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Effects of Psychotropic Drugs on Avoidance Response in Rats: Role of Baseline Performances

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KURIBARA, H. AND S. TADOKORO. *Effects of psychotropic drugs on avoidance response in rats: role of baseline performance*. PHARMAC. BIOCHEM. BEHAV. 11(2) 203–209, 1979.—Effects of d-amphetamine, chlorpromazine and diazepam on the discriminated avoidance response (intertrial interval=25 sec; warning duration=5 sec) in rats were studied with reference to levels of the behavioral baseline. After the administration of d-amphetamine 0.25–2.0 mg/kg SC, the avoidance and response rates increased in all cases dose-dependently. The individual changes of avoidance rates were more marked in the poor performers (initial avoidance rate: 0–33%) with higher baseline response rates than in those with lower response rates. Chlorpromazine 0.5–2.0 mg/kg SC suppressed the avoidance performances in all cases in proportion with the doses. More marked changes were observed in the good performers (68–100%) than in the poor performers regardless of the baseline response rates. After administration of diazepam 0.5–4.0 mg/kg SC, the response rates decreased in almost all cases, while the avoidance rates varied depending on their baseline levels. Diazepam increased the avoidance rates of the poor performers, but conversely decreased the rates in the good performers in proportion with the doses. Moreover, the improvement of the avoidance rates was more marked in the poor performers with higher baseline response rates than in those with lower rates. The present results suggest that the behavioral effects of psychotropic drugs are a function of the avoidance baseline levels.

Discriminated avoidance response Avoidance baseline Baseline levels and drug effects d-Amphetamine Chlorpromazine Diazepam Rats

CONDITIONED avoidance procedures, which require relatively easy experimental operations, have been utilized for the evaluation of psychotropic drugs with rats, and the results have been summarized by many investigators [2, 3, 4, 5, 10, 17]. In general, central stimulants facilitate avoidance performance while depressants suppress it. On the other hand, Bignami *et al.* [1] and Takaori *et al.* [32] reported, on the basis of the Sidman-type avoidance response in rats, that a certain dose of barbiturates and/or benzodiazepine derivatives suppressed the avoidance performance when their avoidance rates in the predrug period were high but on the contrary facilitated it when the rates were low. Moreover, Kuribara *et al.* [21] described obvious differences among strains of rats not only in the acquisition processes of the conditioned avoidance responses, but also in the effects of diazepam. It is also well known that drug effects are sometimes affected by predrug patterns of behavior [3, 4, 5]. Bignami *et al.* [1], Stone [30,31] and Takaori *et al.* [32] reported the correlations between baseline performances and variations of drug effect in the Sidman-type avoidance test. But few investigations have been done using the discriminated avoidance procedure [27,28].

In the present experiment, individual variations in baseline levels of the avoidance and response rates, and the changes of the avoidance behavior after administration of d-amphetamine, chlorpromazine and diazepam were investigated in rats having different baseline levels.

METHOD

Animals

The animals used were 50 adult male rats of the Wistar strain. They were provided from the breeding colony of Gunma University, Medical School. The strain has been maintained by brother-sister mating for more than 25 years in the colony. The animals were moved to our breeding room at 4 weeks of age. Groups of 3–4 animals were housed in stainless steel wire mesh cages [38 (D)×25 (W)×19 (H) cm], fed a diet of solid food MF (Oriental Yeast Co., Tokyo) and tap water ad lib except when they were placed in the experimental chamber for training or drug-testing. The room temperature was maintained at 22 ± 2°C throughout the experimental period but humidity was not controlled.

The training of rats under the discriminated avoidance situation was started at the age of 10–15 weeks and weights of 250–350 g, and thereafter the rats were used for more than 6 months for the purposes of the experiment.

Apparatus

Experimental chambers used were made of acrylfiber and aluminum boards of 20 (D)×25 (W)×19 (H) cm, with an electro-wired floor grid and a lever on the side wall (GT 7705, O'Hara and Co. Ltd., Tokyo). When a rat pressed the lever with a force of more than 10 g, a microswitch closed a circuit to record the response. The chamber was contained in a wooden sound-attenuating box, and fresh air was circulated throughout the box during the experimental period. The temperature in the box was controlled at 23 ± 2°C.

