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Interaction of d-Amphetamine with Pentobarbital and Chlordiazepoxide: Effects on Punished and Unpunished Behavior of Pigeons[1]

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BARRETT, J. E. AND J. M. WITKIN. *Interaction of d-amphetamine with pentobarbital and chlordiazepoxide: effects on punished and unpunished behavior of pigeons.* PHARMAC. BIOCHEM. BEHAV. 5(3) 285–292, 1976. – Key pecking of two pigeons was maintained under a multiple schedule of food presentation. In the presence of one keylight stimulus responding produced food according to a fixed-interval 5-min schedule. Additionally, during this component, each 50th response produced electric shock. When a different keylight stimulus was present, key pecking resulted in food delivery under a variable-interval 3-min schedule. Responding was suppressed by shock presentation (punishment) but was still positively accelerated throughout each fixed-interval cycle; steady response rates occurred during the alternate component when only the variable-interval schedule was in effect. Overall rates of punished responding were largely unchanged with d-amphetamine (0.1–3.0 mg/kg); unpunished responding was generally either increased slightly or was decreased. Pentobarbital and chlordiazepoxide (1.0–17.0 mg/kg) administered alone increased both punished and unpunished responding at most doses. Combinations of d-amphetamine with either pentobarbital or chlordiazepoxide produced increases in punished responding that exceeded those obtained with either of these drugs alone. The combined effects of d-amphetamine and either pentobarbital or chlordiazepoxide on unpunished responding depended on the individual dose combinations. Combinations of d-amphetamine with pentobarbital or chlordiazepoxide produced effects on both punished and unpunished responding that differed substantially from those obtained when any of these drugs were administered separately.

Drug interactions d-Amphetamine Pentobarbital Chlordiazepoxide Punished behavior Pigeons

BEHAVIOR occurring at a low rate due to the response-dependent presentation of a stimulus such as electric shock (punished responding) is typically increased markedly by appropriate doses of benzodiazepines and barbiturates [8, 9, 12, 13, 21]. The amphetamines, however, despite their rather widespread tendency to increase behavior under a wide range of conditions, do not usually increase punished behavior except when the control response rate and shock intensity are low [7, 9, 10, 11, 12]. The benzodiazepines and the barbiturates also produce similar effects on unpunished behavior under conditions when they are given separately and in combination with amphetamine. Rushton and Steinberg [15] reported that combinations of certain doses of amphetamine with amobarbital produced increases in the locomotor activity of rats that were larger than those obtained with either drug alone. Similar effects were obtained with combinations of amphetamine and chlordiazepoxide [16].

Rutledge and Kelleher [18] studied the effects of pentobarbital and methamphetamine alone and in combination on the schedule-controlled key pecking of pigeons. In that experiment, responding was maintained under a multiple schedule where, in the presence of one keylight stimulus, the 31st response produced food (fixed-ratio 31 or FR 31 schedule). When a different keylight color was present, the first response after a 5-min period elapsed resulted in food delivery (fixed-interval 5-min or FI 5-min schedule). Whereas pentobarbital (1.0–10.0 mg/kg) further increased the high response rates under the FR schedule, methamphetamine only decreased responding under this condition. When these two drugs were given together, rates of responding were between those produced by either drug

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alone. Response rates under the FI schedule were increased by both methamphetamine (1.0–3.0 mg/kg) and pentobarbital alone, with combinations of these two drugs producing increases that were greater than those obtained with the individual drugs. Synergistic effects of pentobarbital and amphetamine have also been demonstrated with dogs responding under a schedule in which food was presented when a nose key had been depressed for a cumulative period of time [20]. Under these conditions pentobarbital and amphetamine together increased the frequency of short duration responses more than either drug alone. Richelle [14] found that, with cats, combinations of diazepam and d-amphetamine increased responding under an FI 5-min schedule above that obtained with either drug alone. Further, the rate-decreasing effects of the higher doses of d-amphetamine were antagonized by diazepam. Combinations of pentobarbital and d-amphetamine have also produced both synergism and antagonism under a procedure involving three keys where the scheduled FR requirement associated with the center key determined whether pecking one of two side keys produced food [2].

