Pharmacology Biochemistry & Behavior, Vol. 11, pp. 617–623. Printed in the U.S.A.

Effects of Phencyclidine, *d*-Amphetamine and Pentobarbital on Spaced Responding in Mice[1]

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Received 4 January 1979

BALSTER, R. L. AND J. B. BAIRD. *Effects of phencyclidine, d-amphetamine and pentobarbital on spaced responding in mice.* PHARMAC. BIOCHEM. BEHAV. 11(6) 617–623, 1979.—The effects of acute IP administration of phencyclidine (PCP), *d*-amphetamine (AMPH) and pentobarbital (PB) were determined in 10 mice trained to lever press on a differential reinforcement of low rate 10 sec schedule of sweetened milk presentation. The effects of PCP were highly consistent, with large response rate increases (and a corresponding shift toward shorter interresponse times) at doses of 1 and 3 mg/kg. Higher doses generally decreased response rates and resulted in a bimodal interresponse time distribution. The effects of AMPH were similar to PCP but less consistent. Although some of the subjects showed substantial response rate increases at doses between 0.3 and 10 mg/kg, half of the subjects did not show increased response rates at any dose. The effects of AMPH on the interresponse time distribution were similar to PCP. The effects of PB were least like those of PCP. The effect in most subjects was to produce a dose-related decrease in response rate and a flattening of the interresponse time distribution. Occasional small response rate increases were observed with PB.

Phencyclidine Amphetamine Pentobarbital Differential reinforcement of low rates Mouse Schedule controlled behavior

PHENCYCLIDINE (PCP) has emerged as an important drug of abuse in recent years [5,14]. Although originally developed as a dissociative anesthetic, its early pattern of abuse was as an hallucinogen. It is becoming apparent, however, that PCP is representative of a unique class of psychoactive drugs which shares pharmacological properties in common with a variety of other drug classes. The overt behavioral effects of PCP show marked species differences [3, 4, 6, 8]. In the rodent, sympathomimetic stimulant-like effects predominate whereas in the subhuman primate, PCP shows more barbiturate-like sedative effects.

Wenger and Dews [21] compared the effects of PCP to those of ketamine, *d*-amphetamine (AMPH) and pentobarbital (PB) on multiple fixed-interval fixed-ratio performance in mice. In gereral, PCP, and the closely related ketamine, were qualitatively more like AMPH than PB. To further characterize the effects of PCP on schedule-controlled responding in mice, we compared the effects of PCP, AMPH and PB on differential reinforcement of low rate (DRL) performance.

METHOD

Animals

The subjects were 10 experimentally naive adult male albino mice (ICR, Flow Laboratories, Dublin, VA) weighing between 24 and 31 g at the beginning of the experiment. The animals were maintained at a relatively constant weight by daily feeding of a fixed amount (3 g) of Ralston-Purina Rodent Chow 5001 after each daily session during weekdays, and allowing ad lib access to food following the experimental session onFriday until 23 hours before the next Monday session. They weighed between 28 and 34 g at the end of the experiment. Water was available ad lib in the home cages. The animals were housed individually in standard plastic mouse cages (18×29×13 cm) in a room with windows to the outside which dictated the light-dark cycle. Experimental sessions were conducted during the day.

Apparatus

The experimental chambers were comprised of a test cage inside a sound attenuating outer cubicle constructed by slightly modifying a commercial 68 quart ice chest (Coleman Sno-lite). The test cage (Fig. 1) was constructed from aluminum with a clear plastic door. The diminsions were 23 cm H × 15 cm W × 12 cm D and it contained a grid floor 5 cm from the bottom making the access space for the animals 18 cm H. In one of the side walls a lever, stimulus light and dipper magazine (BRS SLD-002) were mounted. The lever was a 0.8 cm diameter piece of stainless steel tubing 1.5 cm long placed longitudinally half-way into the chamber. The lever was held into the chamber by a small metal arm and electromagnet arrangement. For this experiment the current through the electromagnet was set to require 4 g to constitute a response,

[1]Supported by National Institute on Drug Abuse Grant DA-01442. Send reprint requests to Robert L. Balster, Box 613, MCV Station, Richmond, VA 23298.

