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Drug Discrimination Using a Pavlovian Conditional Discrimination Paradigm in Pigeons

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PARKER, B. K., D. W. SCHAAL AND M. MILLER. *Drug discrimination using a Pavlovian conditional discrimination paradigm in pigeons.* PHARMACOL BIOCHEM BEHAV **49**(4) 955-960, 1994.—Three pigeons were studied using a discriminated autoshaping procedure in which the presence or absence of methadone served as a conditional stimulus signalling which of two key light CSs would be followed by grain access. Drug sessions alternated randomly with no-drug sessions. Methadone (2.0 mg/kg) was administered prior to drug sessions in which a black vertical line on a white background served as CS+ and a diffuse white keylight served as CS− (reversed for bird 681). Saline or no injection was administered prior to no-drug sessions and the CS+/CS− contingencies were reversed. Discriminated performances emerged in which over 80% of the responding occurred to the appropriate stimulus. Stimulus control by methadone was assessed by presenting a range of methadone doses during 10-trial extinction sessions. A graded dose-effect curve was produced with low doses of methadone controlling saline-appropriate responding and higher doses controlling drug-appropriate responding. A range of doses of morphine, cocaine, and pentobarbital were also tested. Morphine produced methadone-appropriate responding while cocaine and pentobarbital did not.

Drug discrimination Pavlovian facilitator Methadone Pigeons

THE basic procedure for establishing a drug discrimination is to reinforce one response following drug administration and reinforce a second response following administration of no drug, a different drug, or a different dose of the same drug (12,13). When animals are trained using this procedure, one response-reinforcer relation exists when the drug is present (e.g., left responses produce reinforcement) and a different response-reinforcer relation exists when the drug is absent (e.g., right responses produce reinforcement). Viewed in this way, it is clear that the relation between the response and reinforcer is dependent or conditional on the presence or absence of the drug as a discriminative stimulus (S^D).

The mechanisms involved in the control of behavior by conditional relations have been investigated extensively in Pavlovian conditioning (8,16,18). In these Pavlovian discrimination procedures, the CS-US relation is conditional on the presence or absence of another stimulus. For example, using autoshaping procedures, pigeons receive food (US) following a brief illumination of a keylight (CS) only if a houselight (conditioned facilitator or positive occasion setter) is present (18). Recent investigations (16,19) have noted the operational similarity of the facilitator in Pavlovian paradigms and the S^D in instrumental conditioning paradigms. Moreover, the stimulus control established by a Pavlovian conditional relation (facilitator) parallels the control established by an instrumental S^D in terms of the shape of postdiscrimination generalization gradients (14). The purpose of the present experiment was to asses whether a moderate dose of methadone could serve as a facilitator of CS-US relations in a Pavlovian conditional discrimination procedure using an autoshaping procedure with pigeons. Specifically, the presence vs. absence of methadone signalled which of two keylight CSs (black vertical line or diffuse white light) would be followed by grain access (US). If methadone serves a facilitator or modulatory function, then the presence of methadone will set the occasion for only one of the two CSs to elicit pecking, while the absence of methadone will occasion a reversed elicitative relationship. Further, if methadone shares properties with conventional facilitators,

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then the discrimination should be dose dependent. Finally, if the methadone facilitator is functionally similar to drug S^Ds in conventional (e.g., two key) instrumental discrimination procedures, then its function should be shared with drugs in the same pharmacological class.

METHOD

Subjects

Three experimentally naive White King pigeons (Palmetto, Sumpter, SC), ranging in age from 3–5 years and weighing 626–655 g, served as subjects. They were maintained at 80% of their free feeding weight by supplemental feeding with mixed grain following sessions and housed in individual cages with water and grit available.

