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Psychotropic Drugs and Sidman Avoidance in Rats: IRT Distribution Changes[1]

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KURIBARA, H. *Psychotropic drugs and Sidman avoidance in rats: IRT distribution changes.* PHARMAC. BIOCHEM. BEHAV. 8(5) 537–542, 1978. – The effects of d-amphetamine, caffeine, chlorpromazine, diazepam and pentobarbital on Sidman avoidance responding (R–S interval, 30 sec; S–S interval, 3 sec) in rats, especially on the interresponse time (IRT) distribution, were studied. d-Amphetamine and caffeine increased the total number of responses. Short IRTs were increased, while longer ones were decreased. Chlorpromazine, diazepam and pentobarbital all increased the number of shocks delivered. After chlorpromazine, no marked change was observed in the total number of responses. However, response bursts and escape responses increased, while IRTs between 3 and 30 sec decreased. After diazepam and pentobarbital, the burst response scarcely increased, and the IRTs in the 3–15 sec range decreased, while the IRTs longer than 33 sec increased. These changes were more marked after diazepam than after pentobarbital. Total number of responses was decreased by both drugs. The present results suggest that in utilizing the Sidman avoidance procedure for psychotropic drug assessment, changes in the IRT distribution give a more precise profile of the drug than is afforded by the total number of responses and shocks delivered.

Sidman avoidance Psychotropic drugs IRT distribution

SIDMAN lever-press avoidance [19] is relatively easy for rats to learn, and thoroughly-trained animals respond repeatedly at a stable rate and avoid shocks [13,14]. When such trained rats are given psychotropic drugs, avoidance responding changes according to the properties of the drugs [4, 6, 8, 9, 10, 11]. These relations have been applied extensively to the evaluation of new drugs at the preclinical level. Neuroleptic drugs have been considered to inhibit the conditioned avoidance response specifically [12,16], but under some conditions, barbiturates and benzodiazepine derivatives also exert inhibitory effects on the responding [23]. It is therefore often difficult to differentiate the properties of these drugs solely by the total numbers of responses and shocks delivered.

In the present experiment, changes in the interresponse time (IRT) distributions were observed as well as total responses and shocks delivered after the administration of d-amphetamine, caffeine, chlorpromazine, diazepam and pentobarbital to define the profiles of these drugs on Sidman avoidance responding.

METHOD

Animals

Male Wistar strain rats inbred for more than 25 years by brother-sister mating in the breeding colony of Gunma University Medical School were used. Five rats, which were weaned at the age of 3 weeks, were kept in one cage and given a solid diet MF (Oriental Yeast Co., Tokyo) and tap water ad lib. At the start of the avoidance conditioning, the animals were 10 weeks of age and weighed 250–270 g. The living conditions were maintained without any change during the conditioning and drug examination periods.

Apparatus

Five experimental chambers were used. They were each 20(D) × 25(W) × 19(H) cm, and a lever was set in the side wall 4 cm over the floor grid. When the animal pressed the lever downward with a force of more than 20 g, the response was effective in postponing shock. Shock was delivered by passing 200 V, 0.5 mA and 50 Hz AC through the grid for 0.5 sec.

Procedure

Sessions consisted of 1 hr of daily training. The temporal parameters of the schedule, that is, response–shock (R–S) and shock–shock (S–S) intervals were 30 and 3 sec, respectively. The experiment was controlled by a mini-computer PDP 8/f (Digital Equipment Corp.) which was programmed in SKED language. The computer also recorded total numbers of responses, shocks delivered, and IRTs. All IRTs were placed in categories of 3.0 sec.