The behavior-controlling and -recording apparatus consisted of relays, timers and electromagnetic counters (GT 7710 and GT 7715, respectively, O'Hara and Co. Ltd., Tokyo), and was kept in the adjacent room. The gross behavior was observed with the use of a TV screen. The TV camera was placed on the window of the sound-attenuating box. In the present experiment, two such set-ups were used.

Discriminated Avoidance Situation

The avoidance procedure utilized in the present experiment was a modification of the schedule of Hoffman *et al.* [15] and Hoffman [16]. Details of the programming and the method of operations have been described by Kuribara *et al.* [21]. The schedule consisted of a 25 sec intertrial interval and a 5 sec warning duration (light and buzzer) without an escape contingency. The shock was an electric current of 150 V, 0.3 mA AC and was passed for 0.3 sec through the floor grid. One session consisted of 2 hr training a day, and was held at 2–3 day intervals until the establishment of the behavioral baseline for both avoidance and response rates, that is, when relatively stable rates were maintained for more than 5 consecutive sessions. Thereafter, however, the session was shortened from 2 hr to 1 hr, and was held every day. After the reconfirmation of baseline stability, the drug tests were started.

In order to exclude the warm-up period data [15, 16, 18, 19], the first 10 min of data collection was not considered in the calculation of the mean values of the avoidance rate (number of avoidance responses/number of warning stimulus presentations) and the average response rate of the remaining time.

Drugs Used

The drugs used and doses administered were d-amphetamine sulfate (0.25, 0.5, 1.0 and 2.0 mg/kg), chlorpromazine hydrochloride (Contomin Inj., Yoshitomi; 0.5, 1.0 and 2.0 mg/kg) and diazepam (Cercine Inj., Takeda; 0.5, 1.0, 2.0 and 4.0 mg/kg). The doses shown are of the salts. d-Amphetamine and chlorpromazine were dissolved in physiological saline solution, and diazepam in a 20% propylene glycol solution. In all cases, a uniform dose volume of 1.0 ml/kg was prepared in varying concentrations so as to contain the above-mentioned drug amounts. Each dose was administered SC immediately before the start of the session, after which the rat's avoidance behavior was observed for 1 hr. Drugs were injected at intervals of 3–4 days, and the day before the test, the same volume of saline or propylene glycol vehicle alone was given as the control injection. On the other days, the avoidance performance was observed in the same way to check the stability of the untreated behavioral baseline. The drug tests were started with d-amphetamine, followed by chlorpromazine and then diazepam, with the dose levels changing from lower to higher using the same animals.

RESULTS

Individual Differences of the Behavioral Baselines

After 20–30 sessions of training, relatively stable rates of avoidance and response were maintained for at least 5 consecutive sessions in about 90% of the rats. However, individual differences in avoidance performances were observed. Table 1 represents the classifications of the baseline performances of 50 rats with the drug experiment results. The baseline avoidance and response rates shown in Table 1 were estimated from the data obtained on the vehicle-administered control days. In this table, the 50 rats are

TABLE 1

DISTRIBUTIONS OF BASELINE AVOIDANCE PERFORMANCES DURING THE DRUG EXPERIMENTS

Avoidance rate		Response rate/min				Drugs tested
		0–2.5 (lower)	2.6–5.0 (intermediate)	5.1--- (higher)	No. of rats showing unstable baseline performances*	
0–33%	(poor performer)	4	9	5		
34–67	(medium performer)	0	6	4	(5)	d-Amphetamine
68–100	(good performer)	0	8	9		
0–33%	(poor performer)	5	5	4		
34–67	(medium performer)	1	6	3	(4)	Chlorpromazine
68–100	(good performer)	0	10	12		
0–33%	(poor performer)	5	7	3		
34–67	(medium performer)	0	7	3	(3)	Diazepam
68–100	(good performer)	4	8	10		

*These animals showed a fluctuation of more than 15% in the avoidance rate and/or response rate from the mean value during each drug experiment.

