingency, and the shock duration was shortened to 0.3 sec. The session was lengthened from 1 hr to 2 hr. After the confirmation of the baseline stability, that is, maintaining stable response and avoidance rates for more than 5 consecutive sessions, the drug tests were started.

Drugs and Experimental Procedures

The drugs used and the dosages given are shown in Table 1. Each dose is expressed in the form of a free base. The commercial preparations of the drugs, except in a few cases, were used without any treatment. Chlorpromazine, triflupromazine, levompromazine, perphenazine, fluphenazine, haloperidol, droperidol and tetrabenazine were dissolved in a physiological saline vehicle, and the other 20 drugs were suspended in a 1% carboxymethyl cellulose-Na (CMC) vehicle. In all cases, a uniform dose volume of 10 ml/kg was prepared in varying concentrations so as to contain the above-mentioned drug amounts. Each dose was administered PO immediately before the sessions, and the rat's avoidance response was observed for 2 hr. The drugs were given at intervals of 4–10 days, and the day before the drug test the same dose volume of saline or CMC vehicle alone was given as the control administration. More than 3 doses, which were geometrically increased, were tested for each drug. The smallest dose had scarcely any effect on the avoidance response, and the highest increased the shock rate to more than 1/min in the Sidman avoidance performance, or decreased the avoidance rate to less than 50% in the discriminated avoidance performance.

Groups of 5–8 rats showing a response rate of 6–8/min and a shock rate of less than 0.4/min under the Sidman avoidance situation, and a response rate of 2.5–4/min and an avoidance rate of more than 85% under the discriminated avoidance situation, were subjected to the drug tests. The same animals received 2–4 drugs. For each drug change, the behavioral baselines were monitored for one week to assess whether or not there were any marked variation in responding levels.

Estimation of the Critical Doses for Suppression of the Avoidance Responses

Doses which increased the shock rate to 1/min in the Sidman avoidance performance, and decreased the avoidance rate to 50% in the discriminated avoidance performance were graphically estimated from the dose-response relation curves for these measurements, and were considered to be the critical doses for suppression of the Sidman and the discriminated avoidance responses, respectively.

RESULTS

Effects of Antipsychotic Drugs on the Sidman Avoidance Response

Figures 1, 2 and 3 show the dose-effect relation curves of 12 phenothiazines, 3 thioxanthenes and 5 butyrophenones, and 8 other derivatives, respectively, for the Sidman avoidance response by plotting the average response and shock rates. Almost all of the drugs suppressed the Sidman avoidance response with dose-dependent decrease in the response rate and increase in the shock rate. However, clozapine increased only the shock rate without a marked change in the response rate. Sulpiride 80–640 mg/kg scarcely affected on the Sidman avoidance response.

The suppressing effects of 28 antipsychotic drugs on the Sidman avoidance response were stronger in the order of pimozide (0.36), droperidol (0.42), triflupromazine (0.43), spiperone (0.46), haloperidol (0.58), clotiapine (0.82), trifluoperazine (1.2), perphenazine (1.7), prochlorperazine (2.4), moperone (2.9), fluphenazine (3.0), flupenthixol (3.6), tetrabenazine (4.4), chlorprothixene (4.5), thioproperazine (4.6), oxypertine (5.5), chlorpromazine (6.0), clozapine (6.2), pipamperone (6.5), spiclomazine (7.1), levomepromazine (9.1), propericiazine (9.9), thiothixene (11.0), perazine (13.2), thioridazine (35.8), clocapramine (36.1), carpipramine (223) and sulpiride (640<). The values in the above parentheses are the critical doses found to suppress the Sidman avoidance response, expressed in the unit of mg/kg.

Figure 4 expresses the correlation between the critical doses for suppression in the Sidman avoidance response estimated from the present experiment and the clinical daily doses routinely used per orally. The result of sulpiride is excluded from the figure. The clinical daily doses are taken from Praag [44] and the others [4, 13, 14, 16, 29, 32, 41]. The straight line and the figures in the panel are the regression line and its slope, and the correlation coefficient calculated by the least square method. There is an excellent positive correlation between the critical doses for suppression in the Sidman avoidance response and the clinical daily doses. However, carpipramine, clocapramine, thiothixene, clotiapine and triflupromazine showed a relatively marked scattering from the regression line.