When the total numbers of responses and shocks

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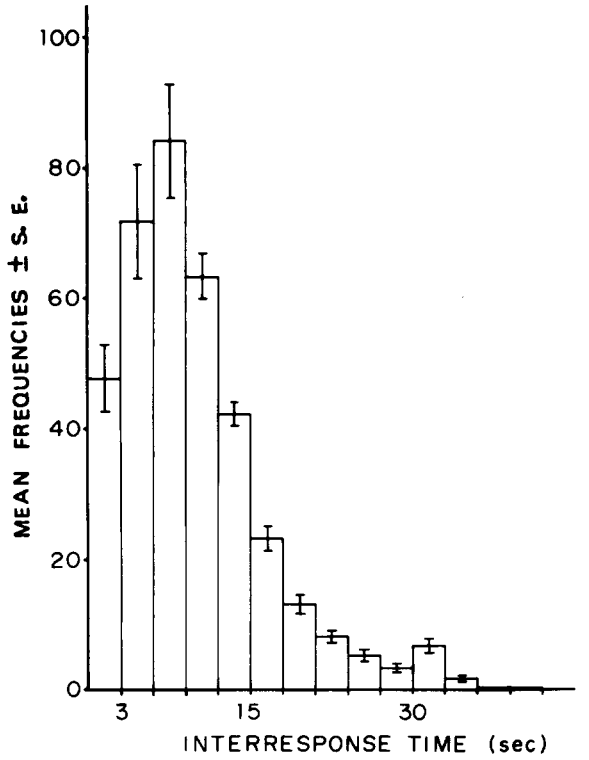

FIG. 1. Interresponse time (IRT) distribution after establishment of behavioral baseline under the Sidman avoidance schedule (R–S interval, 30 sec; S–S interval, 3 sec). All IRTs are placed in categories of 3 sec, and mean IRT in each category for 5 rats in the 16th–20th sessions is given together with standard error.

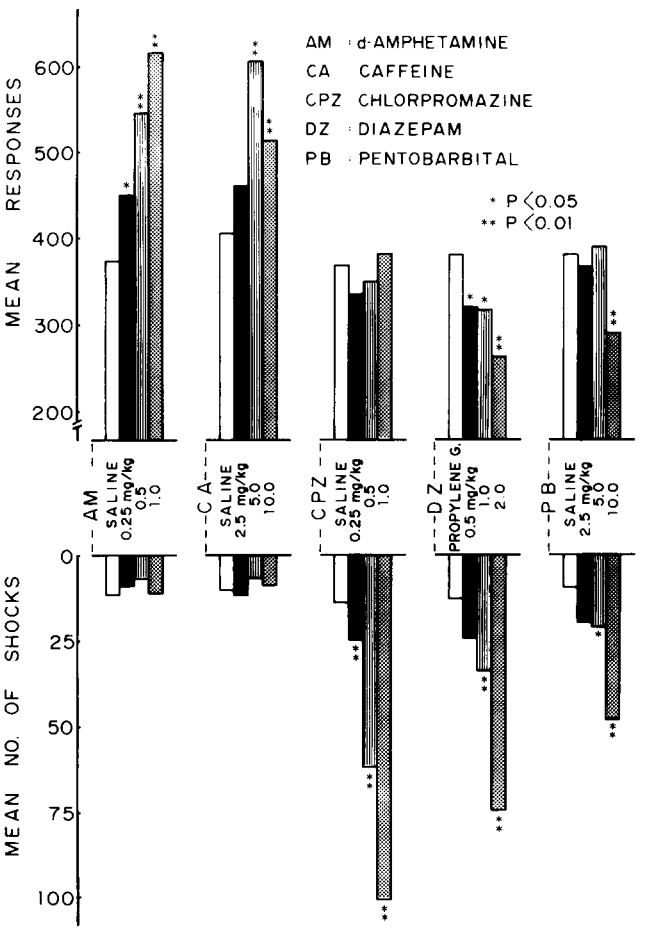

FIG. 2. Dose-effect relations for d-amphetamine, caffeine, chlorpromazine, diazepam and pentobarbital on the Sidman avoidance schedule. Mean total numbers of responses (upper) and shocks delivered (lower) are given. *Significantly different from the control value by Student's t test ($p<0.05$). **$p<0.01$.

delivered, and the IRT distribution remained without marked change for more than five consecutive sessions, the behavioral baseline was regarded as stabilized and drug administration was started.