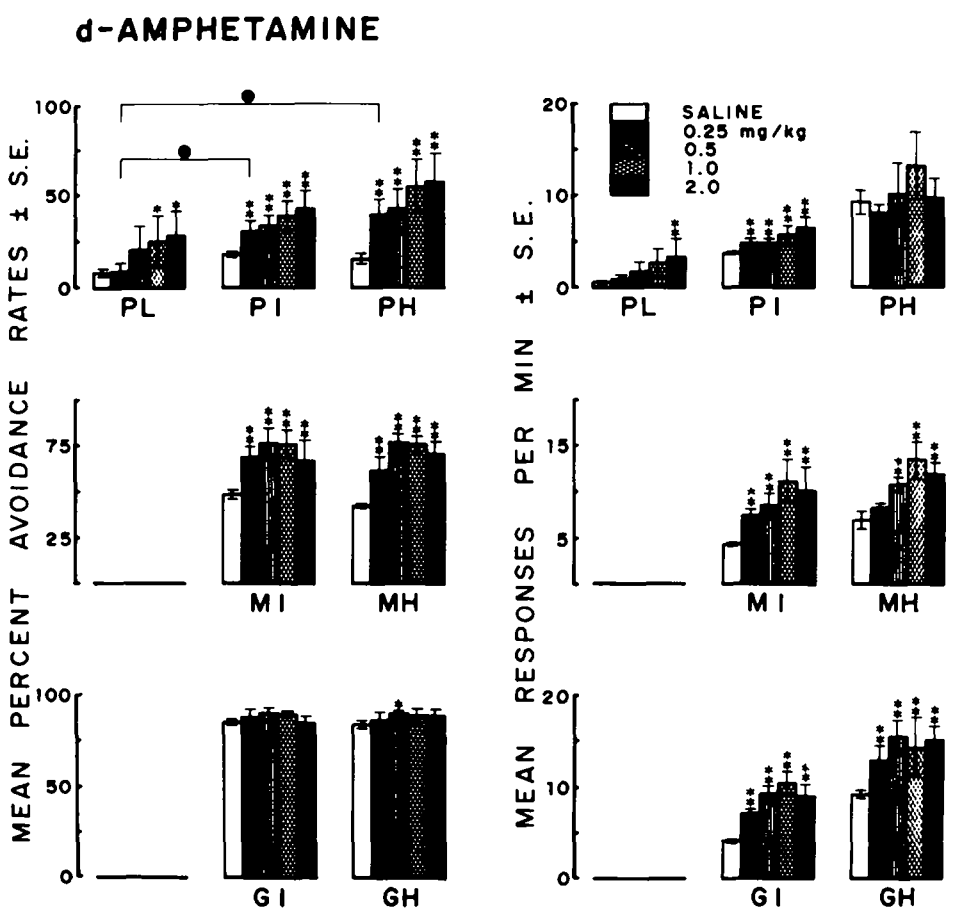

FIG. 1. Dose-effect relations of d-amphetamine at 0.25, 0.5, 1.0 and 2.0 mg/kg SC on discriminated avoidance performance in rats. The rats are classified into 9 groups according to the baseline avoidance and response rates as shown in Table 1, and the dose-effect relations for each group of animals are shown separately with the standard errors by histograms. Rat's baseline avoidance and response levels are indicated by the code of two alphabets. The rats belonging to P, M and G are denoted as having baseline avoidance rates of 0–33%, 34–67%, and 68–100%, respectively, and those belonging to L, I and H are denoted as having baseline response rates of 0–2.5/min, 2.6–5.0/min, and more 5.1/min, respectively. The ordinate denotes the avoidance rates or response rates, and the abscissa the doses of drug tested. Left 3 panels: Dose-effect relations for the avoidance rates. Right 3 panels: Dose-effect relations for the response rates. *Significantly different from the value in saline administered control within the same group of rats ($p<0.05$, Student's t-test). **$p<0.01$. ●Significantly different between the values for the rats belonging to different groups, but given the same dose of the drug ($p<0.05$).

mainly divided into 3 groups according to the baseline avoidance rate, i.e., poor performer (P) (avoidance rate: 0–33%), medium performer (M) (34–67%) and good performer (G) (68–100%). Furthermore, each group of animals are divided into 3 subgroups according to the baseline response rate, i.e., lower emitter (L) (response rate: 0–2.5/min), intermediate emitter (I) (2.6–5.0/min) and higher emitter (H) (more than 5.1/min). Thus, each rat is coded by two alphabets which indicate the baseline levels of avoidance rate and response rate. About 10% of the total displayed unstable avoidance and/or response rates, and were excluded from the drug tests. About 30%, 20% and 40% of the 50 rats belonged to the poor, medium and good performers, respectively. The distribution pattern for the baseline response rates showed a regular form with a mode in the range of 2.6–5.0/min, with about 45% of all animals tested belonging to this range. During the progress of the drug test, a few rats displayed a slight increase in avoidance rate and decrease in response rate, but the variation did not markedly affect the distribution pattern of the baseline performances.