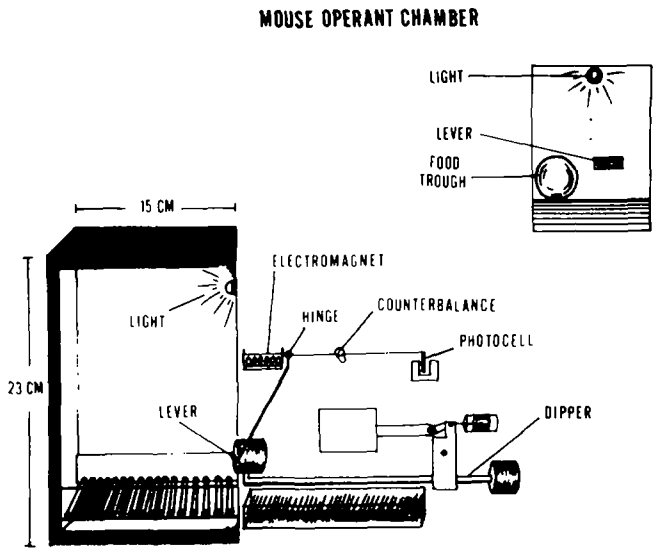

FIG. 1. Diagram of the mouse operant chamber.

as determined from a leaf spring gram gauge (Chatillon Model 65, Kew Gardens, NY). Movement of the lever was detected by an optoelectronics device (GE, H13B1) and Schmidt trigger to produce 5 V DC logic pulses compatible with our solid state interface. The control of experimental contingencies and data recording were carried out by an advanced programmable calculator (Hewlett-Packard, 9825A) and related peripheral devices. Cumulative records were plotted for selected sessions by an X-Y plotter (9862A).

Responding was maintained by sweetened milk (Land-O-Lakes All Dairy Blend; 1 part milk powder, 1 part sugar, 4 parts water) presented by a dipper arrangement. The 0.01 ml dipper remained up in the magazine, dropping into the milk solution and returning to the magazine when reinforcement occurred. Dipper presentations were accompanied by the sound of the solenoid and relay.

Procedure

A week or two after arriving from the supplier, the mice were individually housed for a week before initiating restricted feedings. Over two weeks, food access was gradually reduced to a few hours a day. During the second week, lever press training was initiated. The subjects were shaped to lever press for milk using a continuous reinforcement schedule. Shaping typically required one or two 30 min sessions. After the subjects were lever-press trained and adapted to the deprivation regimen described earlier, schedule-controlled performance was shaped. The mice were trained to respond on a differential reinforcement of low rate (DRL) 10 sec schedule by gradually increasing the shortest reinforced interresponse time (IRT) from 3 to 10 sec. The animals were given at least 2 months of training on the DRL schedule before drug injections were given. Occasional IP saline injections were administered during this period to habituate the animals to the injection routine. Experimental sessions of 30 min were conducted Monday through Friday. The stimulus light was illuminated during the session and flashed off with each lever press. Injections were given 5 min before the session. The subjects were placed in the chamber immediately after the injection.

After DRL training the experiment was initiated. Dose effect curves for PCP, AMPH, and PB were obtained in all 10 subjects. They were divided into 3 groups to counterbalance the order of drug testing. Group 1 (N=4) was tested with PCP, AMPH and PB in that order. Group 2 (N=3) was tested with AMPH, PB and PCP and Group 3 (N=3) was tested with PB, PCP and AMPH in that order. The doses of PCP were 0, 1, 3, 10 and 30 mg/kg. The doses of AMPH were 0, 0.3, 1, 3 and 10 mg/kg, and the doses of PB were 0, 1, 3, 10 and 30 mg/kg. The order of testing these doses was different for each of the subjects within each group. After the completion of all these doses, all 10 subjects were tested with 30 mg/kg AMPH. This was postponed to the end since based on pilot studies we expected marked toxicity and in fact one animal died from this injection.

The following protocol was used for drug testing. Drugs were administered every Tuesday and Friday. Thursdays were used as control sessions. Vehicle injections were tested as a drug dose (0 mg/kg). Data were collected in the form of cumulative records, response rates and reinforcement rates as well as IRT distributions. For IRT distributions, 12 two sec bins were used with responses occurring with IRT's greater than 22 sec counted in the 12th bin.