Drugs

The drugs used and their doses were as follows: d-amphetamine sulfate (AM), 0.25, 0.5 and 1.0 mg/kg; caffeine (CA), 2.5, 5.0 and 10.0 mg/kg; chlorpromazine hydrochloride (CPZ; Contomin Inj., Yoshitomi), 0.25, 0.5 and 1.0 mg/kg; diazepam (DZ; Cercine Inj., Takeda), 0.5, 1.0 and 2.0 mg/kg; and pentobarbital sodium (PB; Mintal Inj., Tanabe), 2.5, 5.0 and 10.0 mg/kg. Drug doses are expressed in terms of the salts. AM, CA, CPZ and PB were dissolved in physiological saline solution, and DZ in 20% propylene glycol. In all cases, a single dose of 1.0 ml/kg was prepared in such a way as to contain the above mentioned amounts, and each dose was administered SC immediately before the start of the session. Sessions lasted for 1 hr. Drugs were injected at intervals of 4–5 days, and on the day before, the same volume of the solvent alone was given as the control injection. On the other days, the animals were tested in the same way without any treatment to check the stability of the behavioral baseline. The order of drug testing was AM, CA, CPZ, DZ and PB. The dose administered was changed from the higher to the lower for two rats, and conversely for the other three rats. When the drug was changed from one to another, it was always checked that there was no marked variation in the behavioral baseline for more than one week.

RESULTS

Behavioral Baseline

After 10–15 sessions, all the animals achieved a stable behavioral baseline. The mean number of responses and shocks delivered for five rats in five sessions immediately before the start of drug examination, that is, in the 16th–20th sessions, were 281.4 ± 8.1 and 14.3 ± 1.4, respectively. The mean IRT distribution in these sessions is presented in Fig. 1, where IRTs are placed in categories of 3.0 sec. The mode of the IRT distribution was in the 6–9 sec section, and about 75% of the total IRTs were located in the first half of the R–S interval. A stable behavioral baseline was maintained during the entire drug series.

Effects of Drugs on Total Numbers of Responses and Shocks Delivered

Figure 2 presents dose-effect relations based on changes in the total numbers of responses and shocks delivered after the administration of AM, CA, CPZ, DZ and PB.

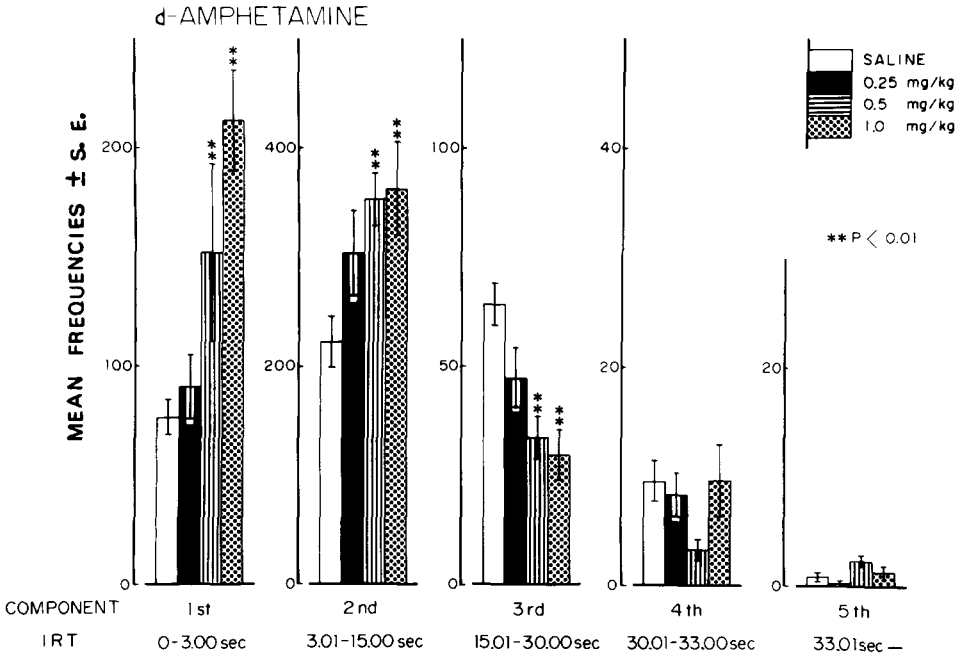

FIG. 3. Effect of d-amphetamine on the IRT distribution. IRTs are divided into 5 components (0–3.00, 3.01–15.00, 15.01–30.00, 30.01–33.00 and 33.01 sec and over), and dose-effect relations in these components are given as a histogram together with the standard errors. The scale of the ordinate differs from one component to another. **Significantly different from the control value ($p<0.01$).