Apparatus

The experimental chamber was a standard two-key unit with interior dimensions of 28 by 28 by 34 cm. The response keys (2.5 cm in diameter) were located 22 cm from the floor and 12.75 cm apart. The right key, which was not used during the experiment, was covered with gray duct tape. Centered beneath the keys, 8 cm from the floor, was an opening (5 by 5 cm) allowing access to a hopper filled with mixed grain. Located behind the left key was an IEE in-line projector that permitted transillumination of the key with a blank white stimulus or a vertical black line (0.3 cm wide by 2.5 cm high) on a white background. The chamber was diffusely lighted from above by a 15-W bulb. Masking noise was provided by a ventilation fan. Standard electromechanical control and recording equipment was located in an adjacent room.

Procedure

Pretraining. Magazine training was the same for all subjects. On day 1, each bird was placed in the chamber with the food hopper raised permitting access to the grain. After the bird had eaten for approximately 20 s, the hopper was lowered. Thereafter, time between hopper presentations was gradually lengthened from an average of 15 s to approximately 60 s and the time of grain availability during each presentation was systematically shortened from 15 s to 5 s. On days 2 and 3, the birds received 44 5-s grain presentations spaced about 1 min apart. When magazine training was completed, the birds were given autoshaping over the next 4 days. Autoshaping to the stimulus subsequently used as the CS+ on saline/no injection sessions consisted of 60 5-s presentations of either the vertical line (bird 411 and 3989) or the blank white (bird 681) stimulus. Each of the stimulus presentations terminated with 5 s of grain access and the intertrial interval (ITI) averaged 1 min (range 50–70 s).

Discrimination training. Pavlovian discrimination training began on day 8. A session consisted of 20 CS+ and 20 CS− trials scheduled randomly with the restriction that no more than three like trials occurred in succession. The presence or absence of methadone served as a conditional stimulus signalling whether the vertical line or white key would be followed by 5 s of grain access. When methadone was administered prior to a session, the vertical line was the CS+ for birds 411 and 3989 (CS− for bird 681) and the white key was CS− (CS+ for bird 681). When saline/no injection occurred prior to the session the CS+/CS− contingencies were reversed. Training sessions were conducted 5 days a week. Each pigeon was administered 2.0 mg/kg methadone (dissolved in isotonic saline to be administered into the breast muscle in a volume of 1.0 ml/kg) or saline/no injection 15 min prior to the onset of each discrimination session. Following 4 or 5 days of initial training with no injection, the daily injection sequence followed a semirandom 50% schedule with the constraint that a particular treatment (methadone vs. saline/no injection) was not administered for more than three consecutive sessions. Initial training sessions were conducted with grain access following each of the CS+ stimuli (100% reinforcement) until each bird met a criterion of 80% of the total session responses to CS+ for at least five consecutive sessions. Upon meeting this criterion, the birds were placed on a lean reinforcement schedule in which only 50% of the CS+ stimuli terminated with grain access. Discrimination training continued until each bird again attained the 80% criterion for at least 5 consecutive days.

Test procedures. Once these criteria were met, two-dose generalization tests of methadone were conducted followed by a test of novel drugs. Doses of novel test drugs were tested once. All drugs were dissolved in saline and adminstered into the breast muscle in a volume of 1.0 ml/kg 15 min prior to the start of the sessions. Tests occurred on Fridays, with regular training sessions occurring on Mondays through Thursdays (no injection, drug, drug, saline, respectively). Tests were conducted in extinction with five CS+ trials interspersed with five CS− trials. Doses of methadone tested ranged from 0.5–2.0 mg/kg, morphine from 0.5–5.6 mg/kg, cocaine from 0.3–5.6 mg/kg, and pentobarbital from 3.0–10.0 mg/kg.

RESULTS

Figure 1 shows acquisition of the methadone present/absent discrimination for each subject. Birds 411 and 681 met the acquisition criterion of five consecutive sessions of over 90% condition appropriate responding in 21 and 19 sessions, respectively. In contrast, bird 3989 did not acquire the discrimination well, taking 46 sessions to reach 80% condition-appropriate responding for three consecutive sessions. During subsequent leaning (50% reinforcement on CS+ trials) sessions, the performance of birds 411 and 681 stabilized rapidly with approximately equal discriminative performances during drug and no-drug sessions. Bird 3989, on the other hand, continued to show a lower level of condition-appropriate responding with more accurate performance during no-drug compared to drug sessions.

