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DRUG DISCRIMINATION IN RATS UNDER CONCURRENT VARIABLE-INTERVAL VARIABLE-INTERVAL SCHEDULES

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Eight rats were trained to discriminate pentobarbital from saline under a concurrent variable-interval (VI) VI schedule, on which responses on the pentobarbital-biased lever after pentobarbital were reinforced under VI 20 s and responses on the saline-biased lever were reinforced under VI 80 s. After saline, the reinforcement contingencies programmed on the two levers were reversed. The rats made 62.3% of their responses on the pentobarbital-biased lever after pentobarbital and 72.2% on the saline-biased lever after saline, both of which are lower than predicted by the matching law. When the schedule was changed to concurrent VI 50 s VI 50 s for test sessions with saline and the training dose of pentobarbital, responding on the pentobarbital-biased lever after the training dose of pentobarbital and on the saline-biased lever after saline became nearly equal, even during the first 2 min of the session, suggesting that the presence or absence of the training drug was exerting minimal control over responding and making the determination of dose–effect relations of drugs difficult to interpret. When the pentobarbital dose–response curve was determined under the concurrent VI 50-s VI 50-s schedule, responding was fairly evenly distributed on both levers for most rats. Therefore, 6 additional rats were trained to respond under a concurrent VI 60-s VI 240-s schedule. Under this schedule, the rats made 62.6% of their responses on the pentobarbital-biased lever after pentobarbital and 73.5% of their responses on the saline-biased lever after saline, which also is lower than the percentages predicted by perfect matching. When the schedule was changed to a concurrent VI 150-s VI 150-s schedule for 5-min test sessions with additional drugs, the presence or absence of pentobarbital continued to control responding in most rats, and it was possible to generate graded dose–response curves for pentobarbital and other drugs using the data from these 5-min sessions. The dose–response curves generated under these conditions were similar to the dose–response curves generated using other reinforcement schedules and other species.

Key words: drug discrimination, concurrent schedules, stimulus control, schedule control, pentobarbital, rats

Drug discrimination is under the joint control of the training drug and the schedule of reinforcement that maintains responding (Holloway & Gauvin, 1989; Massey, McMillan, & Wessinger, 1992; McMillan & Li, 1999a; McMillan, Li, & Hardwick, 1997; McMillan & Wenger, 1984; Snodgrass & McMillan, 1991, 1996; Stolerman, 1991; Young, 1991), as well as the training history (McMillan & Li, 1999b; McMillan, Sun, & Hardwick, 1996). Although the role of the schedule of reinforcement has only recently been investigated extensively in drug-discrimination research, evidence is accumulating to show that if drug-discrimination responding is maintained by interval schedules of reinforcement, drugs that substitute for the training drug produce generalization curves that are graded (Massey et al., 1992; McMillan et al., 1997; Snodgrass & McMillan, 1991). In contrast, when responding is maintained by fixed-ratio (FR) schedules, these dose–response curves are quantal (Massey et al., 1992; McMillan & Li, 1999a; Snodgrass & McMillan, 1991).

Recently, we have extended these observations that graded responding occurs when drug-discrimination responding is maintained under interval schedules to experiments with concurrent interval schedules. Not only did we establish drug discrimination under concurrent reinforcement schedules on which responding on both operanda could produce the reinforcer, but also the generalization curves for the training drug and for other drugs that generalized to the training drug were graded under two concurrently available variable-interval (VI) schedules (Snodgrass & McMillan, 1996) and two concurrently available fixed-interval (FI)

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schedules (McMillan et al., 1997). In contrast, when responding was maintained under concurrently available FR schedules, the dose–response curves were quantal (McMillan & Li, 1999a). The use of concurrent schedules in drug-discrimination experiments offers several advantages over other schedules. For example, many studies on drug discrimination have used FR schedules to maintain responding. When subjects are well trained under FR schedules, almost 100% of responses occur on the drug operandum after administration of the training drug and near 0% occur on that operandum after saline administration. Under these conditions it is not possible to determine if doses of the training drug higher than the training dose can produce more responding than the training dose on the drug operandum. Because responding occurs on both operanda under concurrent schedules, this problem is avoided when drug discrimination is studied under concurrent schedules. Furthermore, the use of concurrent schedules in the study of drug discrimination provides the opportunity to integrate drug-discrimination data with the matching law (Herrnstein, 1970, 1974). The present experiments were an attempt to extend the findings of Snodgrass and McMillan (1996), who used concurrent VI VI schedules to study pentobarbital discrimination in pigeons, to another species, the rat.

METHOD

Subjects

Fourteen male Sprague-Dawley rats were used. At the beginning of training, the rats were 3 to 4 months old and weighed an average of 291 g (range, 230 to 340 g). The rats were individually housed in a vivarium under a 12:12 hr light/dark cycle (illuminated from 7:00 a.m. to 7:00 p.m.). They were maintained at 85% of their free-feeding body weights by food earned during the experiments and supplemental feeding after each experimental session. They had free access to water in the home cage, but not in the test chamber.

Apparatus

Rats were tested in two-lever operant test chambers (Gerbrands Model 7400) enclosed in sound-attenuating chambers (Gerbrands Model 7200). The test chambers were equipped with stimulus lights over the levers and a houselight on the chamber ceiling. A pellet dispenser could deliver 97-mg Noyes food pellets into a food cup mounted between the levers. Masking noise and the circulation of air were provided by a fan located in the rear wall of the sound-attenuating chamber. Programming and recording were controlled through a MED Associates interface by microprocessor equipment located in an adjacent room.

Procedure

The rats were conditioned to lever press by an autoshaping procedure whereby the stimulus lights above each lever were briefly illuminated prior to delivery of a food pellet for 25 trials for the left lever during one session and 25 trials for the right lever during another session. Subsequently, the stimulus lights above the left lever were turned on and each response on the left lever produced a food pellet. Next the stimulus lights above the right lever were turned on and each response on the right lever produced a food pellet. When the rats had earned 50 food pellets for responding on the left lever during one session and 50 food pellets for responding on the right lever during one session, the next phase of training was initiated.

Prior to each subsequent training and test session, the rats were administered the drug or its vehicle (0.9% saline solution) and placed into the darkened operant chamber for a 10-min period. During this period, lever presses had no programmed consequences. At the end of the 10-min period, stimulus lights over the right or left lever were illuminated depending on whether the training drug (5.0 mg/kg pentobarbital) or saline had been administered before the 10-min dark period. The first group of 8 rats was divided into two subgroups. For the even-numbered rats (R462, R464, R466, and R468) each response on the right lever was reinforced after pentobarbital and each response on the left lever was reinforced after saline administration. For the odd-numbered rats (R463, R465, R467, and R469), these conditions were reversed. After each rat had earned 50 pellets under continuous reinforcement of lever pressing during both a pentobarbital and

a saline session, drug-discrimination training was initiated.

For discrimination training, the stimulus lights over both levers were illuminated and responding was reinforced under a concurrent VI VI schedule. For the even-numbered rats, the schedule was programmed to allow the rats to earn four times as many reinforcers for responses on the right lever as on the left lever after pentobarbital administration and four times as many reinforcers for responses on the left lever as on the right lever after saline administration. For the odd-numbered rats, the position of the levers associated with pentobarbital and saline administration were reversed. Training sessions were 30 min and the initial reinforcement schedule was concurrent VI 5 s VI 20 s. Rats were trained under this schedule for 10 sessions. The administration of pentobarbital or saline before sessions alternated. During the next eight sessions, the schedule of reinforcement was unchanged, but pentobarbital and saline administration alternated after every two training sessions. The schedule parameters then were increased to concurrent VI 10 s VI 40 s for eight sessions, concurrent VI 15 s VI 60 s for eight sessions, and finally to concurrent VI 20 s VI 80 s. Under the latter schedule, pentobarbital and saline training sessions alternated.

Each VI schedule component operated independently so that delivery of a reinforcer under one schedule did not affect reinforcer availability under the other. A changeover delay (COD) was used, during which responses could not be reinforced within 3 s whenever responding switched from one lever to the other (Catania, 1966).