Effects of d-Amphetamine

Figure 1 shows the dose-effect relations in both avoidance rate and response rate after the administration of d-amphetamine 0.25–2.0 mg/kg SC. In these panels, the results obtained in the animals of each group shown in Table 1 are presented by histograms.

Both the avoidance and response rates of poor performers increased dose-dependently after d-amphetamine 0.25–2.0

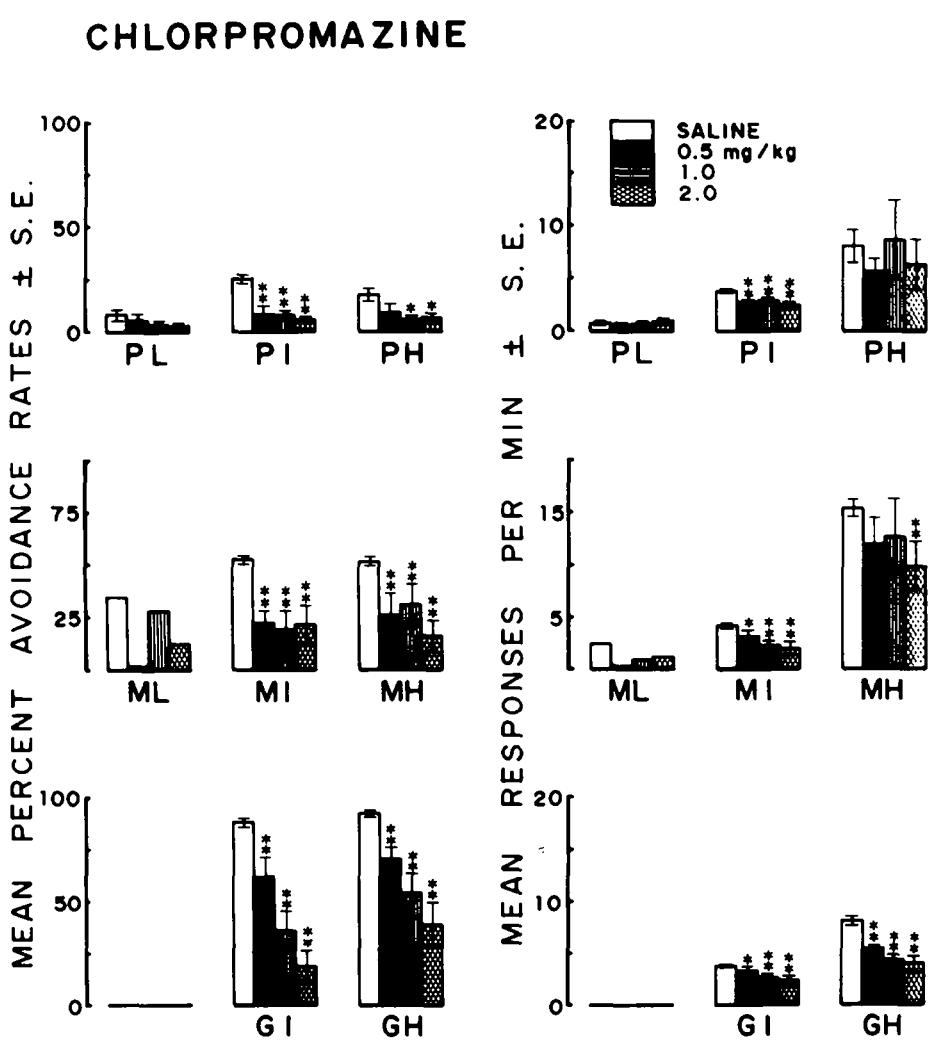

FIG. 2. Dose-effect relations of chlorpromazine at 0.5, 1.0 and 2.0 mg/kg SC on discriminated avoidance performance in rats. The data are presented as in Fig. 1.

mg/kg. The avoidance and response rates of medium performers also increased after d-amphetamine, but dose-related changes were observed when given less than 1.0 mg/kg. The changes with 2.0 mg/kg were smaller than after 1.0 mg/kg. There was no marked change in the avoidance rate of good performers, but the response rate increased.

