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Schedule control of quantal and graded dose–effect curves in a drug–drug-saline discrimination

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Abstract

Pigeons were trained to discriminate among 5 mg/kg pentobarbital, 5 mg/kg morphine, and saline when responding was maintained under fixed-interval (FI) or fixed-ratio (FR) reinforcement schedules. After the discrimination was established, other drugs were substituted for the training drugs. After low doses of pentobarbital and chlordiazepoxide, responding shifted from the saline key to the pentobarbital key under both FR and FI schedules. After low doses of morphine and methadone, responding shifted from the saline key to the morphine key under both reinforcement schedules. After all doses of d-amphetamine, responding occurred largely on the saline key under both schedules. Responding also was confined largely to the saline key after phencyclidine administration under the FR schedule, but under the FI schedule, responding shifted from the saline key to the pentobarbital key at high doses of phencyclidine. When responding was maintained under the FR schedule, the dose–response curves for drugs that generalized to the training drugs were quantal in shape, while under the FI schedule, the dose–response curves for drugs that generalized to the training drugs were graded. These data extend observations that FR schedules generate quantal dose–response curves, and FI schedules generate graded dose–response curves to complex three-key drug discriminations.

Keywords: Drug discrimination; Three-choice discrimination; Pentobarbital; Morphine; Graded responding; Quantal responding; Pigeons

1. Introduction

Drug discrimination is widely accepted as a method to study the discriminative stimulus properties of drugs. Under the usual drug discrimination training procedure, responses on one operandum are reinforced when the training drug has been administered before the session, while responses on the other operandum are reinforced if the drug vehicle has been administered. Using this procedure of differential reinforcement for responding dependent on whether or not the drug has been administered before the session, the presence or absence of the training drug becomes a discriminative stimulus for responding on the operandum that will deliver the reinforcer (Colpaert et al., 1976).

Despite the widespread acceptance of the procedure, there is considerable controversy as to the nature of the drug discrimination response. Colpaert (1991) has argued that the discriminative stimulus effects of drugs are measured quantally. According to this viewpoint, the drug stimulus can vary both quantitatively and qualitatively, but the response to these stimuli is all or none (quantal). In effect, the animal discriminates the presence or absence of the drug and then emits a "yes or no" response.

Other investigators have argued strongly that the response to drug stimuli in drug discrimination is a continuous variable, and the response to drug stimuli is graded (Stolerman, 1991). This viewpoint would suggest that the proportion of responses that occur on the drug manipulandum is determined by the degree to which a dose of drug produces stimuli that are similar to those produced by the dose and drug used as a training stimulus. The condition under which discriminative stimuli are quantal or graded is an important question, not only for drug discrimination research but also for the understanding of discrimination learning of all types.

It has been suggested that one of the variables that determines whether the drug discrimination response is

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quantal or graded is the schedule of reinforcement maintaining responding (Holloway and Gauvin, 1989; Stolerman, 1991). Stolerman (1991) has argued that the use of simple fixed-ratio (FR) schedules where the session terminates with the delivery of the first reinforcer is likely to be quantal in nature, since FR responding typically occurs as a unit. Under other schedules, graded responding has been shown to occur. Holloway and Gauvin (1989) suggested that the schedule of reinforcement may be what determines whether responding is graded or quantal, with FR schedules generating quantal responding and interval schedules generating a distribution of responses across response alternatives.

In a series of experiments on drug discrimination, we have shown that under a wide variety of conditions, the reinforcement schedule is a powerful determinant of whether responding is graded or quantal. For example, responding maintained by interval schedules has been shown to be graded in pigeons and rats under simple fixed-interval (FI) schedules, FI components of multiple schedules, concurrent variable-interval variable-interval schedules, and concurrent FI FI schedules using phencyclidine, pentobarbital, and morphine as training drugs (Massey et al., 1992; McMillan and Hardwick, 1996; McMillan and Li, 1999c; McMillan et al., 1997; Snodgrass and McMillan, 1996). In contrast, responding maintained by FR schedules has been shown to be quantal under simple FR schedules, FR components of multiple schedules, and concurrent FR schedules (Massey et al., 1992; McMillan and Hardwick, 1996; McMillan and Li, 1999a; Snodgrass and McMillan, 1991).

The experiments that have addressed the role of the reinforcement schedule in drug discrimination experiments have been conducted in simple two-choice discriminations between drugs and the drug vehicle. The role of the reinforcement schedule has not been investigated in more complex discriminations involving more than two choices. The purpose of the present experiments was to study drug discrimination using a three-choice procedure, where responding was maintained either by a FR schedule or by a FI schedule to determine if graded responding was obtained under the FI schedule and quantal responding was obtained under the FR schedule as predicted by previous experiments with two-choice procedures.