During the testing phase, other doses of pentobarbital were substituted for the training dose. In the testing phase, the rats continued regular training sessions on Monday, Wednesday, and Thursday under the usual concurrent VI 20-s VI 80-s schedule. The data from the Thursday sessions (training sessions) provided one measure of baseline variability. A range of doses of pentobarbital and other drugs were studied on Tuesdays and Fridays. These sessions were also 30 min and will be referred to as drug test sessions. During drug test sessions, the schedule was changed to a concurrent VI 50-s VI 50-s schedule to minimize the possibility that the rats would be controlled by the difference in reinforcement density under the two VI schedule components used during training, rather than by the drug dose that was administered. To determine whether the change in schedule to concurrent VI 50 s VI 50 s during drug test sessions affected baseline performance, three sessions were conducted under the concurrent VI 50-s VI 50-s schedule after administration of the usual training dose of pentobarbital and three sessions were conducted after the administration of saline.

By the time dose–response curves had been completed for pentobarbital, chlordiazepoxide, phencyclidine and methamphetamine, it had become apparent that during control test sessions and drug test sessions the change in the reinforcement schedule during test sessions was controlling responding. Several unsuccessful training manipulations were performed in attempts to correct this problem, but the results of these failed attempts will not be reported here, nor will the data on the dose–response effects of drugs other than pentobarbital.

One reason that the reinforcement schedule came to control responding might have been that the change from the concurrent VI 20-s VI 80-s schedule to the concurrent VI 50-s VI 50-s schedule was easily discriminable. Under the assumption that changes in concurrent VI VI schedules with longer mean interval values might be less discriminable, 6 new rats were trained to respond under a different concurrent VI VI schedule using a training procedure almost identical to the procedure used for training the first group. The lever pressing of these rats also was autoshaped and then the rats were exposed to drug-discrimination training in a manner identical to rats in the first group. For Rats R492, R494, and R496, responses on the left lever were reinforced initially after 5.0 mg/kg pentobarbital administration and responses on the right lever were reinforced after saline administration. For Rats R491, R493, and R495, responses on the right lever were reinforced initially after 5.0 mg/kg pentobarbital administration and responses on the left lever were reinforced after saline administration.

Subsequently, discrimination training proceeded for these rats in a manner identical to the first group of rats. The only difference

was in the concurrent-schedule values. Whereas the first group was trained under the concurrent VI VI schedule with gradually increasing mean interval values to a final schedule of concurrent VI 20 s VI 80 s, this second group of rats advanced to a final schedule of concurrent VI 60 s VI 240 s. When other doses of pentobarbital and doses of other drugs were substituted for the training dose of pentobarbital, the reinforcement schedule for the second group of rats was changed to a concurrent VI 150-s VI 150-s schedule. Test sessions in which the reinforcement schedule was concurrent VI 150 s VI 150 s were limited to 5 min in an attempt to prevent the schedule change from controlling behavior to the extent that had occurred with the first group of rats. As with the first group of rats, three sessions also were conducted following administration of saline or the 5.0 mg/kg training dose of pentobarbital, to determine if the schedule change disrupted baseline performance. In addition to pentobarbital, the effects of chlordiazepoxide, phencyclidine, and methamphetamine were determined in these rats.

Drugs

Sodium pentobarbital (1.0, 3.0, 5.6, and 10 mg/kg; Sigma), phencyclidine hydrochloride (0.3, 0.56, 1.0, and 1.7 mg/kg; kindly supplied by the National Institute on Drug Abuse), and methamphetamine hydrochloride (0.3, 1.0, 1.7, and 3.0 mg/kg; Sigma) were studied. Doses were calculated as the salts. All drugs were dissolved in 0.9% saline, and injections were intraperitoneal, 10 min before the beginning of the session in a volume of 0.1 ml/100 g body weight.

Data Analysis

Data collected included responses on each lever, time spent responding on each lever (defined as the time accumulated under each schedule component after changeover responses), rate of responding (defined as the total number of responses on both levers divided by the session duration), and the number of changeover delays (a measure of the number of times that the rats switched from responding on one lever to responding on the other lever). The percentage of responses that occurred on the pentobarbital-biased lever was calculated by dividing the number of responses on the pentobarbital-biased lever by the total number of responses on both levers. The pentobarbital-biased lever was defined as the lever on which responses produced the reinforcer under the VI 20-s component after administration of the pentobarbital training dose during training sessions with the first 8 rats and as the lever on which responses produced the reinforcer under the VI 60-s component after administration of the pentobarbital training dose with the other 6 rats. The other lever will be referred to as the saline-biased lever. The percentage of responses on the pentobarbital-biased lever was not plotted for individual rats unless at least 30 responses had occurred during the session (an overall session response rate of one response per minute). The training and test sessions were used as baselines against which to compare the dose–response effects of drugs.

RESULTS

Drug Discrimination with Training under a Concurrent VI 20-s VI 80-s Schedule and Testing under a Concurrent VI 50-s VI 50-s Schedule

Table 1 shows data for the last 10 training sessions under the concurrent VI 20-s VI 80-s schedule and for three test sessions under the concurrent VI 50-s VI 50-s schedule. During training sessions under concurrent VI 20 s VI 80 s, rats obtained 77.6% to 84.3% of their reinforcers after saline administration by responding on the saline-biased lever and 76.6% to 82.8% of their reinforcers after pentobarbital administration for responding on the drug-biased lever. Averaged across subjects, the percentages of reinforcers delivered for responses on the lever on which responses produced the higher rate of reinforcement were close to 80% after both saline and pentobarbital administration. Thus the percentage of reinforcers delivered was close to that programmed to be delivered under the concurrent VI 20-s VI 80-s reinforcement schedule. After saline administration, rats made 60.4% to 80.7% of their responses on the saline-biased lever and after pentobarbital they made 49.3% to 82.5% of their responses on the pentobarbital-biased lever. All rats, except R466 after pentobarbital training sessions,

Table 1

Response rates (responses per second) on the saline-biased (S-B) and pentobarbital-biased (P-B) levers, percentages of responses and reinforcers delivered on the pentobarbital-biased and saline-biased levers, and changeover delays (CODs per minute) for the training sessions under concurrent VI 20 s VI 80 s and for test sessions under concurrent VI 50 s VI 50 s. Data are presented for individual rats and for the group mean.

	Saline					Pentobarbital				
	Rate		% saline biased			Rate		% pentobarbital biased		
Rat	S-B lever	P-B lever	Responses	Reinforcers	CODs	S-B lever	P-B lever	Responses	Reinforcers	CODs
Concurrent VI 20 s VI 80 s										
R462	0.31	0.10	75.8	81.9	0.9	0.12	0.37	75.0	82.8	0.8
R463	0.34	0.23	60.4	78.6	2.0	0.29	0.41	58.7	77.9	2.2
R464	0.30	0.12	70.4	77.6	1.3	0.29	0.28	49.3	80.0	1.5
R465	0.71	0.24	76.2	81.3	2.1	0.42	0.50	54.4	76.6	2.6
R466	0.43	0.15	74.0	80.3	1.2	0.16	0.75	82.5	81.3	2.0
R467	0.43	0.23	65.3	80.7	2.5	0.31	0.52	62.6	78.8	3.4
R468	0.55	0.19	74.8	81.5	1.8	0.46	0.51	52.5	77.7	0.4
R469	0.57	0.14	80.7	84.3	1.4	0.27	0.48	63.6	79.4	2.0
M	0.46	0.18	72.2	80.8	1.7	0.29	0.48	62.3	79.3	1.9
Concurrent VI 50 s VI 50 s										
R462	0.37	0.28	55.3	46.5	1.9	0.19	0.46	71.3	58.4	1.3
R463	0.46	0.31	60.2	55.5	3.0	0.53	0.41	43.5	43.9	3.1
R464	0.51	0.23	69.4	46.7	2.5	0.45	0.39	46.2	51.9	2.6
R465	1.01	0.58	64.4	50.0	4.3	0.83	0.59	41.6	45.3	4.3
R466	0.48	0.37	56.4	49.4	2.5	0.38	0.59	60.9	52.3	3.1
R467	0.47	0.41	53.7	56.1	4.3	0.57	0.40	43.8	45.2	3.8
R468	0.75	0.46	61.8	42.2	3.7	0.70	0.54	43.4	52.8	4.1
R469	0.70	0.30	70.0	56.4	2.6	0.70	0.45	39.1	45.8	2.7
M	0.59	0.37	61.4	50.4	3.1	0.54	0.48	48.7	49.5	3.1

made a lower percentage of responses on the lever on which responses produced the reinforcer under the VI 20-s component of the concurrent schedule than would be expected if the percentage of responses on each key matched the percentage of reinforcers delivered for responding on that key. After saline administration, rats made 0.9 to 2.5 CODs per minute. After pentobarbital, the range was 0.4 to 3.4 CODs per minute.