Figure 2 shows the effects of a range of methadone doses on the discriminative performance of the subjects. Methadone occasioned responding to the appropriate CS in a dose-related manner (left panels) and suppressed the rate of responding (right panels) at higher doses. Control of responding by methadone was sharpest for bird 411, who showed 100% methadone appropriate responding for doses above 1.25 mg/kg with an average of less than 10% methadone appropriate responding for doses of 1.0 mg/kg or below. Bird 681 showed a similar pattern, but with dose 1.25 mg/kg controlling more saline than methadone appropriate responding. Bird 3989, who displayed a mediocre discrimination performance during acquisition, produced a much shallower gradient with averages of 58%, 64%, 68%, and 71% methadone-appropriate responding on doses of 1.0, 1.25, 1.5, and 2.0 mg/kg, respectively.

Morphine occasioned dose-dependent methadone-appropriate responding (Fig. 3, left panels) in all three subjects at doses of 2.0 mg/kg for birds 681 and 3989 and 3.0 mg/kg or greater for bird 411. In contrast, cocaine failed to occasion methadone appropriate responding in any of the subjects, while pentobarbital produced only low levels of methadone-appropriate responding at 10.0 mg/kg for bird 681 and 5.6

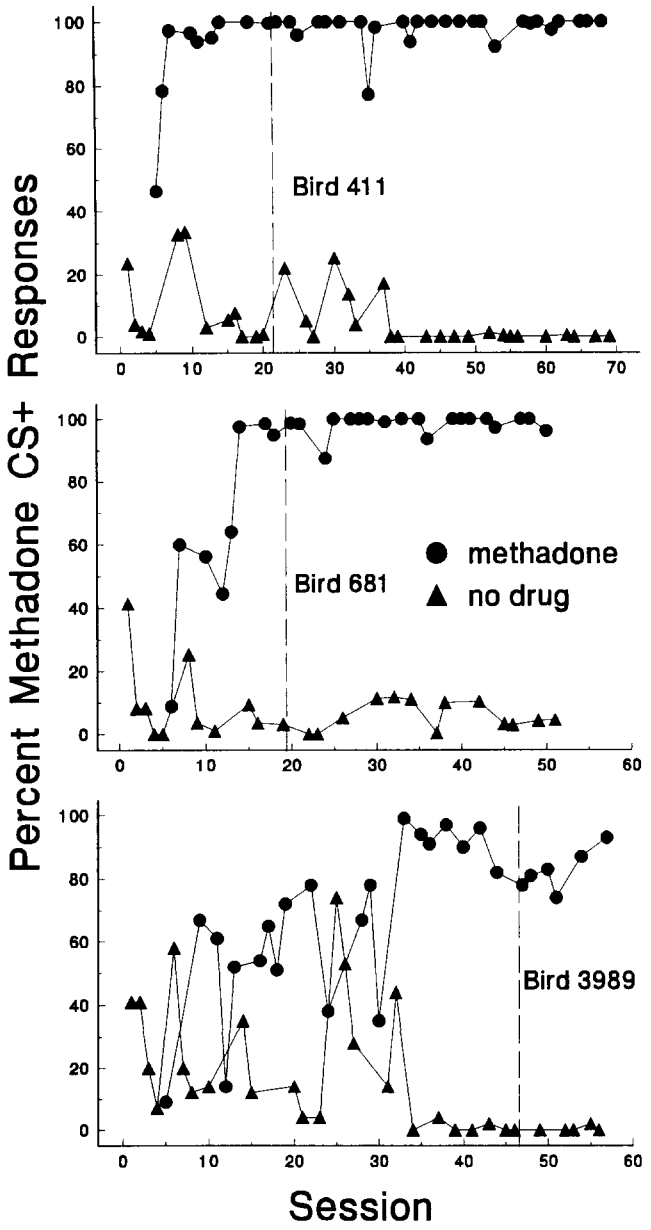

FIG. 1. Acquisition of discrimination between methadone 2.0 mg/kg and no drug (saline or no injection) for each pigeon. The percentage of methadone CS+ responses is plotted as a function of sessions. Reinforcement followed 50% of the CS+ presentations beginning at the vertical line.