The variation of avoidance and response rates after d-amphetamine tended to be related to the baseline levels of performance. In poor performers, the increase of the avoidance rate was more marked in the cases with the higher baseline response rate than in those with the lower response rate. There were significant differences between the avoidance rates of PL vs PI, and PL vs PH after d-amphetamine 0.25 mg/kg ($p<0.05$, Student's t-test).

On the other hand, the variation of response rate after d-amphetamine was also related to the baseline avoidance rate. The changes of response rates in the rats, which showed nearly the same baseline response rate, tended to be greater in the rats with the higher baseline avoidance rates than in those with the lower rates (e.g., PI vs MI, PI vs GI, and PH vs GH).

Effects of Chlorpromazine

Figure 2 shows the dose-effect relations in both avoidance rate and response rate after chlorpromazine 0.5–2.0 mg/kg SC.

In general, the avoidance performance of rats was suppressed dose-dependently after chlorpromazine. Especially marked was the variation in good performers. The decrease of avoidance rate was scarcely affected by the baseline response rate, and rats with an analogous baseline avoidance rate tended to show similar dose-effect relations regardless of the baseline response rates. Moreover, the changes of response rates were also almost independent of the baseline avoidance rates.

Effects of Diazepam

Figure 3 shows temporal changes of the avoidance performance of a representative case (Rat M-6) after SC administration of diazepam 1.0, 2.0 and 4.0 mg/kg, and the vehicle (propylene glycol) by cumulative curves. The downward deflections of the response pen indicate shock presentations.

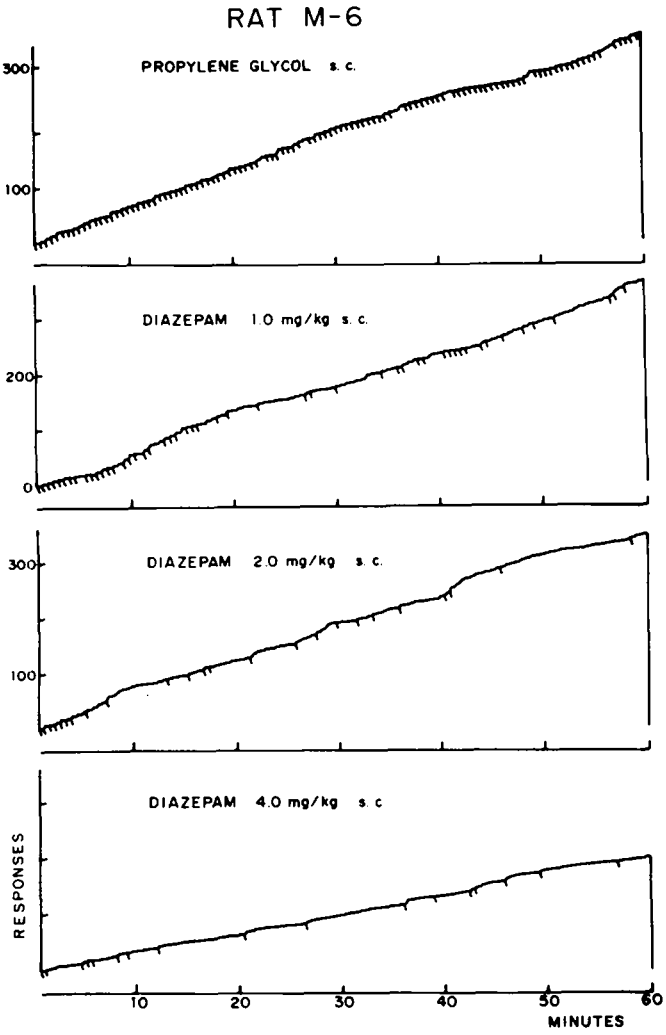

FIG. 3. Representative cumulative curves showing the temporal changes of the avoidance performance after SC administration of diazepam at 1.0, 2.0 and 4.0 mg/kg, as well as propylene glycol. The ordinate and abscissa, respectively, denote the cumulative response and the time. Rat M-6 was a poor performer that displayed baseline avoidance and response rates of 0–33% and more than 5.1/min, respectively.