When the schedule was changed to concurrent VI 50 s VI 50 s for test sessions following the administration of saline, rats obtained 42.2% to 56.4% of their reinforcers following responses on the saline-biased lever. After pentobarbital administration, they received 43.9% to 58.4% of their reinforcers for responses on the pentobarbital-biased lever. Averaged across subjects, the percentages of reinforcers delivered for responses on each lever were close to the 50% programmed under the concurrent VI 50-s VI 50-s schedule. After saline administration, subjects made 53.7% to 70.0% of their responses on the saline-biased lever, and after pentobarbital administration they made 39.1% to 71.3% of their responses on the pentobarbital-biased lever. Under the concurrent VI 50-s VI 50-s schedule, after saline administration the percentage of responses made on the saline-biased lever was only slightly higher (5% to 20%) for most rats than the percentage of reinforcers delivered for responses on that lever, and for Rat R467 the percentage of responses on the saline lever was lower than the percentage of reinforcers delivered for responses on that lever. After pentobarbital administration with the concurrent VI 50-s VI 50-s schedule maintaining responding, for most rats the percentage of responses on the pentobarbital-biased lever was usually close to the percentage of reinforcers delivered for responding on that lever. These data suggest that the change in the reinforcement schedule and not the drug stimulus controlled responding during test sessions under the con-

current VI 50-s VI 50-s schedule. This was especially true after administration of the training dose of pentobarbital. The number of CODs for every rat increased after both saline and pentobarbital when the schedule was changed from a concurrent VI 20-s VI 80-s schedule to a concurrent VI 50-s VI 50-s schedule.

Despite the evidence that the reinforcement schedule rather than the presence or absence of pentobarbital was controlling responding during these test sessions, dose–effect curves were determined for pentobarbital. Subsequently, it was reasoned that any loss of control by pentobarbital during test sessions might develop slowly as the test session progressed. Therefore, the pentobarbital dose–response curves were determined both from data collected over the entire session and from data collected during the first 2 min of the session. Both sets of dose–response curves are shown in Figure 1. The control data show apparent control by pentobarbital during training sessions, a considerable loss of stimulus control by pentobarbital when the schedule was changed from the concurrent VI 20-s VI 80-s schedule to the concurrent VI 50-s VI 50-s schedule, and only partial control by pentobarbital during the first few minutes of these test sessions in some rats, especially R462 and R466. However, the pentobarbital dose–response curves determined under the concurrent VI 50-s VI 50-s schedule do not show consistent graded increases in the percentage of responses on the pentobarbital-biased lever as the dose increased.

When the data from the whole session are considered (Figure 1), the dose–response curves for most rats are rather flat, although the pentobarbital dose–response curves for Rats R462, R466, and perhaps R463 show some tendency for responding on the drug-biased lever to increase with dose. When data from only the first 2 min of the session are considered, the tendency for the percentage of responses on the drug-biased lever to increase as the dose increased became more pronounced in some rats (R462, R467, and R468), but whether the data from the whole session or the first 2 min of the session were used made little difference in most rats. These data suggest that the extended discrimination training produced stimulus control in some but not all rats. However, when the schedule was changed for test sessions, as the test sessions progressed, control over responding was rapidly assumed by the new reinforcement schedule rather than the presence or absence of the training drug.

Because the pentobarbital dose–response curves were usually flat when data from the whole session were considered, and because these dose–response curves were improved only marginally when the data from the first 2 min of the session were analyzed, the dose–response curves for the effects of the other drugs will not be presented.

Drug-Discrimination Training under a Concurrent VI 60-s VI 240-s Schedule and Testing under a Concurrent VI 150-s VI 150-s Schedule

Baseline data for responding under concurrent VI 60-s VI 240-s and concurrent VI 150-s VI 150-s schedules are shown in Table 2. During training sessions under concurrent VI 60 s VI 240 s, rats obtained 79.0% to 88.0% of their reinforcers after saline administration by responding on the saline-biased lever and 70.0% to 81.4% of their reinforcers after pentobarbital administration for responding on the drug-biased lever. Averaged across the subjects, the percentage of reinforcers delivered (82.1% and 78.2%) was close to the programmed percentage under the concurrent VI 60-s VI 240-s reinforcement schedule. After saline administration, rats made 61.8% to 79.0% of their responses on the saline-biased lever and after pentobarbital they made 54.1% to 71.7% of their responses on the pentobarbital-biased lever. All rats, except R493 after saline training sessions, made a lower percentage of responses on the lever on which responses produced the reinforcer under the VI 60-s component of the concurrent schedule than would be expected if the percentage of responses on each lever matched the percentage of reinforcers delivered for responding on that lever. During training sessions, the number of CODs per minute was higher under the concurrent VI 60-s VI 240-s schedule than it had been under the concurrent VI 20-s VI 80-s schedule.

When the schedule was changed to a concurrent VI 150-s VI 150-s schedule for test sessions following the administration of saline, the percentage of reinforcers obtained for responses on the saline lever varied widely

(20.0% to 100%), but the group average of 54.8% was close to that programmed under the concurrent VI 150-s VI 150-s schedule of reinforcement. After pentobarbital administration, rats received 25.0% to 63.3% of their reinforcers for responses on the pentobarbital-biased lever. Averaged across subjects, the percentage of reinforcers delivered for responses on the drug-biased lever was 48.1%, which again is close to the 50% programmed to occur under the concurrent VI 150-s VI 150-s schedule. CODs per minute were not consistently affected across rats when the schedule was changed from concurrent VI 60 s VI 240 s to concurrent VI 150 s VI 150 s.

Because the rats'responding again seemed to be controlled by the reinforcement schedule rather than by the presence or absence of pentobarbital when the training schedule was changed for test sessions, it seemed unlikely that reasonable dose–response curves could be developed from data collected from the usual test sessions. Therefore, the test sessions were shortened to 5 min when the schedule was changed to concurrent VI 150 s VI 150 s for testing the effects of other doses of pentobarbital and other drugs.

The data for the pentobarbital dose–response curve are shown in Figure 2. The control data again show apparent control by pentobarbital during the continuing Thursday training sessions conducted during the period when the dose–response curves were determined and during the first 5 min of these training sessions, except for Rat R496. When the reinforcement schedule was changed to concurrent VI 150 s VI 150 s for 5-min sessions, responding continued to be controlled by the presence or absence of pentobarbital to some extent in all rats.