and 10.0 for bird 3989. In most of these substitution tests, 10% or less of the responses occurred to the methadone CS+. Although there was considerable variability in overall response rates with the novel drugs, in general, higher doses produced lower rates of responding (Fig. 3, right panel).

DISCUSSION

The results of the present study show that the presence or absence of 2.0 mg/kg of methadone can serve as a Pavlovian facilitator modulating the functioning of two keylight CSs in an autoshaping procedure. Methadone set the occasion for one CS to elicit pecks, while the absence of methadone facilitated responding to the other CS. These results demonstrate a unique form of stimulus control into which drugs may enter, i.e., the Pavlovian facilitator or occasion setter. This procedure differs operationally from more conventional two-response procedures in that the keylight stimuli are presented sequentially rather than concurrently, and that the scheduled events occurred regardless of the subjects' behavior. The index of discrimination depended both on the subjects' pecking when the CS+ was presented and refraining from pecking when the CS− was presented. That they were able to do both with a high level of accuracy is particularly apparent from the performances of birds 411 and 681 (Figs. 1 and 2), which indicate that, following administration of the training stimuli, few pecks occurred to the inappropriate CS. Whether the nature of discriminative stimulus control over elicited pecking in this procedure differs functionally from discriminative control over key choice in a two-key procedure cannot be determined based on these data. Neither acquisition (Fig. 1) nor dose–response curves for methadone (Fig. 2) in this study differed greatly from the results obtained in pigeons trained to discriminate the same dose of methadone (administered 20 min prior to sessions) from saline in a two-key FR-schedule procedure (21). More direct comparisons of the two procedures are required to determine whether they differ in more than operational terms.

The production of steep decremental gradients for methadone is consistent with the control established using both nondrug stimuli in the facilitation training paradigm (14), and drug stimuli as S^Ds in two-choice operant procedures (22,23). Morphine readily substituted for methadone in each pigeon. Cocaine, however, when administered at behaviorally effective doses as indicated by reductions in rates of pecking, produced pecking exclusively to the saline CS+. Finally, pentobarbital produced saline-appropriate performance in bird 411 at all doses, and in bird 681 at 3.0 and 5.6 mg/kg. There was limited (i.e., 30–40%) methadone-appropriate responding for bird 681 following 10.0 mg/kg pentobarbital and for bird 3989 at 5.6 and 10.0 mg/kg pentobarbital. Thus, methadone produced stimulus control that generalized to the tested drugs in a pharmacologically specific manner. Further tests employing specific opioid antagonists and agonists will be necessary to assess the precise pharmacological mechanisms underlying the methadone discriminative stimulus in this procedure.

Drugs have previously been shown to function as stimuli in other Pavlovian conditioning procedures. In particular, the role of drugs as unconditioned stimuli has been frequently studied (4). For example, in one study (6), a buzzer (the CS) was paired with an injection of the opiate antagonist nalorphine (the US) in morphine-dependent rhesus monkeys responding on a schedule of food reinforcement. After repeated pairings, the buzzer suppressed responding and produced opiate-withdrawal symptoms in the absence of nalorphine injection. Studies also indicate that drug stimuli may acquire a CS function. In two recent reports (3,13), water drinking of rats was suppressed more substantially by drugs (morphine, phencyclidine, pentylenetetrazol, and pentobarbital) if the drugs had been previously paired with a series of foot shocks (the US), thus suggesting that the drugs had become CSs.