Effects of Antipsychotic Drugs on the Discriminated Avoidance Response

Figures 5, 6, and 7 show the dose-effect relation curves of 12 phenothiazines, 3 thioxanthenes and 5 butyrophenones, and 8 other derivatives, respectively, for the discriminated avoidance response by plotting the average response and avoidance rates. Almost all of the drugs suppressed the discriminated avoidance response with dose-related decreases in the response and avoidance rates. Changes in the response rate and the avoidance rate were nearly parallel. However, as could be seen in the results of the Sidman avoidance test (Fig. 3), clozapine decreased only the avoidance rate without eliciting a marked change in the response rate. Sulpiride (160–640 mg/kg) did not produce any marked change in the response or avoidance rate.

The suppressing effects of 28 antipsychotic drugs on the discriminated avoidance response were stronger in the order of spiperone (0.34), droperidol (0.70), haloperidol (0.77), clotiapine (0.83), trifluoperazine (1.5), perphenazine (1.5), fluphenazine (1.7), triflupromazine (1.7), moperone (2.2), spiclomazine (2.3), propericiazine (3.3), pimozide (3.3), prochlorperazine (4.3), flupenthixol (4.4), oxypertine (4.8), chlorprothixene (5.2), thioproperazine (5.8), tetrabenazine (5.9), perazine (9.0), clozapine (9.0), levomepromazine (9.6), chlorpromazine (11.0), thiothixene (13.1), thioridazine (13.2), pipamperone (16.6), clocapramine (26.6), carpipramine (485) and sulpiride (640<). The values in the above parentheses are the critical doses found to suppress the discriminated avoidance response, expressed in the unit of mg/kg.

Figure 8. shows the correlation between the critical doses for suppression in the discriminated avoidance response estimated from the present experiment, and their clinical daily doses. The clinical daily doses are the same as those used in