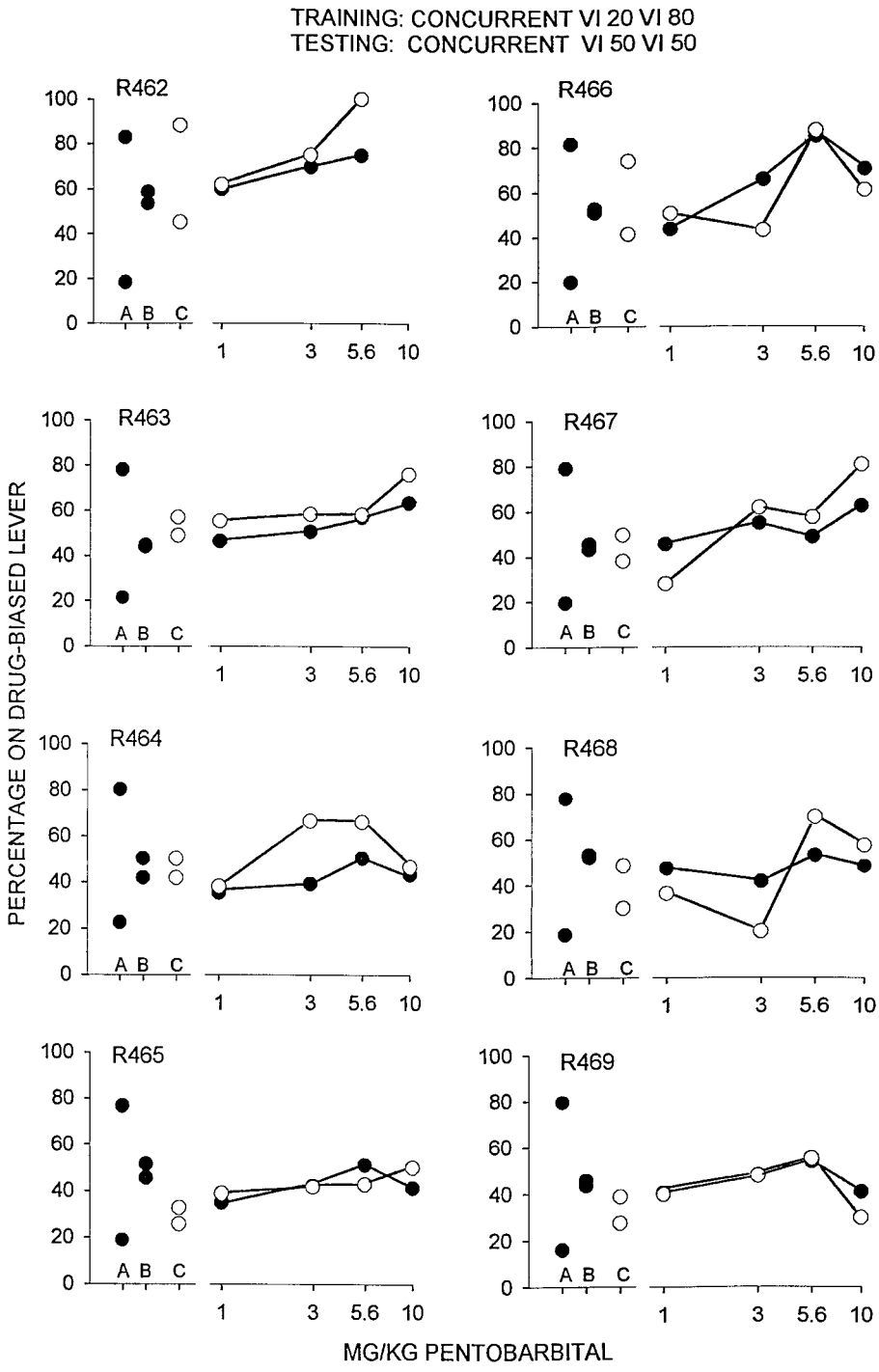
Doses of 1.0 to 5.6 mg/kg pentobarbital produced an increased percentage of responses on the pentobarbital-biased lever for all rats except Rat R492. At the 10 mg/kg dose of pentobarbital, the dose–response curve for pentobarbital turned over for many rats, especially for Rat R496, although the dose–response curve continued to ascend for Rat R495. Only Rat R492 showed the flat pentobarbital dose–response curve seen in the previous experiment.

The effects of chlordiazepoxide during these 5-min sessions are shown for individual rats in Figure 3. Although there are some irregularities in these curves, for most rats, lower doses produced responding on the saline-biased lever, with higher doses producing increased responding on the pentobarbital-biased lever. After the highest doses of chlordiazepoxide, the dose–response curves turned over, especially for Rats R491, R493, and R494.

The dose–response curves for the effects of phencyclidine on responding under the concurrent VI 150-s VI 150-s schedule are shown in Figure 4. With the exception of Rat R496, the 0.3 mg/kg doses of phencyclidine produced responding on the saline-biased lever at the same level as during control sessions. For Rat R496, the lowest dose of phencyclidine produced responding on the pentobarbital-biased lever to the same extent as that seen during control sessions. Ignoring this anomaly of the 0.3 mg/kg dose of phencyclidine, in all rats except R494, responding increased on the pentobarbital-biased lever as the dose of phencyclidine increased. This effect is even seen in Rat R496 if the effect of the lowest dose of phencyclidine is ignored. For Rat R494, the phencyclidine dose–response curve was flatter. After the higher doses of phencyclidine, the dose–response curves turned over for Rats R491, R492, and R496. At 3.0 mg/kg phencyclidine, 3 of the rats did not respond on either lever. Rat R494 did not respond after the 1.8 mg/kg dose of phencyclidine.

Dose–response curves for the effects of methamphetamine are shown in Figure 5. All rats responded on the saline-biased lever to the same extent as during training sessions after all doses of methamphetamine when responding occurred.

The effects of drugs on rates of responding are shown in Table 3. Rats R492, R495, and R496 showed rate decreases after the 10 mg/kg dose of pentobarbital, but this effect was not seen after the 17 mg/kg dose. Responding was sustained in the other rats at all doses studied. High doses of other drugs reduced responding considerably in most rats. At the highest dose of methamphetamine studied (3.0 mg/kg), none of the rats responded. These drugs produced few effects on CODs (Table 4) that could not be attributed to decreases in rates of responding.


TRAINING: CONCURRENT VI 20 VI 80
TESTING: CONCURRENT VI 50 VI 50
R462
R466
R463
R467
R464
R468
R465
R469
PERCENTAGE ON DRUG-BIASED LEVER
MG/KG PENTOBARBITAL
A B C
1 3 5.6 10
0 20 40 60 80 100

DISCUSSION

During drug-discrimination training, responding comes under the joint control of the schedule of reinforcement and the drug stimulus (Holloway & Gauvin, 1989; Koek & Slangen, 1982; Massey et al., 1992; McMillan & Wenger, 1984; Snodgrass & McMillan, 1991). The training dose of the drug produces interoceptive stimuli that become established as discriminative stimuli through differential reinforcement. We have shown recently that drugs can be established as discriminative stimuli in pigeons under conditions in which both response alternatives produce the reinforcer (McMillan et al., 1997; Snodgrass & McMillan, 1996). In the first of these experiments, we showed that pentobarbital could be established as a discriminative stimulus in pigeons using a concurrent VI VI schedule, in which reinforcers were available for responses on one key four times more frequently than for responses on the other key during training sessions. The pattern of responding on the two keys was predicted by the matching law (Herrnstein & Loveland, 1975), although some degree of undermatching (Baum, 1979) occurred. When other doses of pentobarbital were substituted for the training drug, an orderly, graded dose–response curve was generated, with responding on the pentobarbital key increasing with increasing doses of pentobarbital in individual pigeons. These effects were subsequently replicated using concurrent FI FI schedules (McMillan et al., 1997). The purpose of the present experiments was an extension of these observations to a second species, the rat.

In drug-discrimination substitution tests, when other drugs or other doses of the training drug are substituted for the training dose, the behavior is controlled not only by the drug stimulus but also by the schedule of reinforcement that maintains responding. The usual method used to separate stimulus control by the drug from control by the schedule of reinforcement is either to test the effects of the substitute drug during extinction or to base the estimate of stimulus control only on those responses that occur prior to the delivery of the first reinforcer. These approaches may be less useful when drug discrimination has been established under concurrent schedules, because the matching of relative ratios of responding to relative rates of reinforcer delivery can occur under concurrent schedules only if the animal is given adequate time to demonstrate differences in the relative ratios of responding under the two components of the concurrent schedule. For this reason, we have used overall-session data to determine relative response rates in drug-discrimination experiments under concurrent schedules (Snodgrass & McMillan, 1996). However, when overall-session data are used to study the discriminative stimulus effects of drugs under concurrent schedules, it may be difficult to determine whether responding is controlled by the drug stimulus or by the schedule of reinforcement that maintains responding during the substitution of the test drug. Therefore, in our previous experiments we trained pigeons to respond under two concurrently available interval schedules in which the ratio of reinforcers available under the component schedules during training was 4:1. When drug-substitution tests were performed, the concurrent schedule was changed so that the percentages of responses that were reinforced under the component schedules were scheduled to be equal (McMillan et al., 1997; Snodgrass & McMillan, 1996). Tests conducted in pigeons following the training dose of pentobarbital or saline showed that the schedule change did not disrupt baseline control by the drug and that orderly dose–response curves were produced

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Fig. 1. Pentobarbital dose–response curves under the concurrent VI 50-s VI 50-s schedule of reinforcement. Ordinate: percentage of responses on the pentobarbital-biased lever. Points at A show means from Thursday training sessions conducted during periods when dose–response curves were being determined. The higher points at A show the effects of pentobarbital, and the lower points show the effects of saline. Points at B show similar data for 30-min test sessions when the schedule was changed to the concurrent VI 50-s VI 50-s schedule. Points at C show data from the first 2 min of these same sessions. The connected filled points show the pentobarbital dose–response curve conducted over an entire session under the concurrent VI 50-s VI 50-s schedule, and the connected open points show the pentobarbital dose–response curve for the first 2 min of these sessions for individual rats. Note that the *x* axis is logarithmic.