2. Methods

2.1. Subjects

Eight adult male White Carneau pigeons (Palmetto Pigeon Plant; Sumter, SC) were used in these experiments. Pigeons P262, P263, and P264 had served as experimental subjects in previous experiments (see below). Pigeons P381, P382, P383, P384, and P385 were experimentally naive at the beginning of these experiments. The pigeons were individually housed with free access to food and water in a temperature- and humidity-controlled room that was maintained under a 12-h normal phase lighting cycle. The pigeons were maintained at approximately 80–85% of their free-feeding weights for the duration of the study. Supplemental food was provided after experimental sessions as necessary to maintain the 80–85% body weights (range of 429–510 g).

2.2. Apparatus

The experimental chamber was a Gerbrands Model G5610-A (Gerbrands; Arlington, MA) pigeon test cage enclosed in a Gerbrands Model G7211 sound- and light-attenuating cubicle. Two 28-V DC lights illuminated the experimental chamber during the session, except during a food cycle when a light over the food hopper was illuminated. On the front panel of the cage, three Gerbrands response keys (Model G7311) were mounted 7 cm apart, 20 cm above the grid floor. When operative, the left key was red, the center key was white, and the right key green. A food hopper (Gerbrands) through which access to mixed grain could be given was centered between the response keys at floor level. A microcomputer (Gateway 2000; North Sioux City, SD), located in a room adjacent to the room containing the experimental chamber, controlled the reinforcement schedule and recorded the data through a MED Associates (East Fairfield, VT) interface.

2.3. Procedure

The training of pigeons P262, P263, and P264 under concurrent variable-interval and concurrent FI schedules that did not involve drug discrimination procedures has been described in detail previously (McMillan and Li, 1999b; McMillan et al., 1998). In these experiments, the pigeons were trained to respond for food under concurrent reinforcement schedules using the two side keys. Upon the completion of these experiments, drug discrimination training was initiated (described below). The five experimentally naive pigeons were trained to respond on each key during separate sessions until responses had produced the food reinforcer 50 times. During the next few sessions, the number of responses required to produce the reinforcer was increased (FR schedule), or responses could not produce the reinforcer until a gradualy increase in time had elapsed (FI schedule). When discrimination training began, pigeons P264, P383, P384, and P385 were required to respond 20 times (not necessarily consecutively) on the correct key to produce a reinforcer (FR 20 schedule), while for pigeons P262, P263, P381, and P382, the first response on the correct key after 90 s had passed produced the reinforcer (FI 90 schedule). In the present experiments, 5.0 mg/kg pentobarbital, 5.0 mg/kg morphine, or physiologic saline were administered intramuscularly before training sessions. Following the injection, birds were placed in the test chamber, and a 10-min presession period

followed. During this 10 min, the chamber lights were extinguished. and key pecks were not recorded. At the end of the presession period, the house lights and the three key lights were illuminated, and the schedule contingencies were initiated. For all birds, only responses on the center key were reinforced under the FR or the FI schedule (depending on the group) after the administration of saline. For the birds maintained under the FR 20 schedule, responses of two birds were reinforced only on the left key after 5.0 mg/kg pentobarbital administration and only on the right key after 5.0 mg/kg morphine administration during training sessions. For the other two birds maintained under the FR schedule, these contingencies were reversed during training sessions. For birds maintained under the FI 90 schedule, responses of two birds were reinforced only on the left key after 5.0 mg/kg pentobarbital administration and only on the right key after 5.0 mg/kg morphine administration. For the other two birds maintained under the FI schedule, these contingencies were reversed during training sessions. Training sessions continued for 40 min or until 20 reinforcers had been received, whichever occurred first. Training sessions were conducted 6 days/week. During these training sessions, pentobarbital, morphine, and saline administration alternated.

Test sessions were interspersed with training sessions after performance stabilized. During these test sessions conducted on Tuesdays and Fridays, other doses of pentobarbital, morphine, and other drugs were administered, instead of saline or the training doses of pentobarbital and morphine. Training sessions continued on the other 4 days of the week. The procedure used during test sessions was similar to the procedure used during training sessions, except that responses were reinforced when the schedule requirements were met on any of the response keys and the session terminated after the delivery of the first reinforcer. Drug substitution tests were conducted in single test sessions conducted on different days. All dose levels for a single drug were studied before exposure to a different drug. The order of drug testing was pentobarbital, morphine, chlordiazepoxide, methadone, d-amphetamine, and phencyclidine.