Drugs

PCP in the form of the hydrochloride salt was obtained as the veterinary product (Sernylan, Bio-Ceutics, St. Joseph, MO) and diluted with saline. AMPH was *d*-amphetamine sulfate purchased commercially dissolved in saline. PB in the form of the sodium salt was obtained by diluting Nembutal (Abbott Laboratories, North Chicago, IL) with 40% propylene glycol, 10% ethanol, and 50% water. Vehicle injections for each drug corresponded to these diluents. All injections were 5 ml/kg given IP 5 min before the session. Dosages refer to the total salts.

RESULTS

Representative DRL 10 sec control performances for each of the 10 mice are shown in Fig. 2. This figure illustrates the range of day to day variability seen in various subjects. In general, average control response rates between 6 and 7 responses per min were obtained. Optimal DRL 10 sec performance is 6 responses per min. In general, the subjects averaged between 2.6 and 3.4 reinforcers per min of the maximum 6 per min avaliable. This indicates that mice exhibit excellent DRL schedule-controlled performance, cf. [20].

The effects of AMPH, PCP and PB on the average rate of reinforcement are shown in Fig. 3. Control performance for one of the subjects (no. 8225) became highly variable during the determination of the PB dose-response curve (the last drug to be studied in this subject), consequently data for this animal is not included in the PB group averages. With PB, dose-related decreases were seen. Using a *t*-test for differences, comparing reinforcement rates at each drug dose to average control performance, the effects of 10 and 30 mg/kg PB were significant ($p<0.01$). The shape of the dose-effect curve for PB shows a dramatic change between 10 and 30 mg/kg indicating a tendency for all-or-none effects. For AMPH, even the lowest dose tested resulted in some disruption of responding ($p<0.01$) whereas at the highest dose, complete disruption was not observed. The lowest dose of PCP also resulted in some disruption ($p<0.01$) and at 30

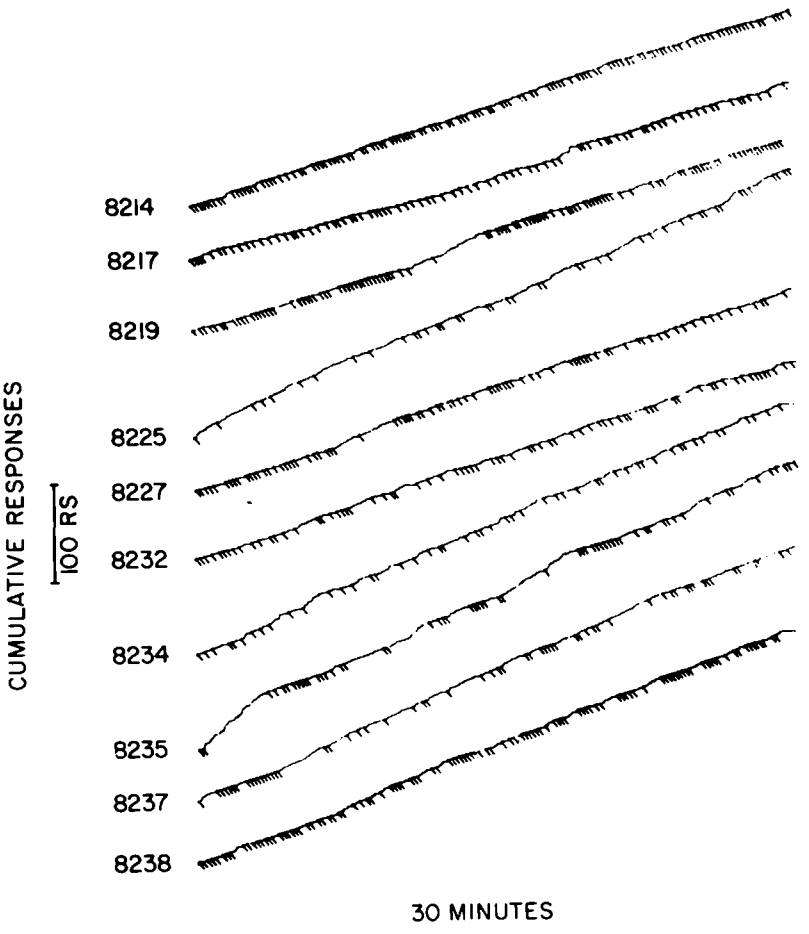

FIG. 2. Cumulative response records for baseline DRL performance for each of the 10 subjects. Diagonal marks on the response pen line indicate the presentation of food.