Table 2

Response rates (responses per second) on the saline-biased lever (S-B lever) and on the pentobarbital-biased lever (P-B lever), percentage of responses and reinforcers delivered on the pentobarbital-biased and saline-biased levers, and changeover delays (CODs per minute) for the training sessions under concurrent VI 60 s VI 240 s and for test sessions under concurrent VI 150 s VI 150 s. Data are presented for individual rats and for the group mean.

	Saline					Pentobarbital				
	Rate		% saline biased			Rate		% pentobarbital biased		
Rat	S-B lever	P-B lever	Responses	Reinforcers	CODs	S-B lever	P-B lever	Responses	Reinforcers	CODs
Concurrent VI 60 s VI 240 s										
R491	0.83	0.32	71.7	88.0	3.4	0.51	1.23	71.7	81.4	5.0
R492	0.88	0.39	75.3	81.8	3.9	0.52	1.08	67.1	79.0	7.0
R493	1.11	0.29	79.0	79.0	3.5	0.60	0.90	59.3	80.3	4.3
R494	0.97	0.29	77.5	82.0	4.3	0.62	0.90	57.3	78.2	6.0
R495	0.72	0.22	75.4	81.0	3.5	0.55	0.66	54.1	80.4	5.4
R496	0.45	0.31	61.8	80.7	4.3	0.42	0.67	65.8	70.0	4.2
M	0.83	0.30	73.5	82.1	3.8	0.54	0.91	62.6	78.2	5.3
Concurrent VI 150 s VI 150 s										
R491	1.06	0.25	65.5	40.0	3.9	0.29	1.50	87.9	63.3	2.8
R492	0.99	0.49	66.0	60.0	5.1	0.60	0.98	59.9	36.7	5.4
R493	1.32	0.35	78.2	33.3	3.2	0.74	0.77	58.0	58.3	3.4
R494	1.35	0.26	67.3	75.0	4.7	0.42	0.63	51.7	42.5	5.5
R495	0.50	0.36	64.8	20.0	4.0	0.30	0.82	59.6	62.5	4.7
R496	0.16	0.05	75.2	100.0	2.3	0.18	0.50	59.4	25.0	3.8
M	0.09	0.29	69.5	54.7	3.9	0.42	0.87	62.8	48.1	4.3

when other drugs were substituted for the training drug.

The present experiments in rats produced training data similar to what we had observed with pigeons, that is, the rats slightly undermatched the frequency of reinforcer delivery available under the two concurrent-schedule components during training sessions (the rats responded less often on the drug key after pentobarbital administration and less often on the saline key after saline administration than predicted by the matching law; Baum, 1979). When the schedule was changed from the training session value of concurrent VI 20 s VI 80 s to the control test session value of concurrent VI 50 s VI 50 s, most rats responded in nearly equal proportion on the two response levers after both saline and the training dose of pentobarbital; for the remaining rats, there was a strong trend in that direction. This result was different from that in pigeons, for which the schedule change showed little tendency to control responding under concurrent VI VI schedules in a pentobarbital discrimination (Snodgrass & McMillan, 1996). Thus it appears that responding by the rats studied here under the concurrent VI 20-s VI 80-s schedule was strongly controlled by the schedule change that occurred during control test sessions, whereas responding by pigeons was much less affected by a similar schedule change.

These findings raise the question of whether or not the rats trained under the concurrent VI 20-s VI 80-s schedule were ever under control by the drug. It is possible that the rats' lever pressing was coming under control of the schedule contingencies regardless of whether or not pentobarbital had been administered before the session. A shift from responding on the saline key to responding on the drug key as the dose of pentobarbital increased during drug testing sessions would be evidence that stimulus control by the training drug had occurred. The dose–response curve did not provide very convincing evidence of a pentobarbital dose–response relation in most rats, especially when data from the whole session were considered, which suggested that stimulus control exerted by the presence or absence of pentobarbital was weak.

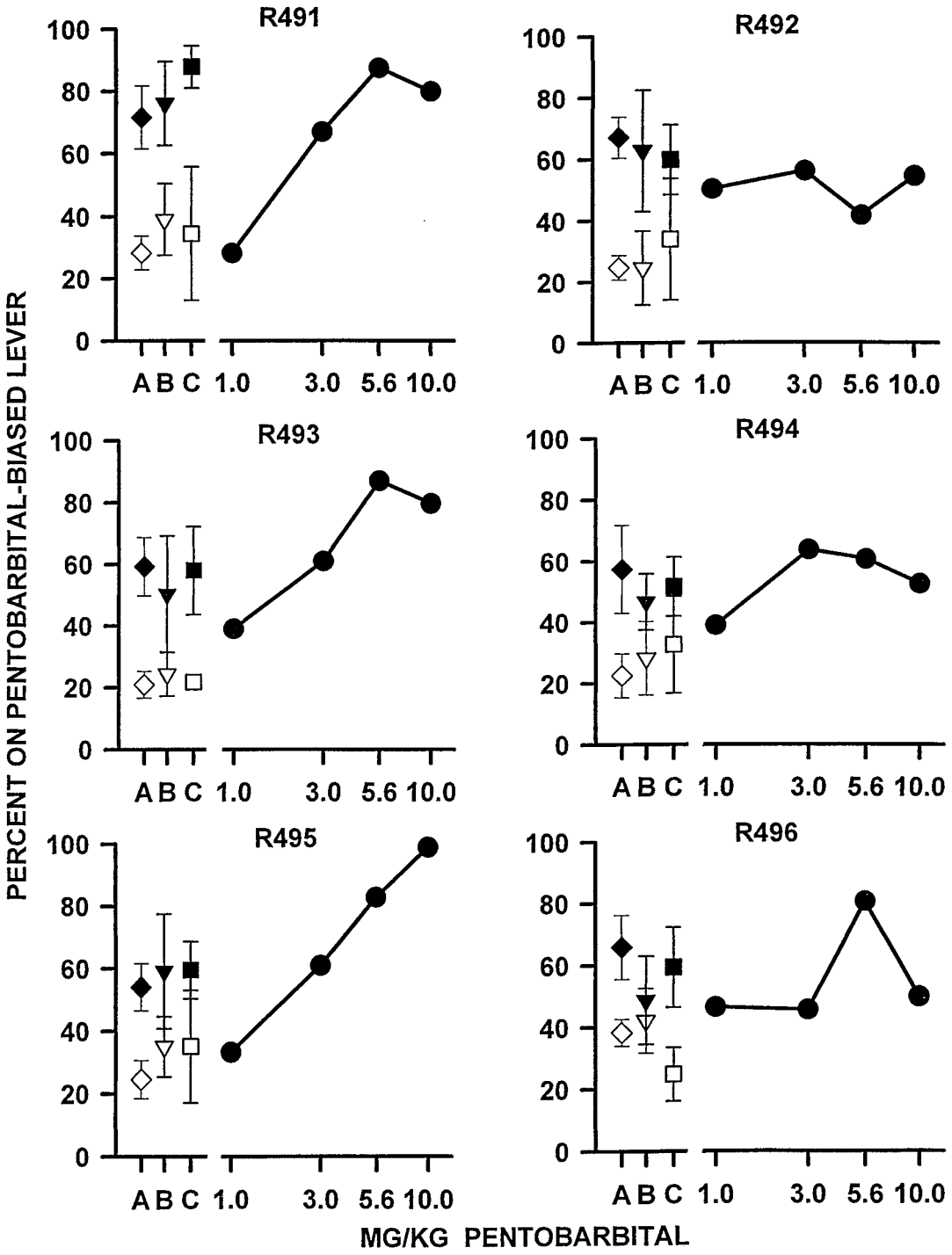

Fig. 2. Pentobarbital dose–response curves under the concurrent VI 150-s VI 150-s schedule of reinforcement. Ordinate: percentage of responses on the pentobarbital-biased lever. Points at A show means from Thursday training sessions conducted during periods when dose–response curves were being determined. The higher points at A show the effects of pentobarbital, and the lower points show the effects of saline. Points at B show similar data for 30-min test sessions when the schedule was changed to the concurrent VI 150-s VI 150-s schedule. Points at C show data from the first 5 min of these same sessions. The connected filled points show the pentobarbital dose–response curve conducted over the 5-min sessions under the concurrent VI 150-s VI 150-s schedule. Note that the *x* axis is logarithmic.