Total number of responses was increased by the administration of AM and CA in a dose-dependent fashion. However, when 10.0 mg/kg of CA was given, the increase in responding was slightly less than that after 5.0 mg/kg. Gross observation of the rats at this time revealed slight tremors. CPZ, DZ and PB all increased the total number of shocks delivered as a function of dose, while the total number of responses changed differently from one drug to another. Thus, after CPZ 0.25–1.0 mg/kg, no marked change in the total number of responses was observed. But more than 0.5 mg/kg of DZ and 10.0 mg/kg of PB decreased responding.

Effects of Drugs on IRT Distribution

Figures 3–7 present mean changes in IRT distributions after the administration of AM, CA, CPZ, DZ and PB. In these figures, the IRTs were divided into the following five components; 1st component, IRT rangint 0–3.00 sec, which was regarded as "burst response", that is, repetition of lever pressing at extremely short intervals; 2nd component, IRT ranging 3.01–15.00 sec, where the response-emitting rate in the baseline performance was the highest, so that about 2/3 of the total IRTs belonged to this component; 3rd component, IRT ranging 15.01–30.00 sec, where shock could be postponed effectively, though the response-emitting rate was low; 4th component, IRT ranging 30.01–33.00 sec, which indicated that, in spite of exposure to shock, the succeeding one after 3 sec could be postponed; and 5th component, IRT ranging longer than 33.01 sec, which meant that the rat pressed the lever only after two or more shocks had been delivered. In all of these figures, the abscissa and ordinate denote the dose and the mean frequency of IRTs with standard errors, respectively. The scale of the ordinate varies for different components.

AM increased IRTs in the 1st and 2nd components, while it decreased those in the 3rd component. Thus AM tended to shift the mode of IRT distribution toward the left.

After CA, the qualitative change of the IRT distribution was similar to that after AM. However, these changes, which were proportional to the dose, were observed only when 5 mg/kg or less was given. A dose of 10 mg/kg CA increased IRTs only in the 1st component, and was ineffective in the other components.

CPZ markedly increased IRTs in the 1st and 4th components. The IRTs in the 5th component were also increased by CPZ. But the amount of change was not so marked when compared with those in the 1st and 4th. In the 2nd and 3rd components, however, the IRTs decreased in proportion with the dosages.

DZ, like CPZ, increased the total number of shocks delivered as seen in Fig. 2, but the effect on the IRT distribution differed from that after CPZ. Thus no marked change was observed in the 1st and 3rd components, while IRTs in the 2nd component decreased, and increased in the 4th and 5th components, dose dependently.

After PB, IRTs decreased in the 2nd component, and increased in the 4th and 5th components. These changes were similar to those after DZ. However, only at a dose of 5 mg/kg PB was effective in increasing IRTs in the 1st component.

DISCUSSION

The Sidman avoidance response [19] is relatively easy for rats to learn [13,14], and its subsequent use is applicable to drug experiments. Under the present schedule,