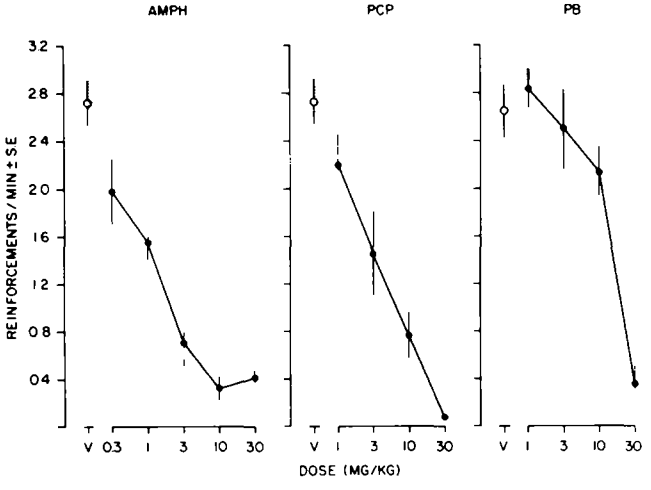

FIG. 3. The effects of *d*-amphetamine, phencyclidine and pentobarbital on the rate of reinforcement for DRL performance. Values represent the means ± 1 standard error for 9 or 10 mice. The points at V represent the results of vehicle administration. The shaded area is ± 2 standard errors for control performance during the testing of each drug.

mg/kg almost a complete loss of reinforcers occurred. Due to the nonlinear nature of these dose-effect curves point estimates of potency were made from quadratic regression lines fit to the data by least squares [7]. The dose of each drug necessary to produce about a 50% decrease in reinforcements to 1.5 reinforcements per min was estimated. For AMPH this dose is 0.72 mg/kg, for PCP 2.9 mg/kg, and for PB 14.4 mg/kg. This indicates that the order of potency was AMPH >PCP>PB.

The effects of AMPH, PCP and PB on average rate of responding are shown in Fig. 4. Average control performances (indicated by the shaded area) did not differ much during the testing of each drug. AMPH and PB only resulted in decreases in mean response rates, whereas consistent large increases in mean response rate occurred with PCP. It is clear from the measures of variability, however, that the effects of AMPH were inconsistent, with some animals showing increases, others showing decreases. The intermediate effect at 10 mg/kg AMPH is the result of averaging two animals showing large rate increases with animals showing decreases or no effect.

The general nature of the individual differences in the effects of these three drugs is shown in Table 1. For this table average response rates ± 2 standard deviations were calculated for each subject from control sessions during each of

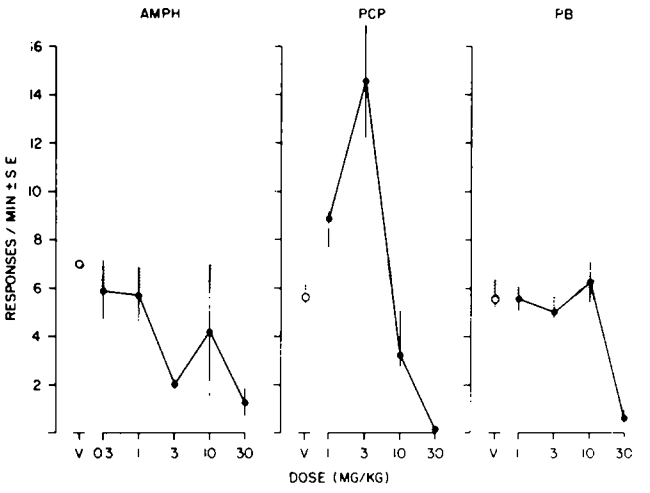

FIG. 4. The effects of *d*-amphetamine, phencyclidine and pentobarbital on the rate of responding for DRL performance. Details of the figure are the same as for Fig. 2.