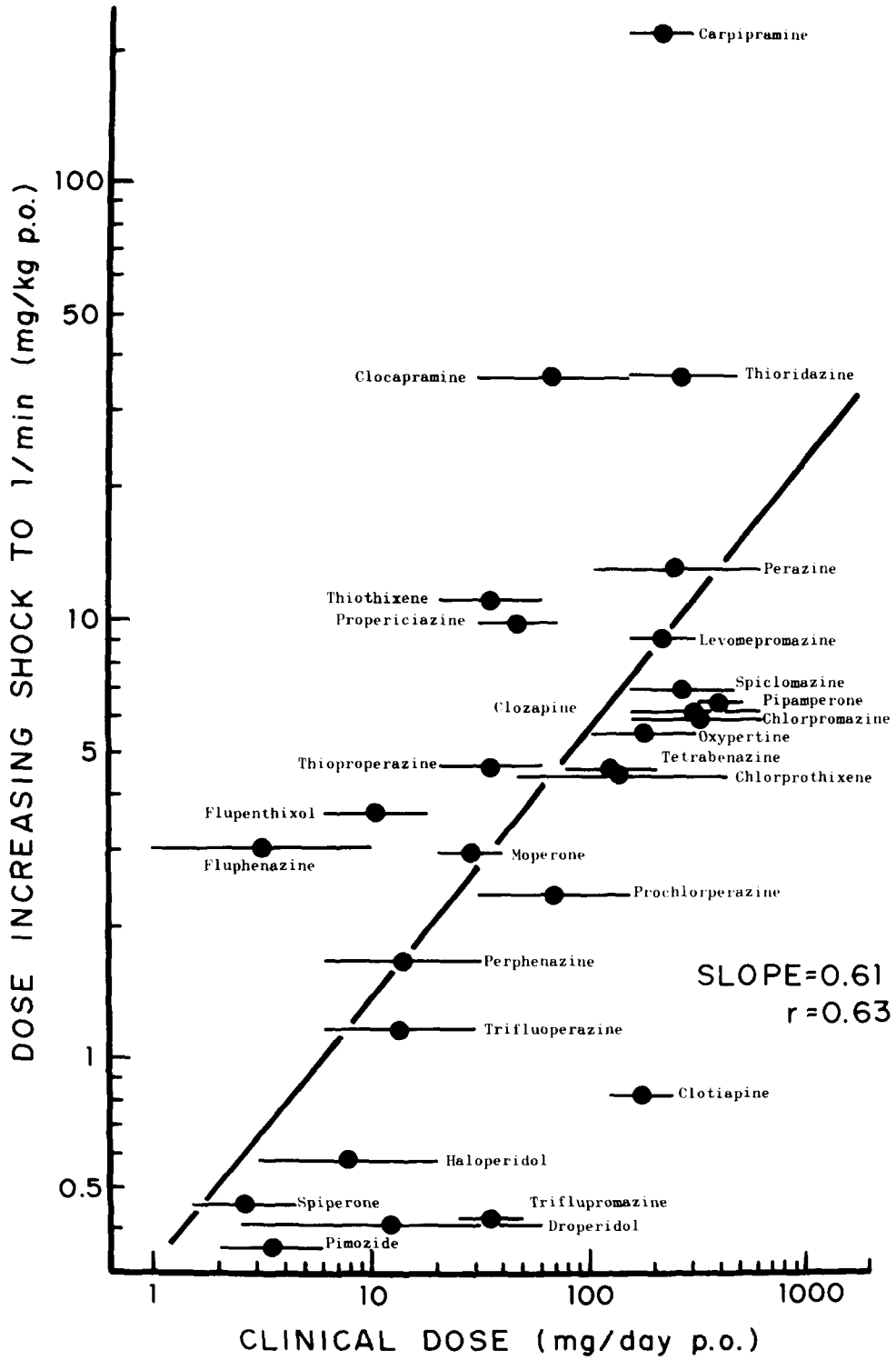

FIG. 4. Correlation between the critical doses for suppression of the Sidman avoidance response of antipsychotic drugs in rats estimated from the present experiment (ordinate) and their clinical daily doses routinely used per orally (abscissa). The straight line and figures in the panel are the regression line and its slope, and the correlation coefficient for these data calculated by the least square method.