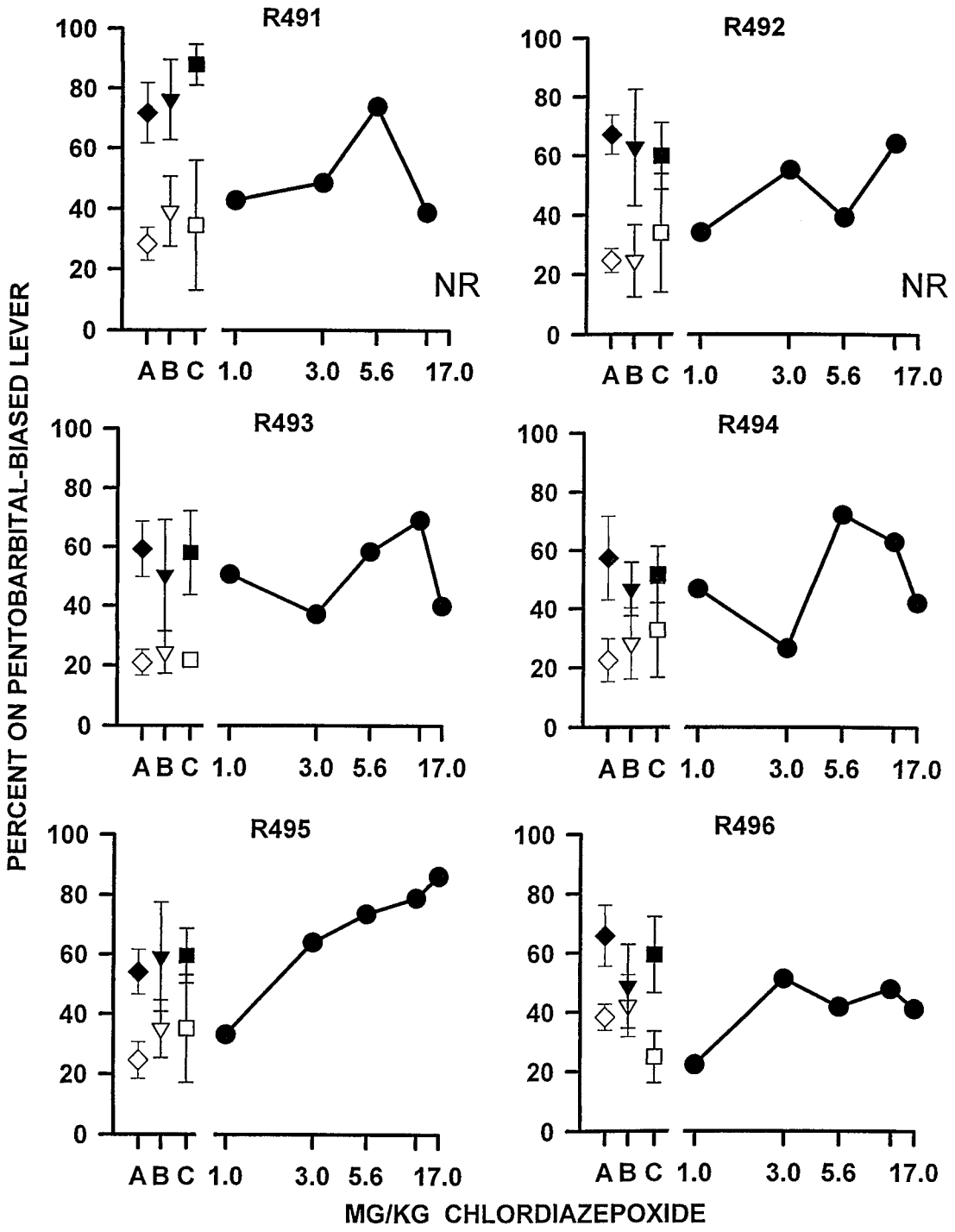

Fig. 3. Chlordiazepoxide dose–response curves under the concurrent VI 150-s VI 150-s schedule of reinforcement. Ordinate: percentage of responses on the pentobarbital-biased lever. Points at A show means from Thursday training sessions conducted during periods when dose–response curves were being determined. The higher points at A show the effects of pentobarbital, and the lower points show the effects of saline. Points at B show similar data for 30-min test sessions when the schedule was changed to the concurrent VI 150-s VI 150-s schedule. Points at C show data from the first 5 min of these same sessions. The connected filled points show the chlordiazepoxide dose–response curve conducted over the 5-min sessions under the concurrent VI 150-s VI 150-s schedule. Note that the *x* axis is logarithmic.