In the experiments summarized above, the behavioral effects of the drugs alone and in combination depended on the characteristics of behavior under study, on the prevailing schedule of reinforcement, and on the behavioral effects of the individual drugs. Combinations of drugs have often produced behavioral effects that were not characteristic of either drug administered separately [cf. 17]. This aspect of drug combinations was the focus of the present series of experiments. Most studies of the effects of drug interactions on schedule-controlled behavior have investigated combinations of drugs which, when given individually, each produce changes in behavior. In view of the previously reported rate-increasing effects of chlordiazepoxide and pentobarbital on punished responding, the combination of either of these drugs with d-amphetamine, which does not generally increase punished behavior, was of particular interest.

METHOD

Animals

Two adult White Carneaux pigeons were maintained at 80% of their free-feeding weights. Both had prior exposure to various schedules of food and shock presentation; neither had previously received drugs.

Apparatus

Experiments were conducted in a single-key pigeon chamber (27 × 30.5 × 26 cm) placed inside a ventilated, sound-attenuating enclosure supplied with white noise. A response key (R. Gerbrands Co.) was centered 22 cm above the floor and was mounted behind a 2 cm dia. opening on the front aluminum wall. The key could be transilluminated with separate pairs of 7-W colored lamps. Responses on the key exceeding a force of approximately 15 g (0.15N) were recorded and also produced the audible click of a feedback relay located behind the front panel. A 4.5 × 5 cm opening centered 15 cm below the response key provided 4-sec access to mixed pigeon grain. When food was presented the grain magazine was illuminated and the keylight was extinguished. Electric shocks (110 V a.c., 200 msec) were delivered through series resistance to gold electrodes implanted around the pubis bone [1]. The electrodes were attached to a plug secured on the pigeon's back by a leather harness that was connected by a coiled telephone cable to a swivel mounted on the ceiling of the chamber. Shock intensity was set at 3 mA for P-12 and at 4 mA for P-242. The impedence of each bird was checked frequently throughout the course of the experiments.

Behavioral Procedure

At the beginning of this experiment responding was maintained under a multiple variable-interval 3-min, fixed-interval 5-min schedule. Under this procedure, key pecking in the presence of a green keylight stimulus produced food on the average of every 3 minutes (VI 3-min constant probability schedule, 3). When the keylight was red, the first key peck after a 5-min interval produced food (FI 5-min schedule). The schedules alternated successively throughout each session and were separated by a 60-sec timeout period during which the keylights were turned off and responding had no scheduled consequences. The VI component of the multiple schedule terminated after a 5-min period; the FI component terminated with the response that produced food or, after 6 minutes, independent of responding if no response occurred between the fifth and sixth minute (60-sec limited hold). Sessions were approximately 2 hours long, and consisted of 10 presentations of each component of the multiple schedule.

After responding stabilized (about 30 sessions), the schedule was modified so that each 50th response during the FI schedule produced shock. The first response after the 5-min period still produced food (conjoint FR 50 shock, FI 5-min food schedule). The FR value reset at the beginning of each FI component. Shocks were delivered only during the FI cycle of the multiple schedule. Approximately 25 sessions preceded the first drug administration. Sessions were conducted five days per week, Monday through Friday.

Drug Procedure

The effects of d-amphetamine sulfate (0.1–3.0 mg/kg) and pentobarbital sodium (1.0–17.0 mg/kg) were first studied separately. Injections of each drug alone were given in conjunction with a second injection of saline. After each dose of pentobarbital and d-amphetamine had been administered at least once, the combined effects of d-amphetamine and pentobarbital were examined. With P-12, 0.3 and 3.0 mg/kg d-amphetamine were given in combination with all doses of pentobarbital, generally on at least two separate occasions. For P-242, doses of 0.3 and 1.0 mg/kg d-amphetamine were given once with all doses of pentobarbital; the 3.0 mg/kg dose of d-amphetamine was given two times with each dose of pentobarbital except at 10.0 and 17.0 mg/kg, where it was given only once. All individual doses of d-amphetamine or pentobarbital were also given on at least two separate occasions. The sequence of injections was mixed.

After the separate and combined effects of d-amphetamine and pentobarbital were determined, each bird received single doses of chlordiazepoxide hydrochloride (1.0–17.0 mg/kg) plus saline. Chlordiazepoxide was then administered in combination with either 0.3 or 3.0 mg/kg d-amphetamine. The effects of chlordiazepoxide alone were redetermined during the course of the drug interaction series.