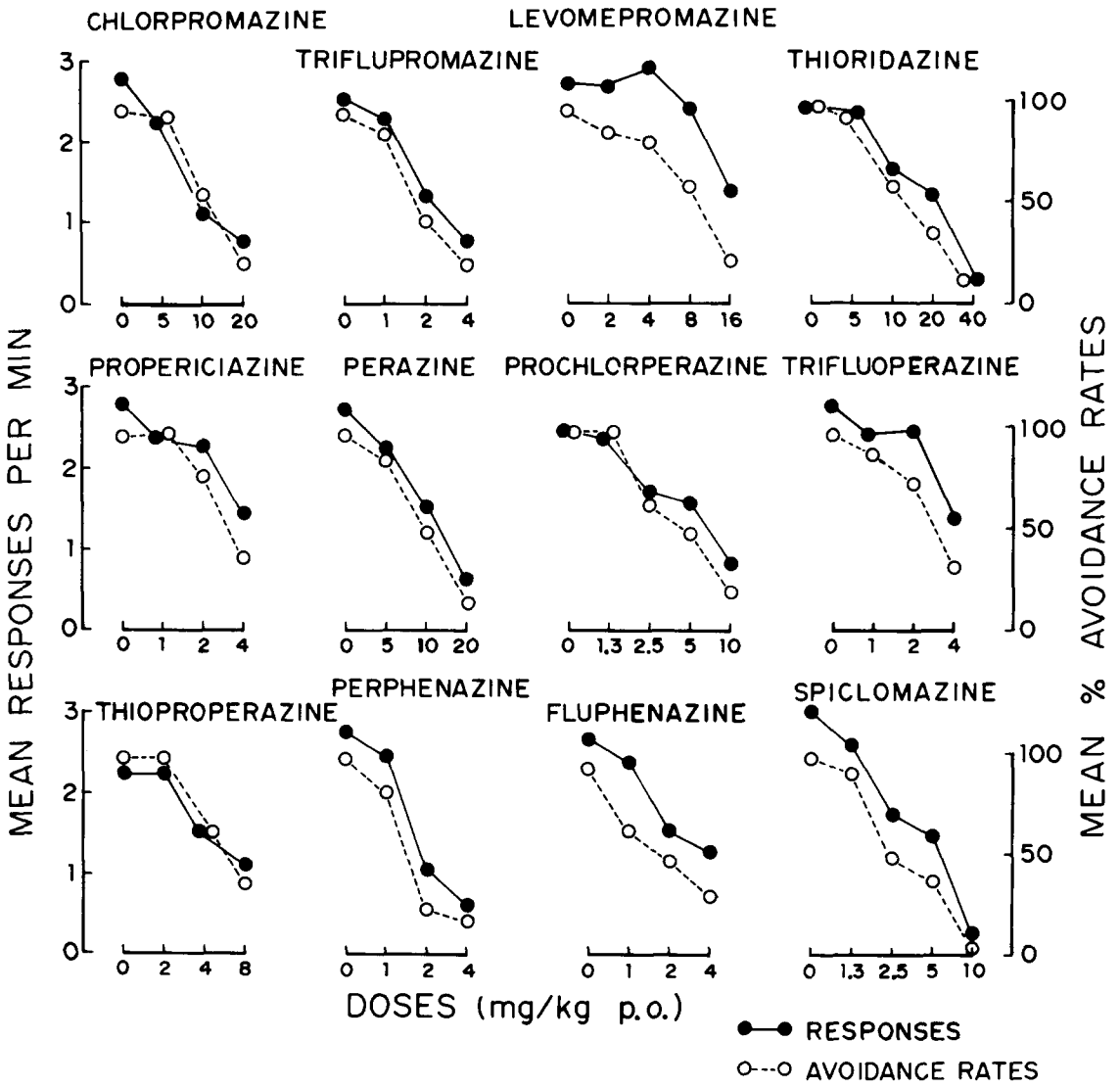

FIG. 5. Dose-effect relation curves of 12 phenothiazine derivatives; chlorpromazine, triflupromazine, levomepromazine, thioridazine, propericiazine, perazine, prochlorperazine, trifluoperazine, thioproperazine, perphenazine, fluphenazine and spiclomazine, for the discriminated avoidance response in rats. The drugs were given PO immediately before the start of the experiment, and then the rat's avoidance response was observed for 2 hr. The average response and avoidance rates are plotted. Five to eight animals were subjected to each drug test. A dose of zero indicates the saline or carboxymethyl callulose-Na administration.

Fig. 4. The result of sulpiride is also excluded from this figure. There is a positive correlation between the critical doses for suppression in the discriminated avoidance response and clinical daily doses. However, as could be observed in the results of the Sidman avoidance test, carpipramine, clocapramine, thiothixene and clotiapine showed a relatively marked scattering from the regression line.

Correlation between the Suppressing Effects of Antipsychotic Drugs on the Sidman and Discriminated Avoidance Responses

Figure 9 is a comparison between the critical doses for the avoidance-suppressing effects of antipsychotic drugs on the Sidman and discriminated avoidance responses. The results of sulpride are not shown in this figure. The critical doses for suppression in both the Sidman and discriminated avoidance responses were almost the same for each drug, and an extremely high level of the correlation coefficient was obtained. However, a few drugs failed to fit the regression line. Here, the suppressing effects of pimozide and triflupromazine on the Sidman avoidance response are estimated 9 and 4 times as potent, respectively, as those on the discriminated avoidance response, while those of spiclomazine, propericiazine and thioridazine on the former response are estimated 0.3–0.4 times as weak as those on the latter task.