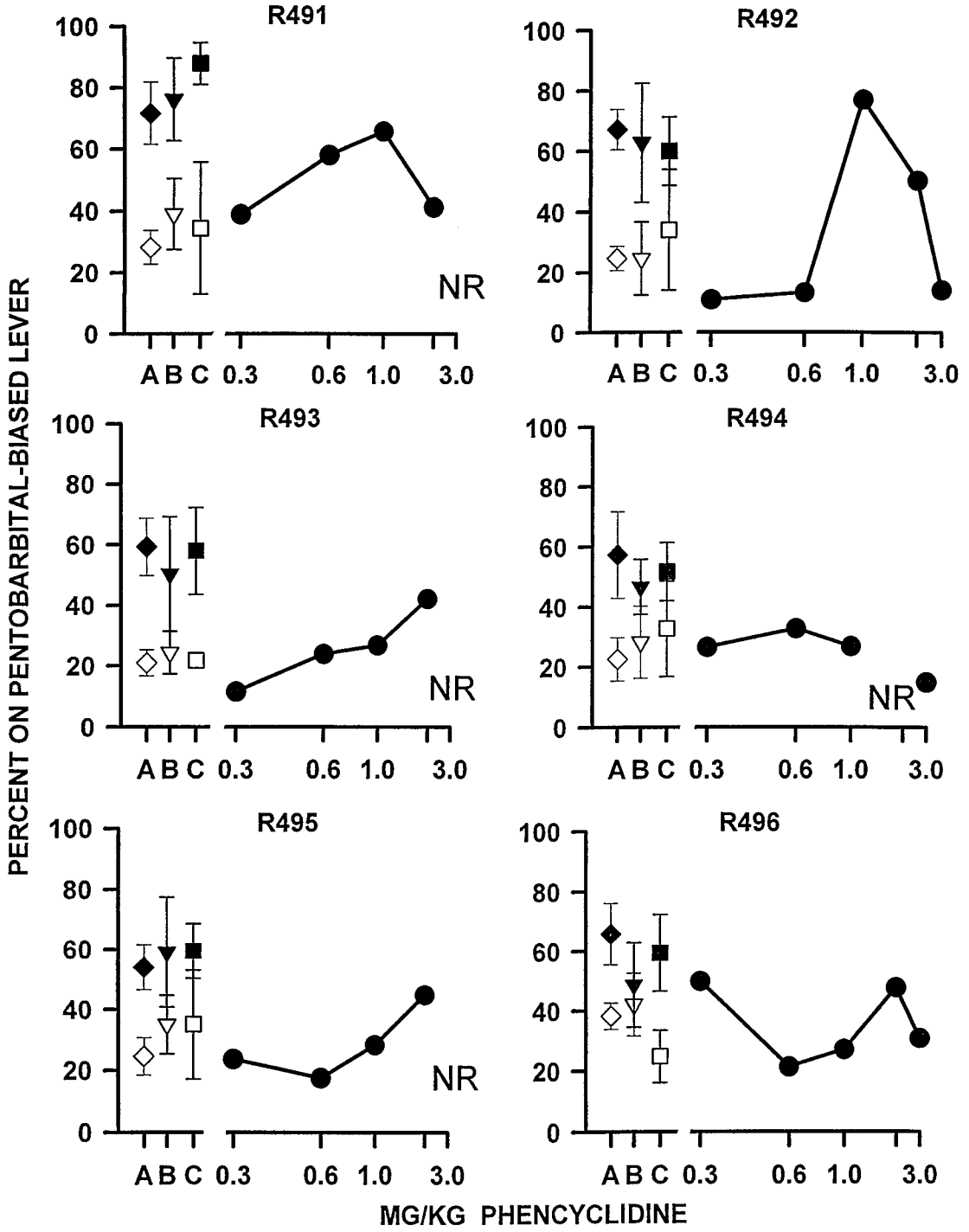

Fig. 4. Phencyclidine dose–response curves under the concurrent VI 150-s VI 150-s schedule of reinforcement. Ordinate: percentage of responses on the pentobarbital-biased lever. Points at A show means from Thursday training sessions conducted during periods when dose–response curves were being determined. The higher points at A show the effects of pentobarbital, and the lower points show the effects of saline. Points at B show similar data for 30-min test sessions when the schedule was changed to the concurrent VI 150-s VI 150-s schedule. Points at C show data from the first 5 min of these same sessions. The connected filled points show the phencyclidine dose–response curve conducted over the 5-min sessions under the concurrent VI 150-s VI 150-s schedule. Note that the *x* axis is logarithmic.

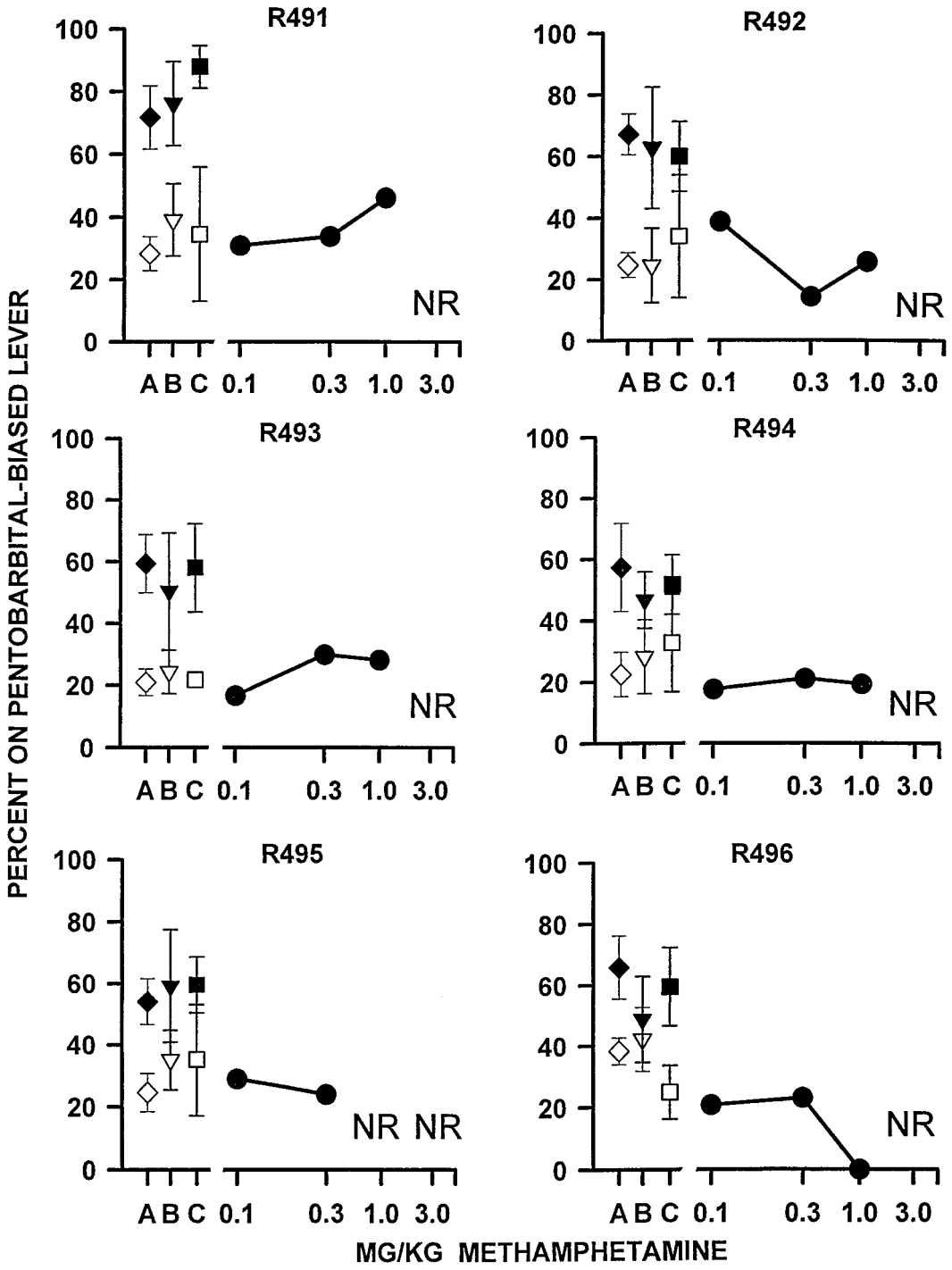

Fig. 5. Methamphetamine dose–response curves under the concurrent VI 150-s VI 150-s schedule of reinforcement. Ordinate: percentage of responses on the pentobarbital-biased lever. Points at A show means from Thursday training sessions conducted during periods when dose–response curves were being determined. The higher points at A show the effects of pentobarbital, and the lower points show the effects of saline. Points at B show similar data for 30-min test sessions when the schedule was changed to the concurrent VI 150-s VI 150-s schedule. Points at C show data from the first 5 min of these same sessions. The connected filled points show the methamphetamine dose–response curve conducted over the 5-min sessions under the concurrent VI 150-s VI 150-s schedule. Note that the *x* axis is logarithmic.

Table 3

Overall rates of responding (responses per second) after drug administration in rats under the concurrent VI 150-s VI 150-s schedule of reinforcement.

		Rat					
Drug	Dose (mg/kg)	R491	R492	R493	R494	R495	R496
Pentobarbital	1.0	1.40	1.33	1.39	1.61	1.11	1.14
	3.0	1.20	1.24	1.28	1.24	1.35	1.26
	5.6	1.37	1.22	1.18	1.32	1.45	1.01
	10.0	1.66	0.53	1.37	2.52	0.65	0.35
	17.0	1.46	1.71	1.80	1.70	1.52	1.18
Chlordiazepoxide	1.0	1.94	1.69	1.39	1.64	1.15	1.16
	3.0	1.71	1.84	1.48	1.74	1.47	1.09
	5.6	1.60	1.83	1.16	1.63	1.06	1.09
	10.0	1.57	0.62	0.43	1.54	0.04	0.33
	17.0	0.04	0.00	0.07	1.77	1.09	1.27
Phencyclidine	0.3	1.71	1.58	1.75	1.86	1.06	1.28
	0.56	1.78	1.67	2.25	2.11	1.37	1.28
	1.0	1.72	2.34	1.67	1.85	1.59	0.12
	1.7	1.54	1.50	0.15	0.02	1.46	0.05
	3.0	0.00	0.10	0.03	0.89	0.06	0.22
Methamphetamine	0.1	1.33	1.10	1.52	1.72	1.37	0.47
	0.3	1.23	1.59	0.89	0.58	1.39	1.04
	1.0	0.42	0.66	0.66	0.57	0.00	0.13
	3.0	0.00	0.00	0.00	0.00	0.00	0.00

When only the first 2 min of the test session were considered, pentobarbital did exert some control over responding for most rats. That is, when the schedule was changed from concurrent VI 20 s VI 80 s to concurrent VI 50 s VI 50 s, there was a better separation between the saline and pentobarbital points. However, the differences between the effects of the pentobarbital training dose and saline during the first 2 min of the session were

Table 4

Changeover delays (CODs per minute) after drug administration in rats under the concurrent VI 150-s VI 150-s schedule of reinforcement.