2.4. Data analysis

The number of responses on each key was determined to calculate the percentage of responses on each key. The sum of the number of responses on the three keys was divided by the total session time to calculate the overall rate of responding. Dose–response curves were considered to be quantal if more than 80% of the responses were confined to one key, while dose–response curves were considered to be graded if less than 80% of the responses occurred on each of the three. χ^2 analysis was used to test differences between FI and FR schedules in meeting these definitions of graded and quantal dose–response curves.

2.5. Drugs

Pentobarbital sodium (Sigma; St. Louis, MO), morphine sulfate (Mallinckrodt; St. Louis, MO), phencyclidine hydrochloride (PCP, National Institute on Drug Abuse; Rockville, MD), d-amphetamine hydrochloride (Sigma), chlordiazepoxide hydrochloride (Hoffman-La Roche; Nutley, NJ), and methadone hydrochloride (Sigma) were studied. All drugs were dissolved in 0.9% physiological saline to a concentration allowing an injection volume of 1 ml/kg and administered intramuscularly into a breast muscle. Physiological saline was used for vehicle control injections. Doses are expressed as the salt forms of the drugs. As in training sessions, test session doses were administered 10 min before the session, and the pigeons were placed in the test chamber during the 10-min presession period.

3. Results

Across the last six training sessions following saline, pentobarbital, and morphine administration, baseline performance was not very different under the FR and FI schedules (Table 1). During these pentobarbital training sessions, pigeons made 93.1% of their responses on the pentobarbital key under the FR schedule and 97.3% under the FI schedule. During morphine training sessions, pigeons made 97.5% of their responses on the morphine key under the FR schedule and 94.6% under the FI schedule. During saline training sessions, pigeons made 99.1% of their responses on the saline key under the FR schedule and 87.1% under the FI schedule. The small percentage of errors that occurred during these training sessions was not consistently associated with any particular response key.

Table 1 shows the mean percentages of responses on each key as the doses of all drugs studied were varied systematically. At low doses of pentobarbital, responding occurred predominantly on the saline key under both reinforcement schedules, although at the lowest dose of pentobarbital (1 mg/kg), more responses occurred on the saline key under the FR schedule than under the FI schedule. As the dose of pentobarbital increased, the percentage of responses on the saline key decreased and the percentage of responses on the pentobarbital key increased, until at the 10 mg/kg dose of pentobarbital, all responses occurred on the pentobarbital key under both schedules. Few responses occurred on the morphine key after any dose of pentobarbital. The effects of chlordiazepoxide were very similar to those of pentobarbital, with responding switching from the saline key to the pentobarbital key as the dose of chlordiazepoxide increased. The group mean showed no consistent differences in the chlordiazepoxide dose–response curves determined under FR and FI schedules, except that at the lowest dose of chlordiazepoxide, fewer responses occurred on the pentobarbital key under the FI schedule than under the FR schedule.

Table 1
Dose–response curves for percentage of responses on the saline key, pentobarbital key, and morphine key when responding was maintained under either a FR or FI schedule for reinforcement