Interactions of d-amphetamine with each chlordiazepoxide dose were usually studied at least twice.

All drugs were dissolved in 0.9% saline and were injected in a volume of 1.0 ml/kg into the pectoral muscle. Doses are expressed in terms of the total salt. Pentobarbital, d-amphetamine and saline were given immediately prior to the session; chlordiazepoxide was given 60 minutes prior to the start of the session.

Drugs were administered no more than twice weekly, typically on Tuesdays and Fridays, given that control patterns and rates of responding continued to appear stable. Control rates of responding were separately determined during the pentobarbital and chlordiazepoxide series.

RESULTS

Control performances. Overall rates of responding under the FI schedule prior to the introduction of shock were approximately 0.510 and 0.642 responses per second for P-12 and P-242 respectively. The FR 50 schedule of shock presentation reduced response rates by approximately 75% (mean punished response rates for the 3 sessions preceding the first drug administration were 0.116 for P-12 and 0.154 for P-242). Unpunished response rates maintained under the VI schedule increased slightly, from 0.675 to 0.697 for P-12 when shock was introduced in the alternate component, whereas VI rates decreased from 0.846 to 0.642 for P-242 after the introduction of shock. Control patterns of punished and unpunished responding under the multiple schedule baseline are shown for both pigeons in the top portion of Fig. 1. Punished responding during the FI schedules was characteristic of that maintained under FI schedules in terms of its positively accelerated patterning [6,19], but occurred at a lower rate throughout each interval. At the beginning of each FI cycle, there was an initial pause followed by a gradual increase to a higher rate of responding until a response produced food. Unpunished responding under the VI schedule occurred at a fairly steady rate throughout each 5-min component.

Effects of d-amphetamine-pentobarbital combinations. Dose-effect curves showing changes in responding with d-amphetamine and pentobarbital alone and in combination are presented in Fig. 2. d-Amphetamine had little effect on overall rates of punished responding. Instances where the 3.0 mg/kg dose increased rates of responding early in the FI cycle can be seen in the cumulative records of Figs. 1 and 4. Responding was markedly suppressed after shock presentation with this dose of d-amphetamine. Pentobarbital generally increased overall punished response rates at the 3.0–10.0 mg/kg doses. When d-amphetamine was given in combination with pentobarbital, increases in punished responding were obtained that exceeded those produced by pentobarbital alone. With P-12, these increases with the drug combination were greatest with the 0.3 mg/kg dose of d-amphetamine and the 17.0 mg/kg dose of pentobarbital. For P-242 increases in response rates above those of pentobarbital alone were produced by the drug combination at all doses of pentobarbital and with all three doses of d-amphetamine.

Changes in the patterns of punished responding with each drug alone and in combination are also depicted in the cumulative response records in Fig. 1. Particularly noteworthy are the substantial increases in punished responding with the pentobarbital and d-amphetamine combinations. The low rates of responding after shock with 3.0 mg/kg d-amphetamine noted earlier were increased when this dose was given in conjunction with pentobarbital. Responding was often positively accelerated between shock presentations when 10.0 mg/kg pentobarbital was given with 3.0 mg/kg d-amphetamine.

The separate and combined effects of pentobarbital and d-amphetamine on unpunished responding are also shown in Figs. 1 and 2. Rates of unpunished responding maintained under the VI schedule with P-12 were decreased with d-amphetamine at the 0.1 and 3.0 mg/kg doses but were unchanged with 0.3 and 1.0 mg/kg. For P-242 all doses except 3.0 mg/kg of d-amphetamine slightly increased responding; 3.0 mg/kg d-amphetamine markedly decreased VI response rates with this bird. Pentobarbital (1.0–10.0 mg/kg) increased unpunished responding with both pigeons.

The effects of combined doses of d-amphetamine and pentobarbital on unpunished responding maintained under the VI schedule differed with each pigeon. Although the 0.3 mg/kg dose of d-amphetamine alone did not affect unpunished response rates with P-12, this dose in combination with 1.0–10.0 mg/kg pentobarbital, which increased responding, reduced responding below that obtained with pentobarbital alone. Also with P-12, combined doses of either 0.3 or 3.0 mg/kg d-amphetamine with the lower doses of pentobarbital resulted in decreases in unpunished responding that were below those obtained with these doses of d-amphetamine in isolation. The separate and combined effects of 1.0 mg/kg pentobarbital and 0.3 mg/kg d-amphetamine with P-12 are shown in the cumulative response records of Fig. 1.