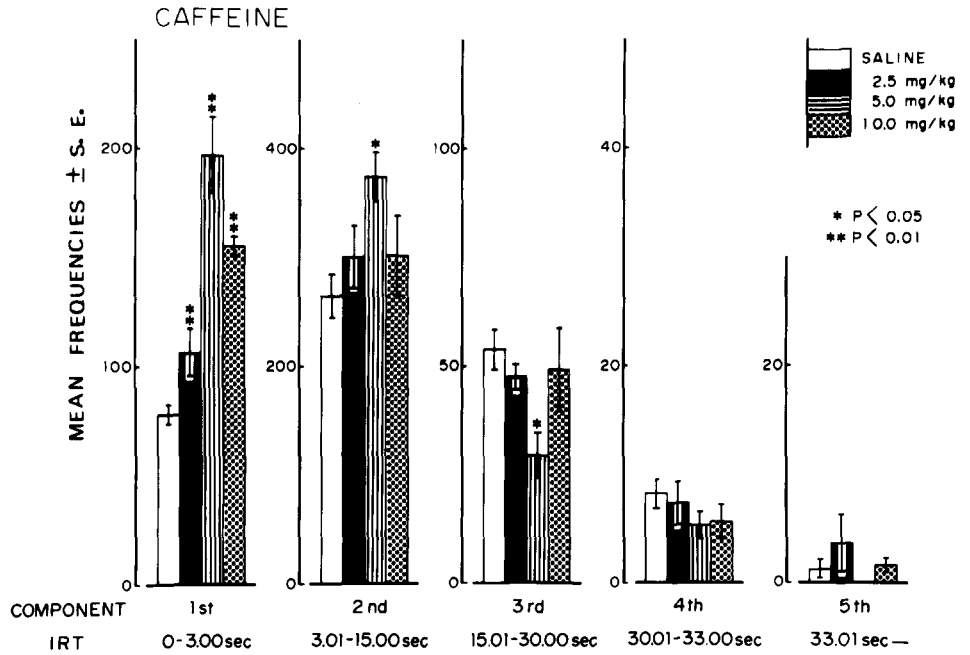

FIG. 4. Effect of caffeine on the IRT distribution (expressed in the same way as Fig. 3). *Significantly different from the control value ($p<0.05$).

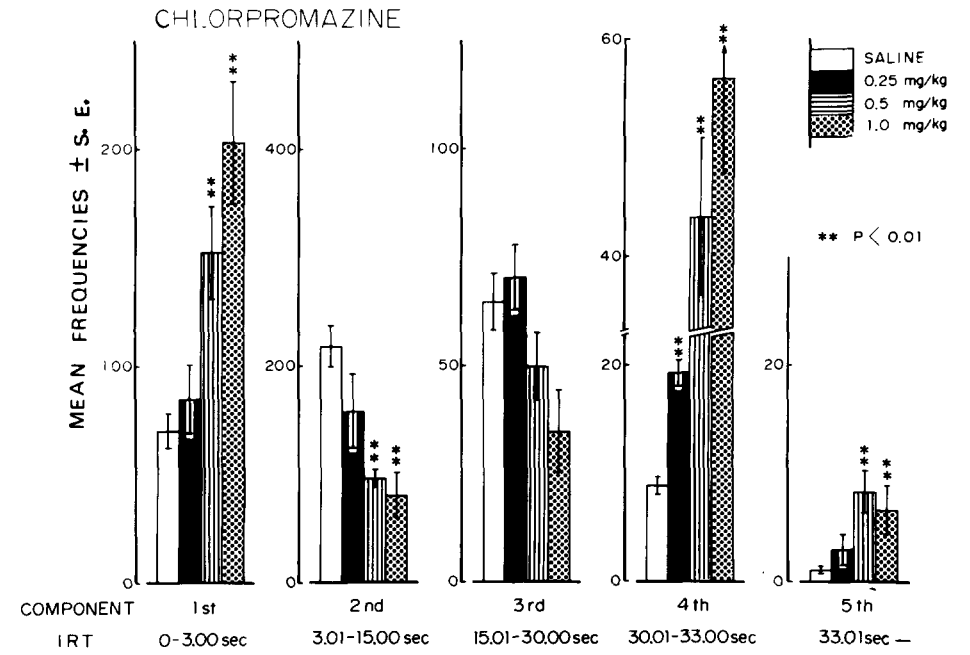

FIG. 5. Effect of chlorpromazine on the IRT distribution (expressed in the same way as Fig. 3).

all responses were effective in postponing the delivery of shock, but no exteroceptive stimulus was given to predict the onset of shock. Thus, in order to avoid the shock, the rat should press the lever within a period shorter than the R–S interval. Under such a condition, the responses most effective in postponing shock are those which are emitted just before the onset of shock, that is, IRTs near the value of the R–S interval. However, as can be seen in Fig. 1, the mode of the IRT distribution was found in the 6–9 sec section, and more than 75% of the total responses were performed in the first half of the R–S interval. This means that, in absence of an exteroceptive stimulus which predicts the onset of shock, the temporal discrimination under the Sidman avoidance schedule may be extremely difficult for rats.