		Saline key		Pentobarbital key		Morphine key	
Drug or training condition	mg/kg dose	FR	FI	FR	FI	FR	FI
Saline training	0	99.1 (1.5)	87.1 (9.0)	0.0 (0.0)	6.6 (4.2)	0.9 (1.5)	6.3 (7.4)
Pentobarbital training	5	4.7 (4.0)	1.8 (1.1)	93.1 (6.8)	97.3 (2.3)	2.2 (3.5)	0.9 (1.4)
Morphine training	5	2.5 (3.7)	4.8 (5.8)	0.0 (0.0)	0.6 (1.0)	97.5 (3.7)	94.6 (6.3)
Pentobarbital	1.0	96.7	79.8	0.0	15.3	3.3	4.9
	3.0	29.2	44.4	67.6	50.4	3.3	5.2
	5.6	4.2	3.8	93.8	96.2	2.0	0.0
	10.0	0.0	0.0	100.0	100.0	0.0	0.0
Morphine	1.0	100.0	91.9	0.0	7.4	0.0	0.7
	3.0	10.3	42.1	0.0	0.0	89.7	57.9
	5.6	0.0	9.8	0.0	0.0	100.0	90.2
	10.0	0.0	0.0	0.0	0.0	100.0	100.0
Chlordiazepoxide	1.0	100.0	72.0	0.0	23.5	0.0	4.5
	3.0	47.7	30.0	52.3	67.9	0.0	2.1
	5.6	25.0	5.2	66.1	94.4	8.9	0.4
	10.0	2.3	3.6	97.7	96.4	0.0	0.0
Methadone	0.3	100.0	73.8	0.0	12.1	0.0	14.1
	1.0	50.0	56.6	0.0	20.5	50.0	22.9
	3.0	0.0	6.8	0.0	13.9	100.0	79.3
	5.6	0.0	2.4	0.0	0.0	100.0	97.6
d-Amphetamine	0.1	100.0	78.6	0.0	10.1	0.0	11.2
	0.3	100.0	87.8	0.0	5.3	0.0	6.9
	1.0	100.0	82.7	0.0	8.6	0.0	8.7
	1.8	100.0	94.7	0.0	3.2	0.0	2.1
	3.0	100.0		0.0		0.0	
Phencyclidine	0.1	100.0	94.4	0.0	4.0	0.0	1.6
	0.3	76.8	65.0	20.0	14.0	3.2	21.1
	0.6	87.2	79.3	7.9	9.2	4.9	11.5
	1.0	97.6	49.8	0.0	40.1	2.4	10.1
	1.8	79.3	27.8	1.1	70.0	19.7	2.3

All values are mean of four subjects. Values in parentheses are standard deviations. Training data are based on six observations in each subject, and dose–response data are based on single observations in each subject.

At the lowest dose of morphine (1.0 mg/kg), responding occurred primarily on the saline key. As with pentobarbital and chlordiazepoxide, a greater percentage of responses occurred on the saline key under the FR schedule than under the FI schedule. As the dose of morphine increased, the percentage of responses on the morphine key increased and the percentage of responses on the saline key decreased under both schedules. Few responses occurred on the pentobarbital key after any dose of morphine. Methadone produced effects that were very similar to those of morphine, with low doses producing responding on the saline key and higher doses producing responding on the morphine key. However, under the FI schedule, much more responding occurred on the pentobarbital key after intermediate doses of methadone than occurred with morphine.

Following the administration of all doses of d-amphetamine, responding was confined to the saline key under the FR schedule. Under the FI schedule, responding occurred predominately on the saline key after all doses of d-amphetamine, but there was considerably more responding on the other two keys than occurred under the FR schedule. With the lowest dose of phencyclidine (0.1 mg/kg), responding was largely confined to the saline key under both schedules. As the dose of phencyclidine increased, less responding occurred on the saline key, especially under the FI schedule where increased responding occurred primarily on the pentobarbital key. Under the FR schedule, some responding occurred on both the morphine and the pentobarbital keys, depending on the dose of phencyclidine.

Many of the mean dose–effect relationships in Table 1 appear to be graded, but the distribution of responses across keys at intermediate doses of these drugs may have been artifacts of averaging. It is possible that intermediate points on the dose–response curves resulted from the averaging of quantal data from subjects that shifted abruptly from responding only on the saline key to responding only on a drug key, but at different doses. Under these circumstances, the averaging of quantal data from individual subjects would produce a graded mean curve. Therefore, the data from individual birds were analyzed.

Fig. 1 shows the pattern of responding on each key following each dose of pentobarbital and morphine for individual animals maintained under the FR schedule. Following the training dose of pentobarbital (bars at C), responding was largely confined to the pentobarbital key. After the 1.0 mg/kg dose of pentobarbital, all responses