the three drug effect determinations. If a test dose resulted in response rates greater than the upper limit, the effect was called a response rate increase and coded I. If the effect was a response rate within 2 standard deviations of the average control rate, the result was coded no effect; and similarly, if the effect was a response rate below the lower limit, the effect was called a suppression and coded S. Suppression where no responding was observed was denoted by a 0. Looking first at the AMPH data, it can be seen that both increases and decreases were seen at doses of 0.3 to 10 mg/kg. At no dose did more than three of the subjects show response rate increases and five of the subjects did not show response rate increases at any dose of AMPH. Response rate increases, when they did occur, were often very large. At 10 mg/kg subject 8234 responded 27.3 times per min. With PCP, reliable response rate increases were seen at 1 and 3 mg/kg. All but one of the subjects showed response rate increases at least at one dose of PCP, and in some cases these were also very large. For example, subject 8238 responded 30.6 times per min after 3 mg/kg PCP. It is interesting to note that the subject that had the greatest response rate increases after AMPH (no. 8234) also had very large response rate increases after 3 and 10 mg/kg PCP. PB generally produced response rate decreases although occasional moderate increases in response rate were seen in five of the subjects. The highest response rate of 12.2 responses per min after PB was seen after 10 mg/kg in subject 8238. After 30 mg/kg this subject did not respond. This is indicative of the steepness of the PB dose-response curve. Inconsistent effects were seen at 10 mg/kg, whereas 30 mg/kg disrupted 8 of the 9 subjects and completely suppressed responding in 5.

Interresponse time (IRT) distributions are provided in Fig. 5. The figure shows the percentage of responses for each subject in each bin averaged for all subjects responding at greater than 0.5 response per min for each of the treatments except for the lowest dose of AMPH. The IRT distribution for this dose was almost identical to that after 1 mg/kg AMPH. IRT distributions for subjects responding less than 0.5 response per min were excluded from the analysis. The number of remaining subjects averaged for each treatment is indicated in the figure. Control IRT distributions after saline administration (VEH for AMPH and PCP) are typical bimodal distributions for DRL responding. The propylene glycol-ethanol vehicle for PB may have had some effect as evidenced by the relatively large percentage of very long IRT's. In general, the effect of PB was unlike AMPH and PCP in that no consistent shift in the distribution was seen, only a tendency to flatten somewhat. For the two subjects responding above 0.5 responses per min after 30 mg/kg, responding tended to occur equally in each bin. For AMPH and PCP, on the other hand, large increases in the first and last bins were seen. Lower doses of AMPH tended to shift the IRT distribution towards shorter IRT's although increases in the last IRT bin were always observed. This re-

TABLE 1

INDIVIDUAL DIFFERENCES IN THE EFFECTS OF PHENCYCLIDINE, d-AMPHETAMINE AND PENTOBARBITAL ON DRL PERFORMANCE IN MICE

	AMPH						PCP					PB				
Subject	V	.3	1	3	10	30	V	1	3	10	30	V	1	3	10	30
8214	I	—	—	S	S	S	—	—	I	S	S	I	—	—	—	0
8217	—	I	—	0	S	S	—	I	—	S	0	—	I	I	S	0
8219	I	I	I	S	S	S	S	I	I	S	S	—	—	—	I	S
8225	—	S	S	S	0	S	S	I	I	S	0					
8227	—	S	S	S	S	S	—	I	S	S	S	S	S	S	S	—
8232	—	S	S	0	S	S	I	—	I	0	0	—	I	—	—	S
8234	—	I	I	—	I	—	—	S	I	I	0	I	S	S	—	0
8235	—	—	—	S	I	0	S	I	I	S	S	S	S	I	I	0
8237	—	S	S	S	S	S	—	I	I	S	0	—	S	S	S	S
8238	—	I	I	0	S	S	—	I	I	S	S	S	S	S	I	0
Totals																
I	2	4	3	0	2	0	1	7	8	1	0	2	2	2	3	0
—	8	2	3	1	0	1	6	2	1	0	0	4	2	3	3	1
S+0	0	4	4	9	8	9	3	1	1	9	10	3	5	4	3	8

I=Response rate increase; —=No effect; S=Response rate suppression; 0=No responding.