For P-242 the combinations of 0.3 and 1.0 mg/kg of d-amphetamine with most doses of pentobarbital produced increases in unpunished response rates that were above those obtained with either drug alone. When 3.0 mg/kg of d-amphetamine was given with pentobarbital, the effects on response rates under the VI schedule were typically less than those obtained with 1.0–10.0 mg/kg pentobarbital alone, but were above those obtained with the 3.0 mg/kg d-amphetamine dose alone. Interactions of pentobarbital with this dose of d-amphetamine produced effects similar to those seen with P-12.

Effects of d-amphetamine-chlordiazepoxide combinations. Figure 3 shows that chlordiazepoxide (1.0–10.0 mg/kg) administered with saline increased punished response rates under the FI schedule for both birds. When the 0.3 and 3.0 mg/kg doses of d-amphetamine were given in combination with most doses of chlordiazepoxide, substantial increases in punished responding were obtained that were well above those produced by chlordiazepoxide alone. With P-12 the interaction of 3.0 mg/kg d-amphetamine with the 1.0–10.0 mg/kg doses of chlordiazepoxide produced greater increases than the interaction of chlordiazepoxide with 0.3 mg/kg of d-amphetamine. With P-242 greater increases with 3.0 mg/kg d-amphetamine and chlordiazepoxide were obtained with the 1.0, 10.0 and 17.0 mg/kg doses of chlordiazepoxide.

Chlordiazepoxide (1.0–10.0 mg/kg) plus saline increased unpunished responding maintained under the VI schedule with both birds. With P-12, the interaction of d-amphetamine and chlordiazepoxide generally decreased response rates below those obtained with chlordiazepoxide alone but rates were still above those that occurred when only d-amphetamine was administered.

For P-242 combinations of 0.3 mg/kg of d-amphetamine with chlordiazepoxide (5.6–17.0 mg/kg) resulted in increases in unpunished responding under the VI schedule