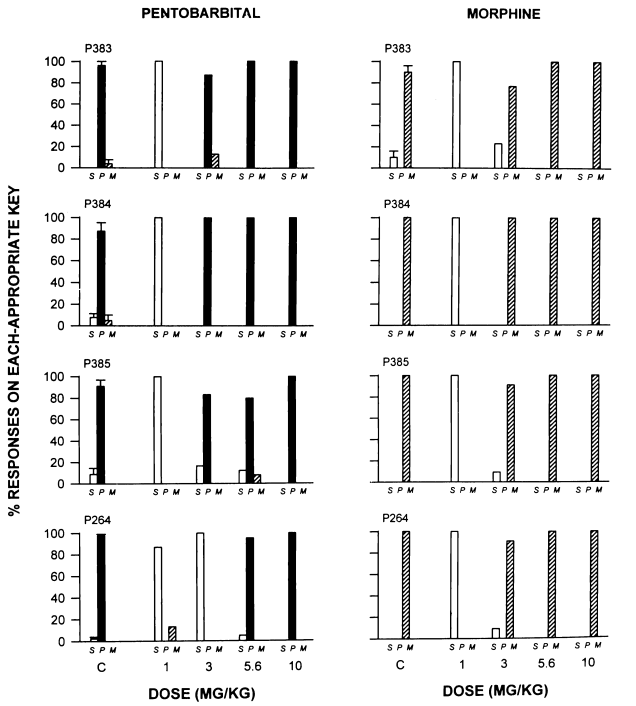

Fig. 1. Percentage of responses on the saline key (white bars), pentobarbital key (black bars), and morphine key (gray bars) after different doses of pentobarbital (first column) and morphine (second column) in pigeons trained under the FR 20 schedule. Abscissa: mg/kg dose of pentobarbital or morphine, Ordinate: percentage of responses on each key for individual subjects. Bars at C show mean from training sessions, where 5.0 mg/kg pentobarbital or morphine was administered before the session. Brackets at C show ±1 standard deviation around the mean control performance. Each bar on the dose–response curve represents one observation in a single

occurred on the saline key for three of the birds and more than 80% of the responses occurred on the saline key for bird P264. As the dose of pentobarbital increased, responding shifted to the pentobarbital key at 3.0 (P383, P384, and P385) or 5.6 mg/kg (P264). After pentobarbital administration, the sum of the percentage of responses on the saline and morphine keys was less than 20%, and in many cases, the birds did not respond on these keys at all. Similar quantal dose–response curves were obtained in individual birds with morphine. At the lowest dose of morphine, all birds responded entirely on the morphine key, while at higher doses, responding shifted to the morphine key. Only at the 3 mg/kg morphine dose in bird P383 did more than 20% of the responses occur on the pentobarbital and saline keys combined. Thus, the dose–response curves for the individual birds maintained under the FR schedule were quantal for both pentobarbital and morphine, with shifts from responding predominantly or entirely on the saline key to responding predominantly or entirely on the pentobarbital or morphine key.

The top section of Table 2 shows the highest percentage of responses, summed across two keys on which the least responses occurred, which were observed at any dose of each drug in individual subjects maintained under the FR schedule of reinforcement. In only two instances during the determination of the dose–response curves for pentobarbital, morphine, methadone, chlordiazepoxide, phencyclidine,

Table 2
Sum of the highest percentage of responses made on the two "nonpreferred" response keys at any dose of each drug in individual birds

	Drug	Bird			
		383	384	385	264
FR schedule	Pentobarbital	13	0	0	0
	Morphine	23	0	9	9
	Methadone	0	0	0	0
	Chlordiazepoxide	35	0	0	0
	Phencyclidine	20	5	0	0
	d-Amphetamine	0	0	0	0
		265	263	381	382
FI schedule	Pentobarbital	13	18	26	35
	Morphine	40	1	15	42
	Methadone	37	15	51	36
	Chlordiazepoxide	21	3	50	45
	Pentobarbital[a]	44	36	50	33
	Morphine[a]	48	34	51	36
	Phencyclidine	37	18	40	47
	d-Amphetamine	37	22	17	20

[a] Second determination of dose–effect curve.