Several studies (5,10,20,24) have shown that presession administration of drugs [including opioid agonists; (15)] can suppress behavior (food-reinforced lever-pressing of monkeys, and drinking of a saccharin solution in rats) to a greater extent if sessions are followed by illness induced by lithium chloride

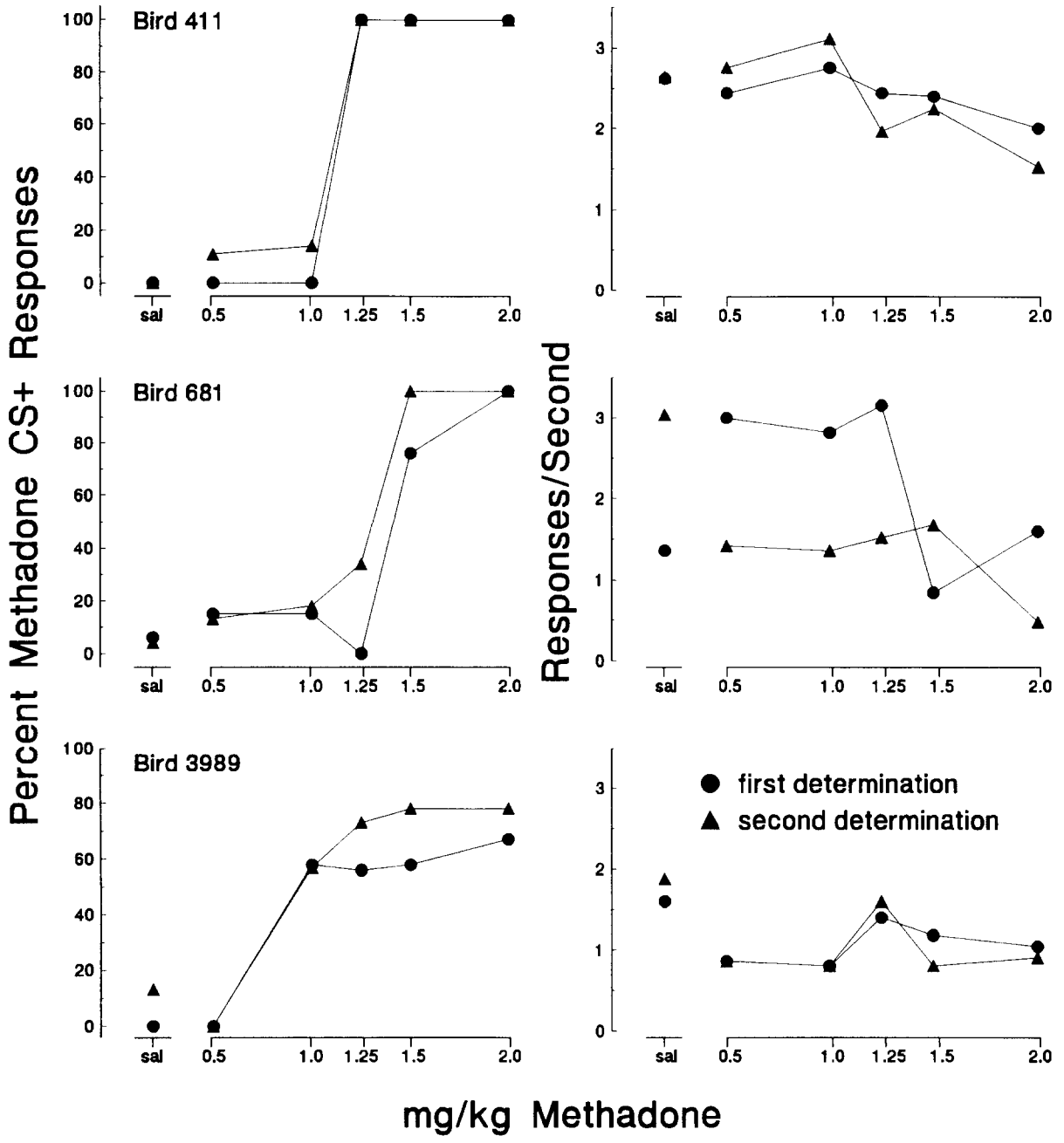

FIG. 2. Dose-effect curves for doses of methadone for each pigeon. The percentage of methadone CS+ responses (left panels) and overall rate of elicited pecks (right panels) are plotted as a function of methadone dose for two determinations.