When the effects of psychotropic drugs on Sidman avoidance responding in rats are examined, the change in IRT distributions provides information beyond that

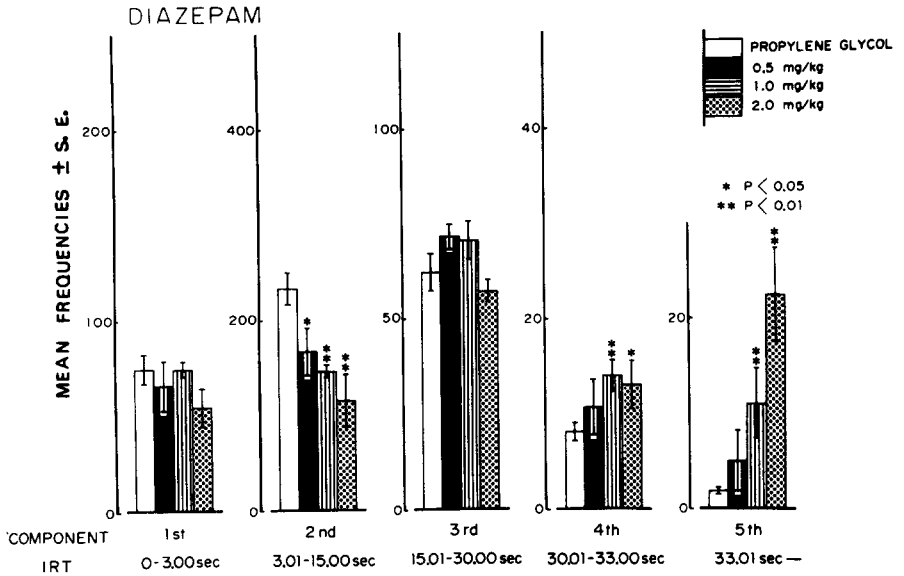

FIG. 6. Effect of diazepam on the IRT distribution (expressed in the same way as Fig. 3).

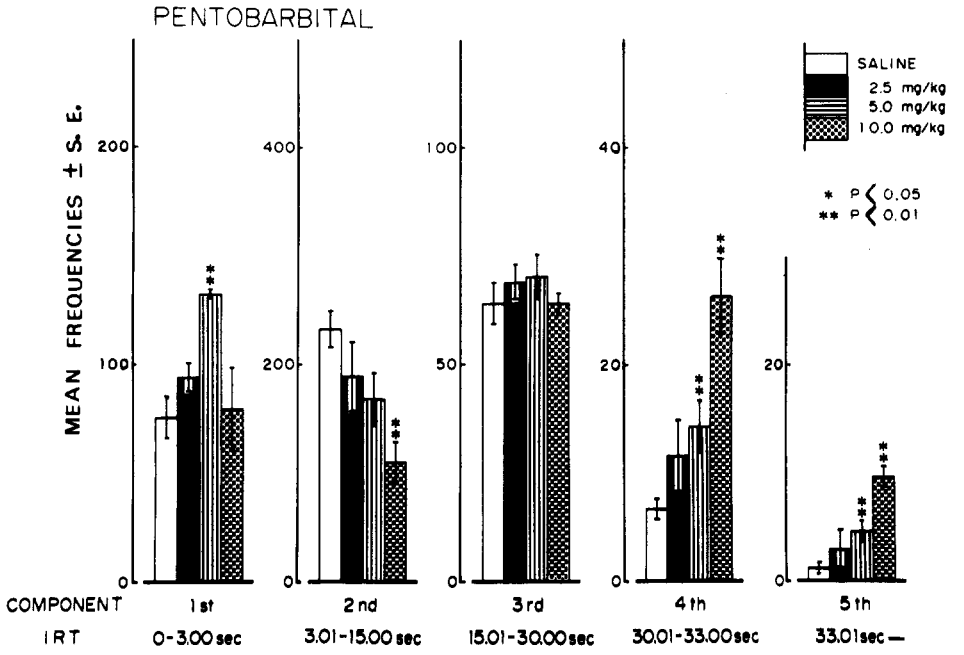

FIG. 7. Effect of pentobarbital on the IRT distribution (expressed in the same way as Fig. 3).