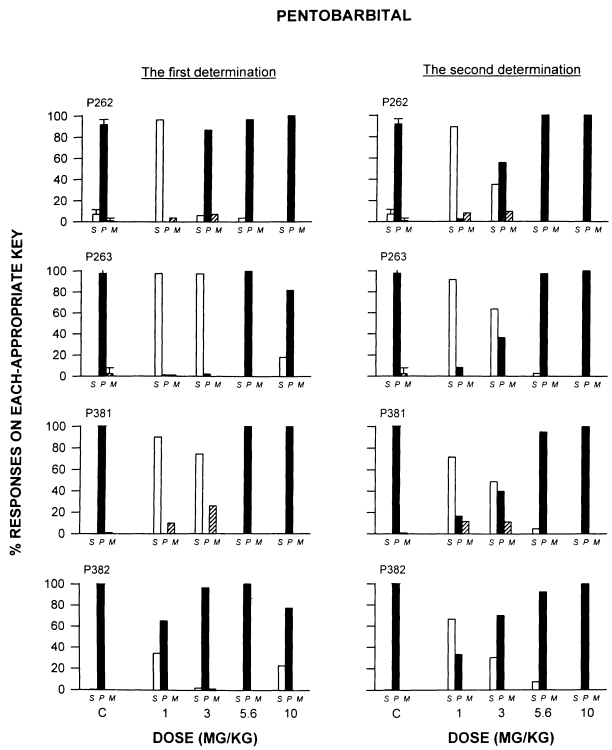

Fig. 2. Percentage of responses on the saline key (white bars), pentobarbital key (black bars), and morphine key (gray bars) after different doses of pentobarbital in pigeons trained under the FI 90-s schedule. Abscissa: mg/kg dose of pentobarbital. Ordinate: percentage of responses on each key for individual subjects. The first column shows the first determination of the pentobarbital dose–response curve, and the second column shows the second determination. Bars at C show mean from training sessions, where 5.0 mg/kg pentobarbital was administered before the session. Brackets at C show ±1 standard deviation around the mean control performance. Each bar on the dose–response curve represents one observation in a single subject.

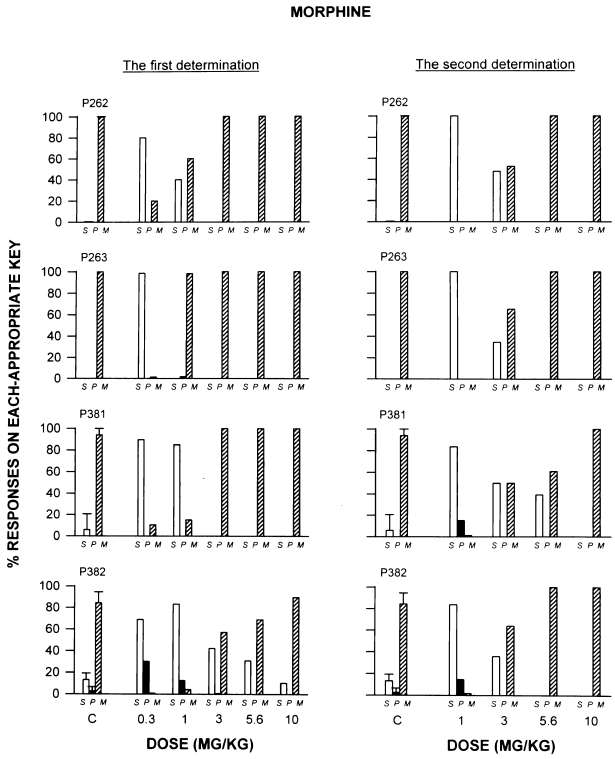

Fig. 3. Percentage of responses on the saline key (white bars), pentobarbital key (black bars), and morphine key (gray bars) after different doses of morphine in pigeons trained under the FI 90-s schedule. The first column shows the first determination of the dose–response curve, and the second column shows the second determination. Abscissa: mg/kg dose of morphine. Ordinate: percentage of responses on each key for individual subjects. Bars at C show mean from training sessions, where 5.0 mg/kg morphine was administered before the session. Brackets at C show ±1 standard deviation around the mean control performance. Each bar on the dose–response curve represents one observation in a single subject.

and d-amphetamine in the four birds (24 dose–response curves) did the sum of the responses on the two keys where fewer responses occurred ever exceed 20% of the total number responses. Both of these were for bird P383. This is further evidence that the dose–response curves maintained under the FR schedule were quantal.

Fig. 2 shows the two dose–response curves for pentobarbital when responding was maintained under the FI schedule. For the first determination of the pentobarbital dose–response curve, dose–response curves were graded in pigeons P381 and P382, with more than 20% of responses occurring on two or more response keys at some doses, but unexpectedly, the pentobarbital dose–response curve was quantal in pigeons P262 and P263. For this reason, the pentobarbital dose–response curve was redetermined. The second pentobarbital dose–response curve was graded in all four pigeons.

Fig. 3 shows the dose–response curves for the two determinations of the morphine dose–response curve for the individual birds maintained under the FI schedule. As anticipated, the dose–response curve for morphine was graded for birds P262 and P382, with two or more doses producing more than 20% of the responses on more than one key. However, for pigeons P263 and P381, the dose–response curve was quantal. Therefore, the dose–response curve was redetermined. As with pentobarbital, the morphine dose–response curve was graded in all four pigeons under the FI schedule when the morphine dose–response curve was determined for a second time. The graded response was particularly apparent at the 3.0 mg/kg dose.