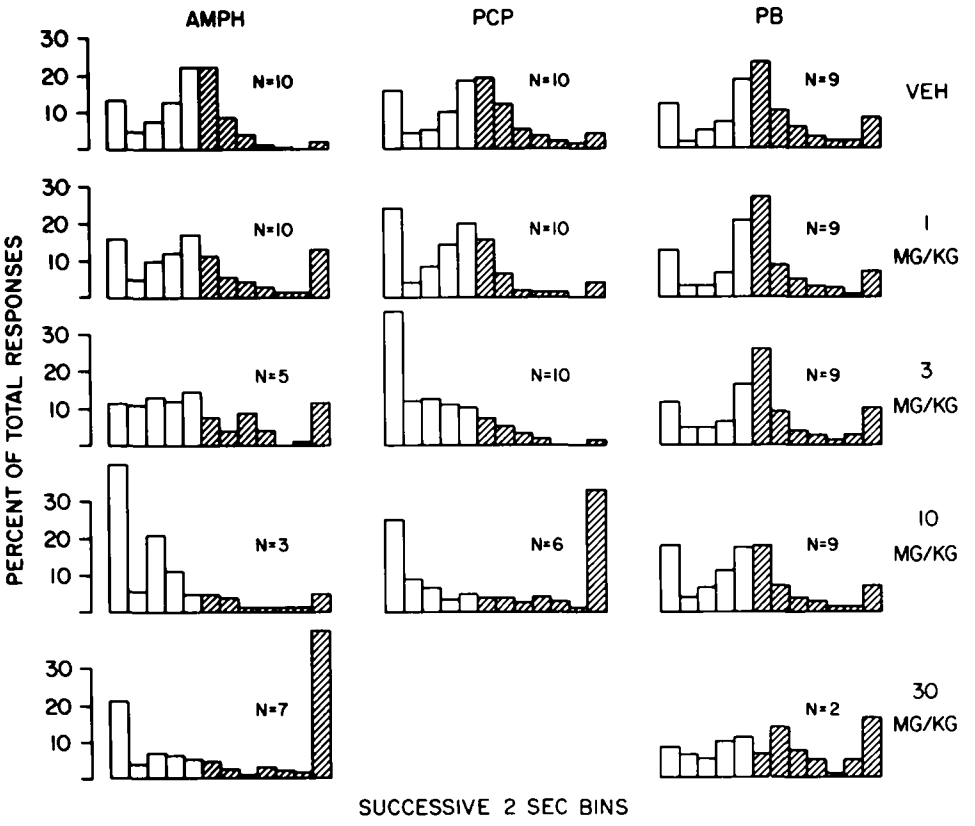

FIG. 5. The effects of *d*-amphetamine, phencyclidine and pentobarbital on interresponse times for DRL performance. Each IRT histogram is divided into 2 sec bins, the first is the mean percent of the total responses that were spaced 0–2 sec, the last is the mean percent of the total responses that were spaced by more than 22 sec. The shaded portions of the histograms are reinforced IRT's. The data for subjects with overall response rates less than 0.5 responses per min is not included. The IRT distributions for each remaining subject expressed as the percent of the total for that subject for that session were averaged to produce the histograms presented here.

flects the fact that both response rate increases and decreases were seen at 1 and 10 mg/kg AMPH. PCP, where more consistent results were seen, showed a shift toward shorter IRT's at 1 and 3 mg/kg without concomitant increases in long IRT's. Only at 10 mg/kg did increases in both the first and last bin occur as were seen with AMPH.

DISCUSSION

In general, the results of this study are in agreement with the study by Wenger and Dews [21] in that the effects of PCP on schedule-controlled responding were more like AMPH than PB. In their study PCP, AMPH and ketamine each produced increases in fixed-interval response rates at doses that decreased responding in the fixed-ratio component. The effects of PB were qualitatively similar on both schedule components. We found that both PCP and AMPH could produce large increases in DRL responding whereas PB generally decreased responding. The effects of PCP, however, were much more consistent than those of AMPH. PCP and AMPH also resulted in more similar IRT distributions. Shifts toward shorter IRT's were seen with both drugs. PB, on the other hand, resulted in a general flattening of the IRT distribution, with increases in both short and long IRT's.