		Rat					
Drug	Dose (mg/kg)	R491	R492	R493	R494	R495	R496
Pentobarbital	1.0	4.4	5.8	5.2	5.2	3.1	3.0
	3.0	3.6	4.6	4.8	6.4	4.0	3.2
	5.6	3.2	5.6	3.8	7.6	3.0	3.4
	10.0	4.2	1.8	4.6	4.6	1.2	2.2
	17.0	4.0	5.6	5.2	5.8	5.2	3.6
Chlordiazepoxide	1.0	6.0	5.6	5.0	7.0	3.1	2.1
	3.0	4.8	5.2	4.0	4.8	4.8	4.2
	5.6	4.2	5.2	4.6	6.8	4.1	5.2
	10.0	4.2	1.6	1.0	7.4	2.0	3.6
	17.0	0.2	0.0	0.8	6.2	4.2	3.3
Phencyclidine	0.3	3.6	2.2	2.8	6.0	3.6	4.8
	0.56	3.8	2.2	3.4	4.6	4.0	2.6
	1.0	4.2	6.2	1.2	5.6	3.6	1.0
	1.7	4.4	4.4	1.2	0.0	7.0	5.0
	3.0	0.0	0.6	0.0	3.8	0.0	2.8
Methamphetamine	0.1	4.6	5.8	3.2	4.8	4.4	2.2
	0.3	4.2	3.8	5.4	3.6	5.0	2.4
	1.0	3.0	4.6	3.6	4.0	0.0	0.2
	3.0	0.0	0.0	0.0	0.0	0.0	0.0

small in most rats, and the pentobarbital dose–response curves determined for the first 2 min of the test session were often flat. Thus, although the presence or absence of pentobarbital did exert weak stimulus control of responding in these experiments, stimulus control was not adequate for the study of dose–response curves in most rats.

For the first 8 rats, the VI components of the training session were 20 s and 80 s, and during test sessions both VI components were 50 s. For the other 6 rats, the VI components of the training schedule were 60 s and 240 s, and during test sessions both VI components were 150 s. Furthermore, all drug tests for the second group of rats were limited to 5 min to decrease the exposure to the concurrent VI 150-s VI 150-s schedule. These schedule changes established adequate stimulus control by the training dose of pentobarbital to allow the determination of dose–response effects of pentobarbital and other drugs.

In general, increasing doses of pentobarbital produced increased responding on the pentobarbital-biased lever; however, at the higher doses of pentobarbital the dose–response curve appeared to be descending for several rats. This tendency for the pentobarbital dose–response curve to ascend and then descend has been observed previously with pigeons when responding was maintained under concurrent interval schedules (McMillan et al., 1997). Similar effects have been seen with chlordiazepoxide, both in the current experiments and in experiments with pigeons using concurrent interval schedules of reinforcement (McMillan et al., 1997). Why the dose–response curve often descends after high doses under these schedules is not clear. One possibility is that doses higher than the training dose produce stimulus effects that are somewhat different from the stimulus effects of the training dose, causing a decreased proportion of responses to occur on the drug-biased lever. Another possibility is that the high doses of the drugs have made the animals more sensitive to the schedule change that was used during testing. Because responses had an equal probability of being reinforced on either lever during test sessions, a drug-induced increase in the sensitivity of the subject to the schedule change would cause the dose–response curve to descend after high doses. That high doses of pentobarbital would cause increased sensitivity to schedule changes seems unlikely, especially because we have found that high doses of pentobarbital decrease rather than increase matching under concurrent VI VI schedules in pigeons (McMillan, Li, & Snodgrass, 1998). Yet another possibility is that after high doses of pentobarbital neither the drug nor the schedule controls responding and the animals begin to respond randomly on the two keys.

Phencyclidine has been reported to produce variable effects in animals trained to discriminate pentobarbital from saline. For example, Willetts and Balster (1989) found that phencyclidine only partially substituted for pentobarbital in rats trained to discriminate 5 mg/kg pentobarbital from saline, whereas Snodgrass and McMillan (1991) found that phencyclidine substituted partially for pentobarbital in some rats and completely in others. Partial to complete substitution of phencyclidine for pentobarbital has also been observed in pigeons in drug-discrimination experiments (McMillan et al., 1996; Snodgrass & McMillan, 1996). A similar range of effects was found in the present experiments. As anticipated, methamphetamine did not substitute for pentobarbital as a discriminative stimulus. Thus, the dose–response curves that were obtained in the second group of rats were very similar to the effects of these same drugs in both pigeons and rats under both simple and concurrent reinforcement schedules.

The fundamental purpose of performing these experiments was to extend to rats the observations that we have made previously using concurrent reinforcement schedules to study drug discrimination in pigeons. We were not very successful in achieving this in the group of rats that was trained to discriminate pentobarbital from saline under a concurrent VI 20-s VI 80-s schedule with substitution tests conducted under a concurrent VI 50-s 50-s schedule. In this group the reinforcement schedule appeared to control responding to a greater extent than the drug state. However, we were more successful with a second group of rats, demonstrating not only that drug discrimination could be established in rats using concurrent VI VI schedules, but also that substitution tests with other drugs generated dose–response curves simi-

lar to those developed with rats using other reinforcement schedules and similar to those developed with pigeons using concurrent schedules.

Why it was so difficult to establish drug discrimination under concurrent schedules in the first group of rats remains unclear. It may be that rats are more sensitive to schedule changes and respond more rapidly to schedule changes than do pigeons when reinforcement schedules are changed. However, it should be noted that in the first group of rats the components of the training schedule were VI 20 s and VI 80 s, whereas in pigeons we typically used longer VI components, such as VI 60 s and VI 240 s. We did not use the same VI schedules in rats that we had used previously in pigeons because previous laboratory experience suggested that when a 97-mg food pellet is the reinforcer, responding during interval schedules longer than 3 min was not well maintained. We therefore used shorter VI values but maintained the same ratio of the durations of the VI components of the concurrent schedules that were available to both species. Under these conditions, we were not very successful in establishing pentobarbital as a discriminative stimulus. When the parameters of the concurrent schedule used for rats were increased to the same concurrent VI 60 s VI 240 s used in pigeons, we were much more successful in establishing pentobarbital as a discriminative stimulus. These data are consistent with data from Mark and Gallistel (1994), who maintained responding by rats under concurrent VI schedules of brain stimulation. Midsession reversals of the relative rates of reinforcer delivery resulted in rapid rates of transition to new response patterns, especially for short VI components in which the changes in relative reinforcer rates occur in a relatively short period of time. Dreyfus (1991) also has reported that changes in relative reinforcement rates can control the responding of pigeons fairly quickly when the overall rates of reinforcement are high.

Thus, our initial difficulties in establishing pentobarbital as a discriminative stimulus under concurrent schedules in rats may have been caused by the reinforcement schedule chosen rather than by differences in species. In this regard it should be mentioned that we also have had some difficulties in maintaining stimulus control by pentobarbital in pigeons under concurrent reinforcement schedules when the pigeons have had less extensive training than those birds who contributed to our initial reports (McMillan & Li, 1999b).

In summary, these experiments showed that rats can be trained to discriminate between pentobarbital and saline under concurrent VI VI schedules, although under some schedules stimulus control can be difficult to observe because of the exceedingly powerful control over responding by the schedule of reinforcement in these experiments. Furthermore, when other drugs were substituted for pentobarbital, they produced effects similar to those seen with other procedures and in other species.

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