The lower section of Table 2 shows the highest percentage of responses summed across two keys on which the least responses occurred that were observed at any dose of each drug in individual subjects maintained under the FI schedule of reinforcement. In only eight instances in the determination of 32 dose–effect curves did the pigeons make less than 20% of their responses on the two "non-preferred" response keys. This is further evidence that the dose–response curves usually were graded when respond-

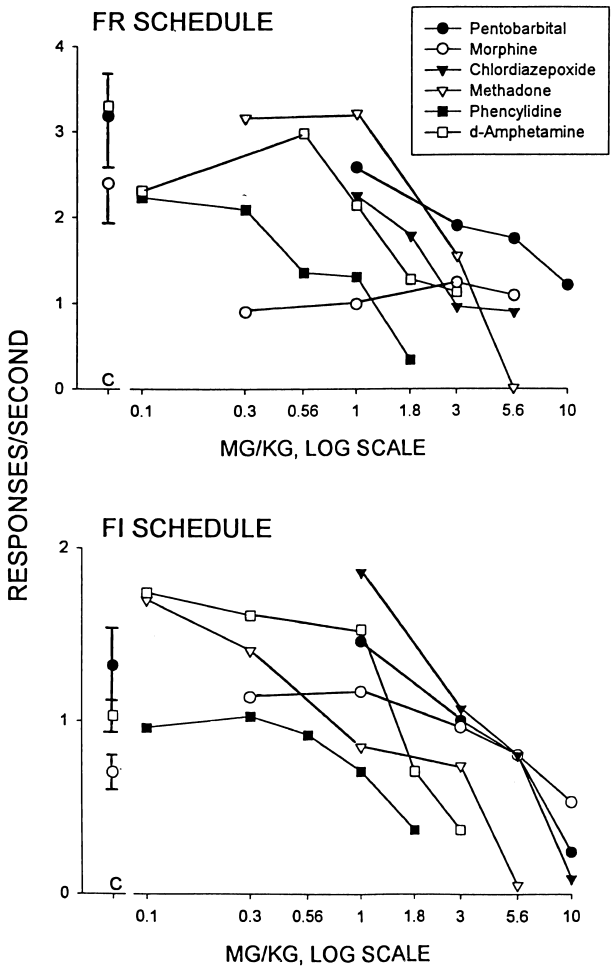

Fig. 4. Effects of drugs on overall rates of responding maintained under the FR 20 schedule (top frame) and the FI 90-s schedule (bottom frame). Abscissa: mg/kg dose, log scale. Ordinate: rate of responding in responses/s for the entire session. Points at C show mean ±2 standard deviations for training sessions following the administration of pentobarbital (filled circles), morphine (unfilled circles), and saline (unfilled squares). Each point on the dose–effects curves shows mean of single observations in each of four subjects.

ing was maintained under the FI schedule. Differences between FI and FR schedules in meeting the definition of graded vs. quantal dose–response curves were statistically significant ($P \leq .001$).

Fig. 4 shows the effects of these drugs on overall rates of responding. During training sessions, morphine produced somewhat lower rates of responding than saline and pentobarbital when responding was maintained under both FR and FI schedules. Low doses of chlordiazepoxide, morphine, methadone, and D-amphetamine produced small increases in rates of responding. Higher doses of all drugs reduced rates of responding under both schedules of reinforcement.

4. Discussion

The question of whether biological responses are graded or quantal has a long history in biology. For example, the postsynaptic action potential is an all or nothing event that propagates unattenuated to the nerve terminal, yet whether or not the action potential reaches threshold depends on the graded changes in the membrane potential, which in turn depend on the quantal release of neurotransmitter packets. Thus, this biological response may be graded or quantal depending on the level at which it is measured. Similar issues have been debated in discrimination learning where stimulus generalization has been considered to be either a continuous relationship between stimulus and response dimensions or a quantal relationship where the occurrence of the response is an all or nothing event (Bickel and Etzel, 1985). A similar question has raised controversy in drug discrimination research, where it has been suggested that drug discrimination responses are quantal responses expressed in an all or nothing manner (Colpaert et al., 1976), while others have argued that the discriminative stimulus effects of drugs are neither inherently quantal nor graded but rather responding is graded or quantal depending on the conditions under which the responses are measured (Stolerman, 1991). This is a fundamental question for drug discrimination research, just as it is for discrimination learning and for all of biology.