The effects of AMPH and related drugs on DRL responding have been studied by others with mixed results. Studies with rats [1, 12, 17, 18, 19, 22] are fairly consistent in showing response rate increases after some doses of AMPH, methylphenidate or cocaine. Studies with pigeons [10,13] do not show reliable response rate increases from AMPH. This may be due to the poor performance of pigeons on DRL schedules under control conditions. Fischman and Schuster [9] found that *d*-methylamphetamine produced only response rate decreases in rhesus monkeys. The effects of caffeine on DRL performance in mice have recently been reported [20]. Response rate increases at intermediate doses can be inferred from inspection of the IRT distributions which were shifted toward higher proportions of short IRT's. The consistency of these rate increases for the four subjects cannot be determined. In our study, mice show considerable individual variability in response to AMPH. Five of the 10 mice failed to show response rate increases at any dose of AMPH whereas responding in the other five was increased after at least one dose of AMPH. In one mouse this response rate increase was very large (> 400%). This same animal also showed sizeable response rate increases from PCP. When the data for all 10 subjects were averaged, AMPH did not result in increases in average response rate. The IRT distri-

butions after AMPH reflect this inconsistency. The distributions were obtained by averaging data from animals with response rate increases and data from animals with response rate decreases. The animals with increases contribute to the shift toward shorter IRT's and the animals with response rate decreases contribute to the increases in the longest IRT's due to pausing in the session.

The effects of PCP on DRL responding have not been studied previously. Our results show the effects of PCP to be similar to AMPH as reported by others in rats [1, 12, 17]. Doses of 1 and 3 mg/kg produced consistent response rate increases and shifted the IRT distribution progressively toward shorter IRT's. Since, unlike AMPH, these increases occurred in most of the subjects at these doses, the average IRT distributions better represent the results for individual animals. At 10 mg/kg, where response rate increases and decreases were observed, the IRT distribution was bimodal with peaks in the first and last bin, more similar to those observed with AMPH.

The sensitivity of DRL performance to disruption by PCP is similar to the sensitivity of other behavioral measures in mice. The lowest effective dose was 1 mg/kg and an ED_{50} estimate for decreasing reinforcement rate was 2.9 mg/kg. Using multiple fixed-interval fixed-ratio performance, Wenger and Dews [21] found the minimally effective dose for disruption to be about 3 mg/kg IP. In a recent study [2] the ED_{50} of PCP for effects on a simple motor performance was 2.8 mg/kg IP; and the subcutaneous ED_{50} for PCP on the rotarod has been shown to range from 2.3 to 3.0 mg/kg [11,15].

The effects of barbiturates on DRL performance of rats have been studied by Kelleher *et al.* [12], Stretch and Dalrymple [19], and Sanger and Blackman [16]. Kelleher *et al.* [12] studied the effects of phenobarbital on a DRL 18 sec schedule with a 3 sec limited hold. Overall response rates were not significantly increased, although there was some increase in the frequency of short IRT's. These increases in short IRT's were accompanied by pausing, therefore the overall effect was to flatten the IRT distribution. Stretch and Dalrymple [19] studied the effects of PB on DRL 15 sec with a 5 sec limited hold. They also found that PB tended to flatten the IRT distribution, i.e., increase the frequency of both short and long IRT's. At 10 mg/kg there was a tendency for response bursts to alternate with periods of non-responding. At 2.5 and 5.0 mg/kg they observed overall increases in response rates above control values. Response rate increases were also seen after phenobarbital by Sanger and Blackman [16]. Although PB did not increase average response rates in our experiment, the results are generally consistent with these studies, and we did see small response rate increases in some of the subjects. The general tendency in all these studies was for barbiturates to flatten the IRT distribution.

In conclusion, PCP produced reliable response rate increases in DRL performance of mice similar to those seen in some mice with AMPH. The effect of PCP and AMPH were unlike those of PB, where there is little effect on DRL performance until response rate decreasing doses were reached. The greater similarity of PCP to AMPH than to PB is consistent with other studies of the effects of these drugs in rodents.

ACKNOWLEDGEMENTS

William L. Woolverton provided helpful comments on an earlier version of this manuscript. We appreciate the assistance of Roxanne Pross, Donna Williams, and John E. Burkhalter in preparing the manuscript and figures.

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