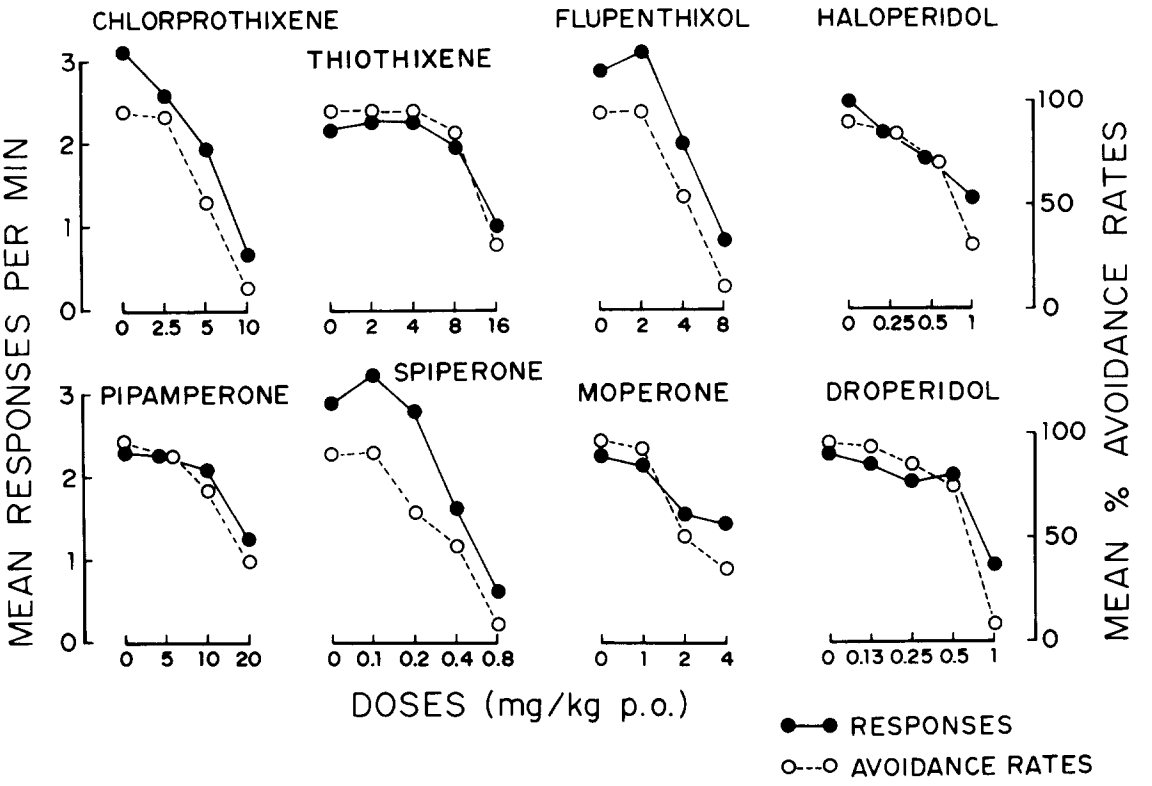

FIG. 6. Dose-effect relation curves of 3 thioxanthene derivatives; chlorprothixene, thiothixene and flupenthixol, and 5 butyrophenone derivatives; haloperidol, pipamperone, spiperone, moperone and droperidol, for the discriminated avoidance response in rats. The data shown as in Fig. 5.

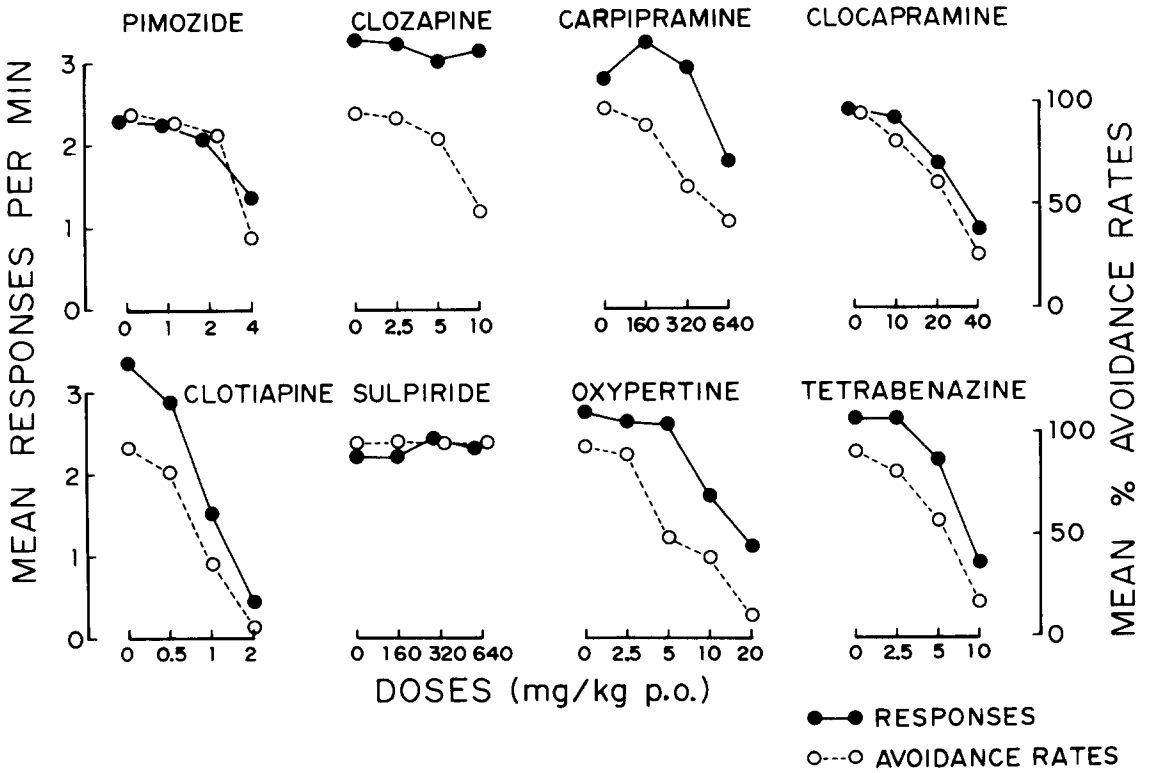

FIG. 7. Dose-effect relation curves of 8 antipsychotic drugs; pimozide, clozapine, carpipramine, clocapramine, clotiapine, sulpiride, oxypertine and tetrabenazine, for the discriminated avoidance response in rats. The data shown as in Figs. 5 and 6.