(LiCl) than if sessions are followed by saline. If, in these taste-aversion paradigms, the food or saccharin reinforcer is conceived of as a CS that is occasionally paired with a LiCl-US, then the presession drug stimuli may function in much the same way as methadone functioned in the present study, i.e., as a Pavlovian facilitator. Although discrimination in these studies is typically assessed by reductions in levels of behavior following drug, a rate-independent index of discrimination using the taste-aversion paradigm has been developed [e.g., (20)]. Rats trained to discriminate flumazenil in this manner were given access to two bottles, one containing the saccharin solution and the other containing water. The relative amount of saccharin consumed was a dose-dependent function of flumazenil and other putative benzodiazepine antagonists. Although acquisition of discrimination using the taste-aversion paradigm is often reported to be extremely rapid [e.g., from 4 to 10 sessions; (5,10,20)], other investigators (24) have reported no obvious differences in rates of acquisition of stable baselines of discrimination relative to the two-response FR-schedule procedure (24). Some studies (5,24) have also reported that suppression of saccharin or food consumption in the presence of drug stimuli may wane across sessions, so

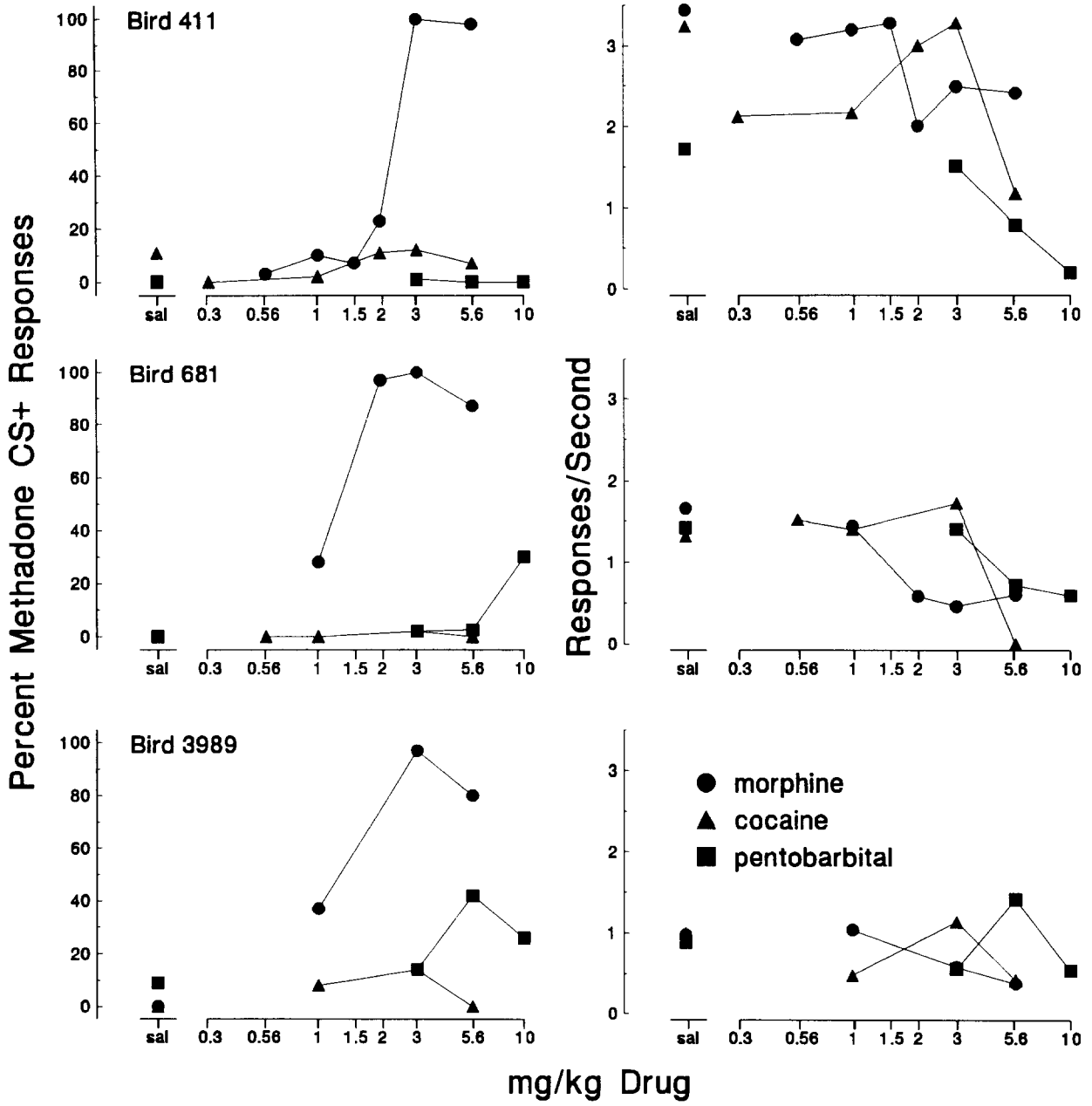

FIG. 3. Dose-effect curves for doses of morphine, cocaine, and pentobarbital for each pigeon. The percentage of drug CS+ responses (left panels) and overall rate of elicited pecks (right panels) are plotted as function of drug dose.

that maintaining long-term baselines of drug discrimination in single subjects may be difficult. This may limit the time available for dose-effect testing, tests of other drugs, and tests with drug antagonists. In contrast, discrimination of methadone in the present procedure was maintained at consistently high levels during several months and despite tests of several other drugs. Although it is too early to assert the superiority of one or the other procedure, the present results certainly encourage further work using the autoshaping procedure.