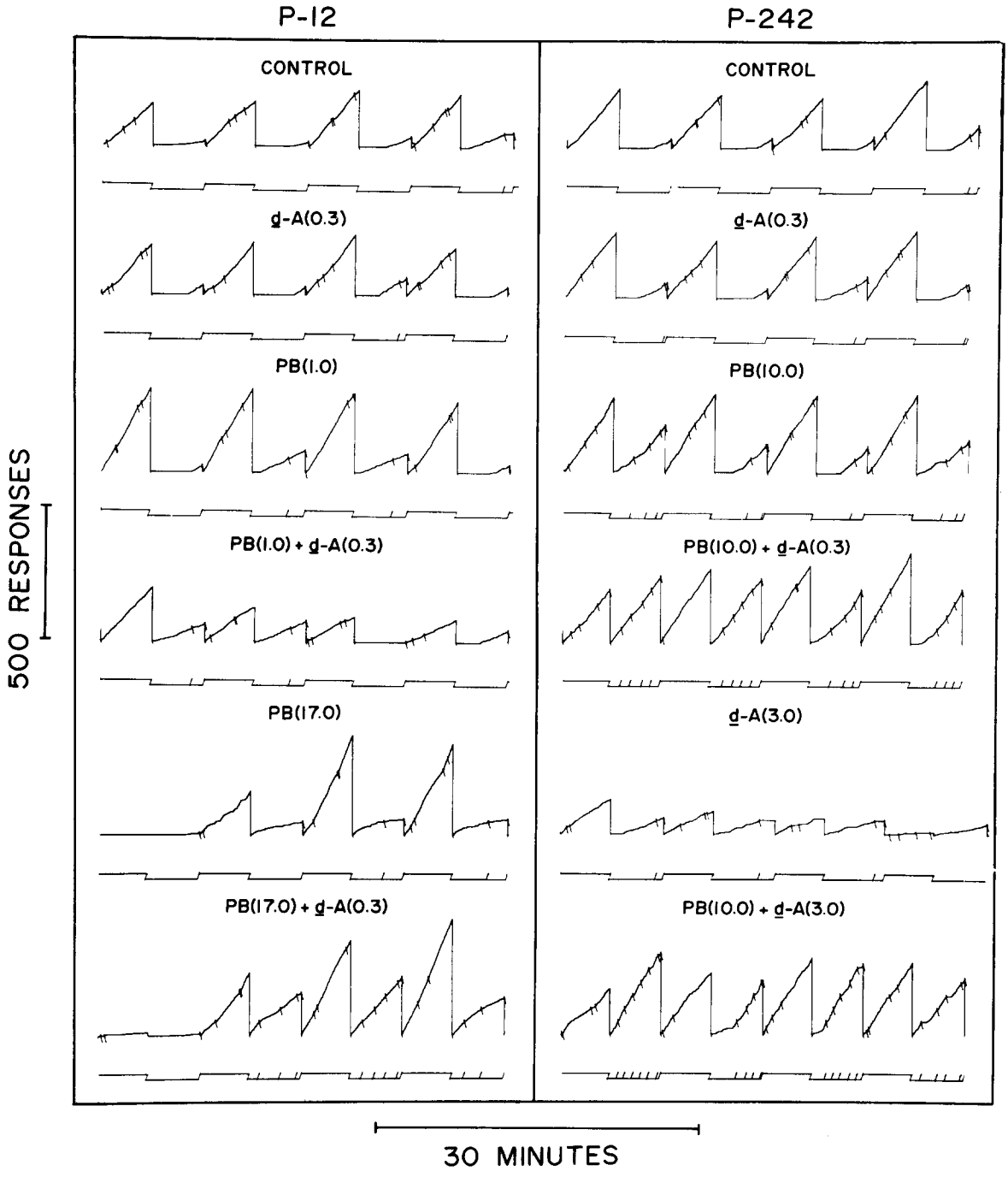

FIG. 1. Cumulative response records for both pigeons under the multiple schedule depicting portions of control conditions and selected doses of d-amphetamine or pentobarbital alone and in combination. The schedule consisted of a 3-min variable-interval food presentation component and, under different stimulus conditions, a 5-min fixed-interval schedule during which each 50th response produced electric shock. The lower event pen line was displaced during the condition where pecking produced both food and shock. Food delivered under the variable-interval schedule produced a diagonal mark on the cumulative record. Under the fixed-interval schedule, food presentation is represented by a simultaneous diagonal slash on the response record and by the return of the pen to basline. Shocks during the fixed-interval schedule deflected the response pen and produced a momentary upwards excursion of the event pen. Time is represented on the abscissa and cumulative responses on the ordinate. The pen reset to the baseline after the end of each schedule component.