available from a consideration of the only numbers of responses and shocks delivered. According to the present experiment, AM and CA, which are central stimulants, increased total number of responses. And when the effects were compared by dose, the former was assumed to be about 10 times as potent as the latter. The analysis of the changes in IRT distributions revealed that the shorter IRTs were increased and longer ones were decreased by both drugs. Such a finding has been reported not only in the behavior maintained by Sidman avoidance schedules, but also in the discriminated Sidman avoidance schedule [2, 5, 21], in which the delivery of shock is predicted by an extroceptive warning stimulus, and also in the differential reinforcement of low rate (DRL) schedule [1, 8, 20]. These changes in IRT distribution are possibly attributable to the psychomotor-stimulant effect of AM and CA. The present experiment, however, failed to reveal any reason for the difference in effects between AM and CA.

CPZ, DZ and PB, which are central depressants, all increased the total number of shocks delivered nearly in parallel with the dosages. Thus, these drugs inhibited avoidance responding. There were, however, differences among drugs with regard to the changes in total number of responses and IRT distributions. CPZ decreased IRTs in the 2nd and 3rd components, while it markedly increased them in the 1st and 4th components. Because of the counter-

balancing of the two reverse changes, the total number of responses appeared unaltered. The increase of IRTs in the 4th component indicated that the rat pressed the lever immediately after exposure to shock, and postponed the succeeding shock. Therefore, this response may be considered to be analogous with an escape response. In spite of marked increase in the number of shocks, the IRTs in the 5th component, which were considered to be equivalent to escape failures, increased less. It has been reported that CPZ and the other neuroleptic drugs, when given in doses less than those producing muscle incoordination and/or catalepsy, decrease only the avoidance response but not the escape response [6, 7, 8, 10, 12, 16]. These findings were supported by the results of the present experiment. On the other hand, the increase of IRTs in the 1st component might be attributed to the burst responses which were associated with an increased number of shocks delivered. A similar phenomenon was often observed in the course of training preceding the establishment of the behavioral baseline.

As to the inhibitory effect of DZ on avoidance responding, the muscle-relaxing effect could be considered to have been a main contributor. Gross observation frequently revealed marked ataxia in animals that received more than 0.5 mg/kg of DZ. At that time, they often received shock while clinging to the lever. Thus, they were evidently unable to press the lever. The author [15] has already shown, by means of rota-rod and traction performances in mice, that DZ is more apt to produce muscle relaxation than CPZ. The fact that repeated administration of DZ easily produces tolerance to the inhibitory effect on avoidance responding [22] also suggests that the effect might be rather different from that of CPZ.

The inhibitory effect of PB on avoidance responding was more similar to that of DZ than of CPZ. Actually, the behavioral effects of PB resemble those of DZ in many respects [3, 4, 6, 8, 9, 23]. But with regard to the increase of IRTs in the 4th component, PB gave more marked evidence than DZ, while the former elicited less increase than the latter in the 5th component. At a dose of 5.0 mg/kg, PB increased the IRTs in the 1st component. These results may be due to the differences between the properties of PB and DZ.

It has generally been said that in a small dose of benzodiazepine derivatives or barbiturates increase only the number of shocks delivered without affecting total number of responses, whereas in a subanesthetic dose or at a motor-dysfunction-inducing dose, they decrease the total number of responses, while at the same time inhibiting escape responses [7, 17, 23]. In the present experiment, however, relatively small doses of DZ and PB produced an inhibition of avoidance responding: a decrease in the total number of responses and an increase in shocks delivered. These results suggest the possibility that under certain experimental conditions, a small dose of benzodiazepine derivatives or barbiturates may be sufficient to produce inhibition of avoidance responding.

The induction of the burst responses were in the order of CPZ, PB and DZ. The order of increasing in IRTs in the 5th component was DZ, PB and CPZ, while the order of manifesting the muscle-relaxing effect was also DZ, PB and CPZ [15]. It is of interest that the last two orders are the reverse of the first.

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