In the current procedure, generalization tests were conducted in extinction, thus circumventing the problem of how or whether reinforcement should be delivered under test conditions. Investigators often recognize problems regarding the interpretation of discriminative performance following presentation of a reinforcer (an event which, during training, is as reliably correlated with the contingencies as the drug stimulus conditions). The only behavior that can be attributed to the drug stimulus conditions with certainty is that which occurs during the first ratio. The present procedure avoids this problem by conducting generalization tests under extinction. Testing in extinction is valid in this procedure because the absence of food presentation following one keylight CS does not reliably signal a positive correlation between the other CS and food. Subjects are trained under conditions in which the CS+

is followed by food on only 50% of the trials, thus preparing them for testing conditions during which food is not presented [a similar kind of preparation for tests in extinction occurs when variable-interval or fixed-interval schedules are used in training; see (1,2,9)]. Rates of pecking during tests of the training drugs (saline and 2.0 mg/kg methadone) were not appreciably different from those obtained during training sessions, indicating that pigeons did not treat the 10-trial extinction test differently from training sessions.

In summary, this experiment showed that the stimuli produced by the presence or absence of 2.0 mg/kg methadone modulated the function of two keylight CSs, thus setting the occasion for one CS to elicit pecks in the presence of methadone and a second CS to elicit pecks in methadone's absence. Generalization tests showed that this modulating role was a dose-dependent function of methadone or morphine. Cocaine produced behavior similar to that obtained following saline in all three pigeons. Pentobarbital produced saline-appropriate behavior in one pigeon and 20–40% methadone-appropriate behavior in two pigeons at higher doses. Thus, these results add Pavlovian facilitation to the list of types of stimulus control that can be exerted by drug stimuli. Future experiments should assess more fully whether the pharmacological mechanisms that underlie drug discrimination produced with this procedure correspond to those identified using operant procedures. In addition, research in classical conditioning may suggest ways to explore the effects of novel associative relations between drug and external stimuli.

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