During recent years, our laboratory has conducted a large number of studies supporting Stolerman's (1991) viewpoint that in simple two-choice drug discriminations, whether or not the dose–response curve is quantal or graded depends on the schedule of reinforcement. Under FR schedules of reinforcement, dose–response curves usually are quantal, with animals making the nondrug response after low doses of the training drug and then shifting to making the drug response after higher doses of the training drug without passing through points on the dose–response curve where graded responding occurs to both alternatives (Massey et al., 1992; McMillan and Li, 1999a; Snodgrass and McMillan, 1991). In contrast, under FI and VI schedules of reinforcement, graded responding occurs with an increasing proportion of responses occurring on the training drug key as the dose of the training drug increases to an asymptotic level (Massey et al., 1992; McMillan and Hardwick, 2000; McMillan and Li, 1999b; Snodgrass and McMillan, 1991, 1996). These effects have been shown to occur with different training drugs (Massey et al., 1992; McMillan, 1987; McMillan and Hardwick, 1996) and different species (McMillan and Hardwick, 2000).

These drug discrimination experiments, where the reinforcement schedules have been manipulated systematically, have been done in two-choice experiments where animals were trained to discriminate between a training dose of a drug and the drug vehicle. The present experiments extend these findings to more complex three-choice discriminations. When pigeons were trained to discriminate among 5.0 mg/kg pentobarbital, 5.0 mg/kg morphine, and saline under an FR schedule, individual animals responded on the saline key at low doses of pentobarbital, chlordiazepoxide, morphine, and methadone, and then switched to responding almost entirely on the pentobarbital key after higher doses of pentobarbital or chlordiazepoxide, or to responding entirely on the morphine key after higher doses of morphine and methadone, with very few responses occurring on other keys at any doses. In contrast, pigeons trained to make the same discriminations among pentobarbital, morphine, and saline under an FI schedule usually showed a gradual shift from responding on the saline key to responding on the pentobarbital key after increasing doses of pentobarbital and chlordiazepoxide, and a gradual shift from responding on the saline key to responding on the morphine key after increasing doses of morphine and methadone. These experiments provide additional evidence that the schedule of reinforcement is a major determinant of the shape of the dose–response curve in drug discrimination experiments rather than any intrinsic properties of the drug stimuli.

It should be noted that under the FR and FI schedules, baseline stimulus control by the training drugs was very similar. When responding stabilized under the FR schedule, the birds averaged 96.6% of their responses on the correct key. When responding stabilized under the FI schedule, the birds averaged 93.0% of their responses on the correct key. Thus, differences in baseline differences in stimulus control by the drug under different reinforcement schedules do not explain the differences between the ratio and interval schedules in producing quantal and graded dose–response curves.

When the mean dose–response curves for pentobarbital, chlordiazepoxide, morphine, and methadone are examined, the dose–response curves generated under FR and FI schedules are strikingly similar. d-Amphetamine also produced very similar effects (responding largely confined to the saline key) under both FR and FI schedules. However, the effects of phencyclidine were different depending on the schedule. Under the FR schedule, responding after phencyclidine administration was largely confined to the saline key, but under the FI schedule, there was at least a partial generalization between pentobarbital and phencyclidine.

Examination of the data from individual subjects suggests that the effects of phencyclidine were also graded or quantal depending on the reinforcement schedule. Under the FR schedule, responding was quantal in that the responding of all birds was confined to the saline key, while under the FI schedule, responding was graded with increasing doses of phencyclidine producing increased responding on the pentobarbital key (Table 1). It is not clear why the 1.8 mg/kg dose of phencyclidine produced considerable responding on the pentobarbital key when responding was maintained under the FI schedule, but responding was confined to the saline key when responding was maintained under the FR schedule. The 1.8 mg/kg dose of phencyclidine reduced responding to low levels under both reinforcement schedules, so higher doses were not studied.

The idea that the schedule of reinforcement is a powerful determinant of the effect of a drug on behavior is hardly novel. Since the classic study of Dews (1955) showed that the effects of pentobarbital on rates of responding depended on whether responding was maintained by a FR or a FI schedule of reinforcement, there have been a host of experiments demonstrating the importance of the interaction between drugs and schedules of reinforcement (for reviews, see Blackman and Sanger, 1978; McMillan and Leander, 1976; Weiss and Laties, 1976; and many others). Despite this very large literature on the influence of the reinforcement schedule in determining drug effects on behavior, reinforcement schedules have been largely ignored in the drug discrimination literature, where the emphasis has been on differential discrimination of drugs of different classes and attempts to determine which pharmacological effects at cellular and subcellular levels mediate their discriminative stimulus effects. The present experiments emphasize once again that the behavioral response to the drug is determined by an interaction between the pharmacological effects of the drug and the conditions under which the behavior is studied, most notably, the reinforcement schedule maintaining responding.

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