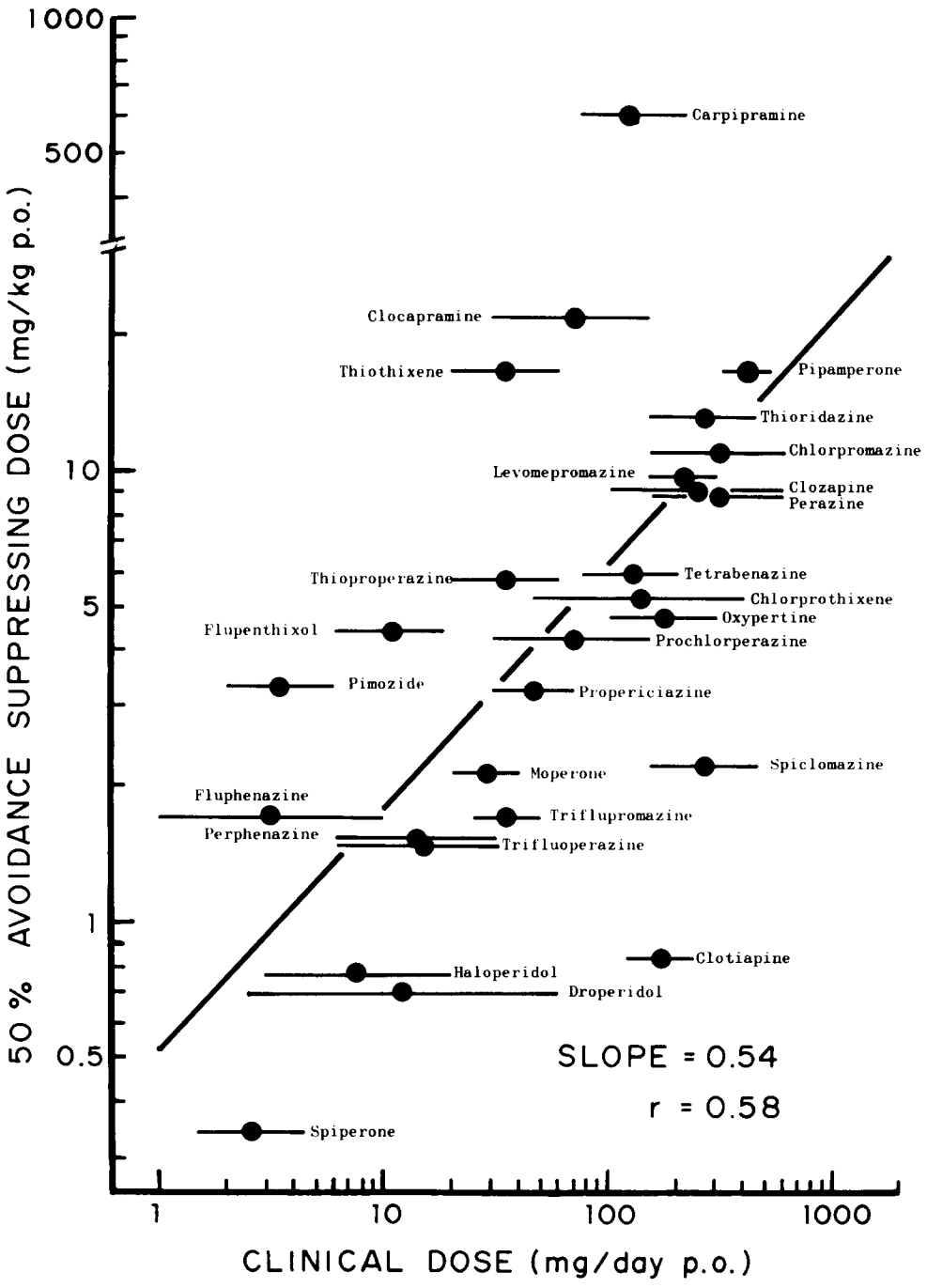

FIG. 8. Correlation between the critical doses for suppression of the discriminated avoidance response of antipsychotic drugs in rats estimated from the present experiment (ordinate) and their clinical daily doses routinely used PO (abcissa). The straight line and figures in the panel are the regression line and its slope, and the correlation coefficient for these data calculated by the least square method.