The rat shown in this figure belonged to the PH group with an avoidance rate of 0–33% and a response rate of more than 5.1/min.

As can be seen in this figure, after the administration of diazepam 1.0–4.0 mg/kg, the number of shocks delivered decreased dose-dependently. Especially after 2.0 and 4.0 mg/kg, the avoidance rates attained 80 and 90%, respectively, while after propylene glycol, the rate remained only 10% or less. Even though a marked increase of avoidance rate was observed, the response rate decreased after diazepam 4.0 mg/kg.

Figure 4 shows the dose-effect relations in both avoidance rate and response rate after diazepam 0.5–4.0 mg/kg SC as in Figs. 1 and 2.

The avoidance performances in individual cases varied after diazepam depending on the baseline avoidance and response rates. Thus, the avoidance rate of poor performers increased dose-dependently after diazepam. Especially in the poor performers with intermediate and higher baseline response rates (PI and PH), a marked increase of the avoidance rates was observed. On the other hand, the avoidance rates of medium and good performers decreased in parallel with the doses.

Diazepam showed a decrease in the response rates even though it produced an increase of the avoidance rate in the poor performers. A slight increase in the response rate was observed only in the poor performers with lower baseline response rate.

On the other hand, an increase in the avoidance rate of poor performers was more prominent in rats with a higher baseline response rate than in those with a lower rate. The avoidance rates between PL vs PH and PI vs PH after 1.0 mg/kg as well as PL vs PH after 4.0 mg/kg were significantly different ($p<0.05$), while the suppression of the avoidance rate was observed independently of the baseline response rates in medium and good performers.

DISCUSSION

As can be seen in Table 1, the established baseline levels of avoidance performances differed markedly in individual animals even though the same strain of rats was used. However, there was no definite correlation between the levels of baseline avoidance rate and response rate. One of the reasons is considered to be due to colony differences in the rats. The existence of colony differences in the same strain of rats has also been reported by Nakamura and Anderson [26]. But according to our data [24], when the rats were trained under the discriminated avoidance situation with an escape contingency as described by Hoffman and his co-workers [15,16], almost all the animals reached a high avoidance rate exceeding 90%, and the low avoidance rate was hardly observed. These results suggest that the individual differences in the avoidance performances are dependent on the types of schedule.

Data obtained with the poor performers have hardly been utilized at all for drug evaluations [27,28], but it may give us some important information concerning the profile of psychotropic drugs. Moreover, in previous investigations, only the avoidance rate has been used as an indicator for the drug effect. But a change in the response rate would also be important in evaluating the drug effect. This is because the sensitivity of individual animals to the drugs sometimes varies depending on their baseline avoidance and/or response rates [3, 4, 5, 27, 28].

A dose-dependent increase in the response rate of the poor, medium, and good performers, as well as an increase in the avoidance rate of the poor and medium performers were observed after d-amphetamine. The present results are comparable with many reports published previously [11, 12, 13, 14, 27, 29], but the increase of avoidance rates in the poor performers was observed more markedly in the cases with a higher baseline response rate than in those with lower rates. Many investigators [2, 11, 12, 13, 14, 20, 26, 29] have proposed that amphetamines have a freezing-attenuating effect. However, the improvement of discriminative ability to the warning stimulus after d-amphetamine as described by Hearst and Whalen [14] could not be confirmed with the present results, because the number of intertrial responses was augmented in the medium and good performers. The increase of the avoidance rate after d-amphetamine in the