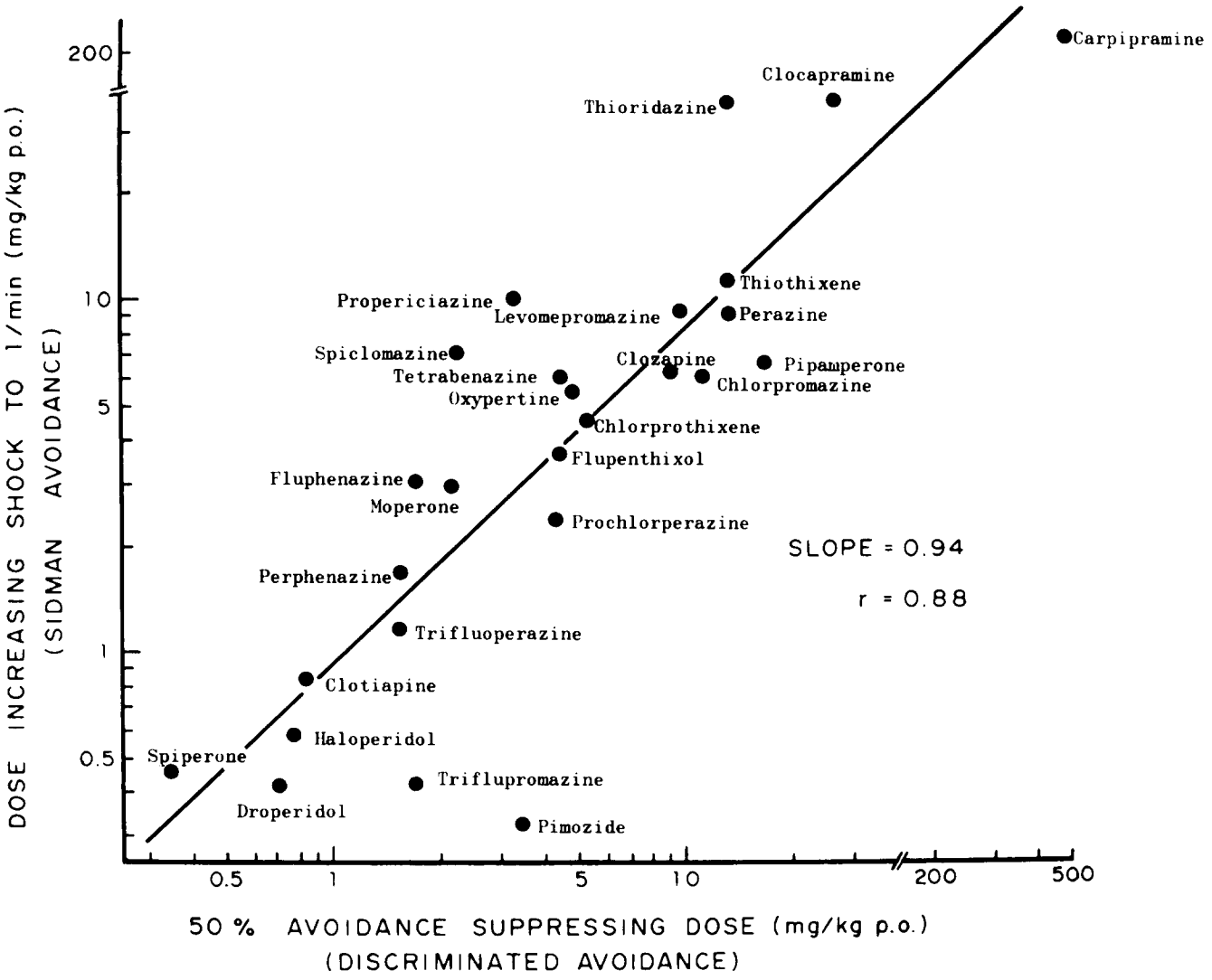

FIG. 9. Correlation between the critical doses for suppression of the Sidman avoidance response (ordinate) and those for suppression of the discriminated avoidance response (abscissa) of antipsychotic drugs in rats. The straight line and figures in the panel are the regression line and its slope, and the correlation coefficient for these data calculated by the least square method.

DISCUSSION

The main purpose of the preclinical evaluation of a drug is to establish a sound basis for the prediction of its clinical effects, such as property, potency, persistence, *etc.* It has been reported that the antipsychotic activity of drugs can be estimated with the neurochemical methods of Seeman and Lee [36,37], and Snyder and his collaborators [10–12, 40, 43], and the behavioral methods of Cook and Catania [5], Fjalland [17], and Nakamura *et al.* [32].

The present experiment demonstrates that the antipsychotic drugs suppress both the Sidman and discriminated avoidance responses in rats with a dose-dependent decrease in the response rate and an increase in the shock rate in the former case, and a decrease in the response and avoidance rates in the latter case. The orders in the avoidance-suppressing activities of the 28 drugs tested in the present experiment are coresponded closely to their neurochemical results [19–21, 36, 37, 40, 43], and their behavioral results [5, 17, 22, 23, 33–35]. However, sulpiride did not produce any change in the avoidance responses. It has been shown that sulpiride produces a specific blocking effect on the alpha-dopamine receptor, which does not elicit a change in the adenylate cyclase activity [24], and that its behavioral properties are quite different as compared with those of the other antipsychotic drugs [9,24]. The present results suggest that the antipsychotic effect of sulpride is not readily predicted by avoidance tests.

Clozapine increased the shock rate in the Sidman avoidance performance and decreased the avoidance rate in the discriminated avoidance performance without eliciting a marked change in the response rate. It has been suggested that clozapine has a strong anti-cholinergic effect in addition to its dopamine receptor blocking effect, and that it does not

produce any significant extrapyramidal side-effects [2, 3, 9, 42]. Extrapyramidal disorders can be detected as a catalepsy in gross behavior, and may elicit a suppression of general activity, e.g., decrease in the response rate. Hill and Tedesch [19] considered the suppression of avoidance responses after the administration of antipsychotic drugs to be more closely related to extrapyramidal side-effects than to the antipsychotic effect at the clinical level. Thioridazine is also considered to have a strong anti-cholinergic effect, and to elicit few extrapyramidal side-effects [9, 19, 30, 31]. But this drug decreased the response rates in both the Sidman and discriminated avoidance performances. The correlations among the clinical antipsychotic activities, the ability to produce extrapyramidal side-effects, and the avoidance-suppressing and cataleptogenic effects of antipsychotic drugs need to be studied in detail.

The antipsychotic effects of oxypertine and tetrabenazine develop through an interference with catecholamine storage [44], which is different from the receptor blocking mechanism of the other drugs. The qualitative changes in the Sidman and discriminated avoidance responses after oxypertine and tetrabenazine administrations are similar to those seen after administrations of the other antipsychotic drugs. This result can be registered as one of the advantages of the avoidance test in the investigation of the antipsychotic drugs.

The present experiment reveals that the critical doses for suppression in both the Sidman and discriminated avoidance responses are highly correlated with the clinical daily doses. It suggests that the avoidance test is applicable for the preclinical evaluation of the antipsychotic drugs, and that this test may give informations important in estimating their clinical daily doses. However, there were a few drugs which displayed a scattering from the regression line for the correlation between the critical doses for avoidance-suppressing effects and the clinical daily doses. Here, avoidance-suppressing effects of carpipramine, clocapramine and thiothixene were relatively less potent than the clinical efficacies, while the former effect of clotiapine was relatively more potent than the latter. The correlation coefficients between the critical doses for the avoidance-suppressing effects and their clinical daily doses are lower than those of Seeman and Lee [36,37], Snyder and his coworkers [10–12, 40, 43], and Nakamura *et al.* [32]. This may be due to the difference of property, time of onset, duration, etc. of the effect of each drug. In the present experiment, the effect of a drug was observed for 2 hr after PO administration, and the average change in the avoidance response was considered as an index of drug effect. Nakamura *et al.* [32] took the data of the maximum effect being manifested. In addition, the clinical daily dose given to the patient is divided into several subdoses. This can be suggested as one of the reasons for the differences in the present data. In the comparison between the clinical and animal data, the onset and duration of action, as well as the maximum potency of the drug effect, have to be considered.

Both the Sidman and discriminated avoidance response in rats are basic operant behaviors associated with negative reinforcement, and have been applied for the preclinical evaluation of psychotropic drugs [5–8, 15, 18, 21–23, 26, 28, 33, 34]. The avoidance performances are done continuously under the Sidman avoidance situation, and discretely under the discriminated avoidance situation. The present experiment demonstrates, as can be seen in Fig. 9, that the avoidance-suppressing activities of almost all of the drugs on the Sidman and discriminated avoidance responses are nearly the same, showing an extremely high correlation coefficient between the critical doses for the avoidance suppression measured by the two avoidance procedures. This finding suggests that the avoidance test used either in the Sidman or the discriminated avoidance procedure with rats may be sufficient for the minimal purpose of this experiment in which the drug effect on the avoidance response is examined. However, trifluprom azine and pimozide suppressed the Sidman avoidance response more than the discriminated avoidance response. Also, thioridazine, spiclomazine and propericiazine suppressed the discriminated avoidance response more markedly than the Sidman avoidance response. Pimozide is considered to display a specific dopamine receptor blocking effect without a noradrenaline receptor blocking effect [1]. Thioridazine and spiclomazine show a stronger noradrenaline receptor blocking activity than dopamine receptor blocking activity [1,16]. The correlation between the neurochemical and behavioral effects of antipsychotic drugs needs further investigation.

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