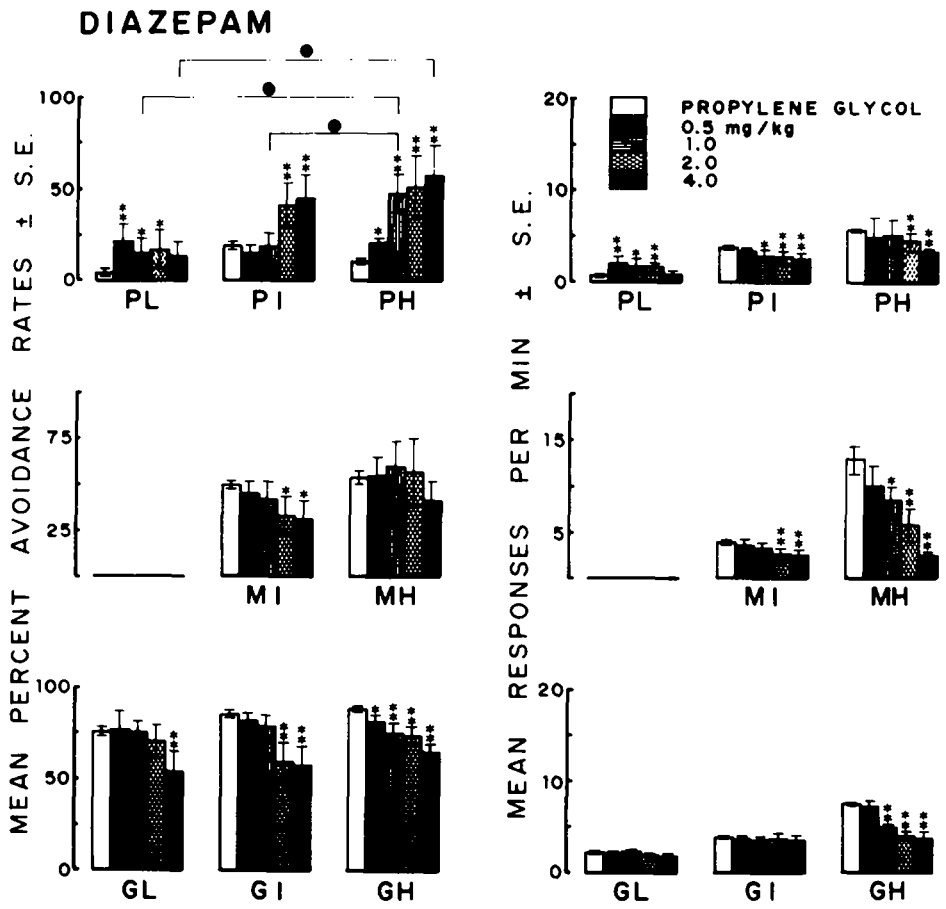

FIG. 4. Dose-effect relations of diazepam at 0.5, 1.0, 2.0 and 4.0 mg/kg SC on discriminated avoidance performance in rats. The data are presented as in Figs. 1 and 2. However, in the control experiment, 20% propylene glycol solution was administered.

poor performers is thought to be caused by the motor-accelerating effect of the drug.

Chlorpromazine showed a marked decrease of both the avoidance and response rates in all animals. These results are consistent in many reports [2, 3, 4, 5, 10, 12, 13, 17, 29]. The findings suggest that neuroleptic drugs suppress the avoidance performance specifically so that the avoidance procedure can be used for the quantitative drug evaluation.

The effects of diazepam on avoidance performance in the medium and good performers were similar to those of chlorpromazine, with dose-dependent decrease of both the avoidance and response rates. However, the dose of diazepam which suppressed avoidance performance usually produced marked ataxia, thus elicting imperfect lever pressing because of a motor dysfunction. This observation is also supported by our laboratory's experimental results using the rota-rod and traction performances in mice [22] and the Sidman-type avoidance procedure in rats [23].

On the other hand, diazepam improved the avoidance performance only in the poor performers, together with the dose-dependent increase of the avoidance rate and the decrease of the response rate in the rats with a higher baseline response rate. Similar results have been reported by Bignami *et al.* [1], Kuribara *et al.* [21], and Takaori *et al.* [32] on the basis of the Sidman-type and/or discrimated avoidance performances in rats. According to the present results, diazepam improves the avoidance performances only in poor performers with a simultaneous decrease of the intertrial responses and an increase of the effective responses during the warning period. The decrease of intertrial responses was also observed in the medium and good performers after diazepam. Dews and Morse [5] reported that a similar phenomenon was observed after administrations of various anti-anxiety drugs. Kamin [18], Gupta and Holland [12,13], and Sansone *et al.* [29] suggested that the rate of intertrial responses indicated the level of emotionality and/or anxious states of the animals. The avoidance test using poor performers may be as beneficial as the conflict or punishment procedure introduced by Geller *et al.* [6, 7, 8, 9], and McMillan [25] to evaluate the anti-anxiety drugs. However, a stable method for obtaining animals displaying a relatively high baseline response rate with a low avoidance rate has not yet been found.

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