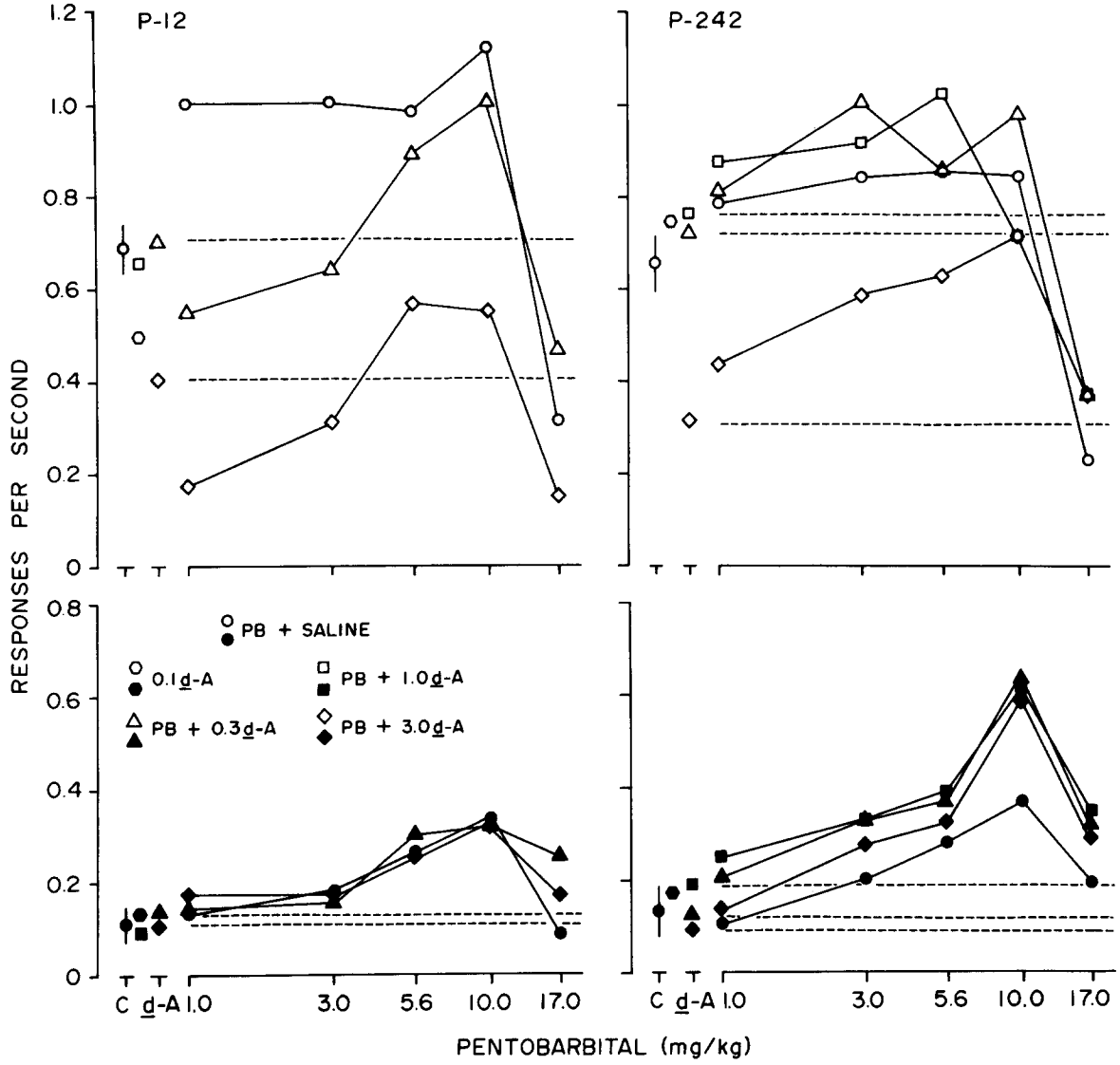

FIG. 2. Effects of d-amphetamine and pentobarbital alone and in combination on punished (bottom, filled symbols) and unpunished (top, open symbols) responding for both birds under the multiple schedule. Vertical lines denote ± 1 SE from the mean control rate of responding, based on at least 13 non-injection or saline control days. Dashed-horizontal lines represent effects of d-amphetamine doses alone. C: control rates of responding: d-A: effects of each dose of d-amphetamine alone (0.1–3.0 mg/kg).

that were above those obtained with either drug in isolation. Although 3.0 mg/kg d-amphetamine markedly decreased responding under the VI component, in combination with doses of chlordiazepoxide from 1.0–5.6 mg/kg responding was increased, although still not above that of chlordiazepoxide alone. Combinations of either 10.0 or 17.0 mg/kg of chlordiazepoxide with 3.0 mg/kg of d-amphetamine produced increases in responding that were substantially greater than those obtained with either drug alone.

The effects of d-amphetamine and chlordiazepoxide, alone and in combination, on the rates and patterns of punished and unpunished responding are shown in the cumulative response records of Fig. 4. The marked increases in punished responding are particularly evident for both pigeons with the d-amphetamine-chlordiazepoxide combinations. As was the case with the 3.0 mg/kg d-amphetamine-pentobarbital combinations, the pronounced decreases in responding after shock with 3.0 mg/kg d-amphetamine were also attenuated when this dose was given with chlordiazepoxide.

DISCUSSION

In accord with previous research, food maintained responding suppressed by shock presentation in the present experiment was increased by pentobarbital and chlordiazepoxide but was affected little by d-amphetamine [8, 9, 12, 13, 21]. Slight increases in punished responding early in the FI were obtained with the highest dose of d-amphetamine (3.0 mg/kg), a finding consistent with Foree, Moretz and McMillan [7] and McMillan [12], but these increases in

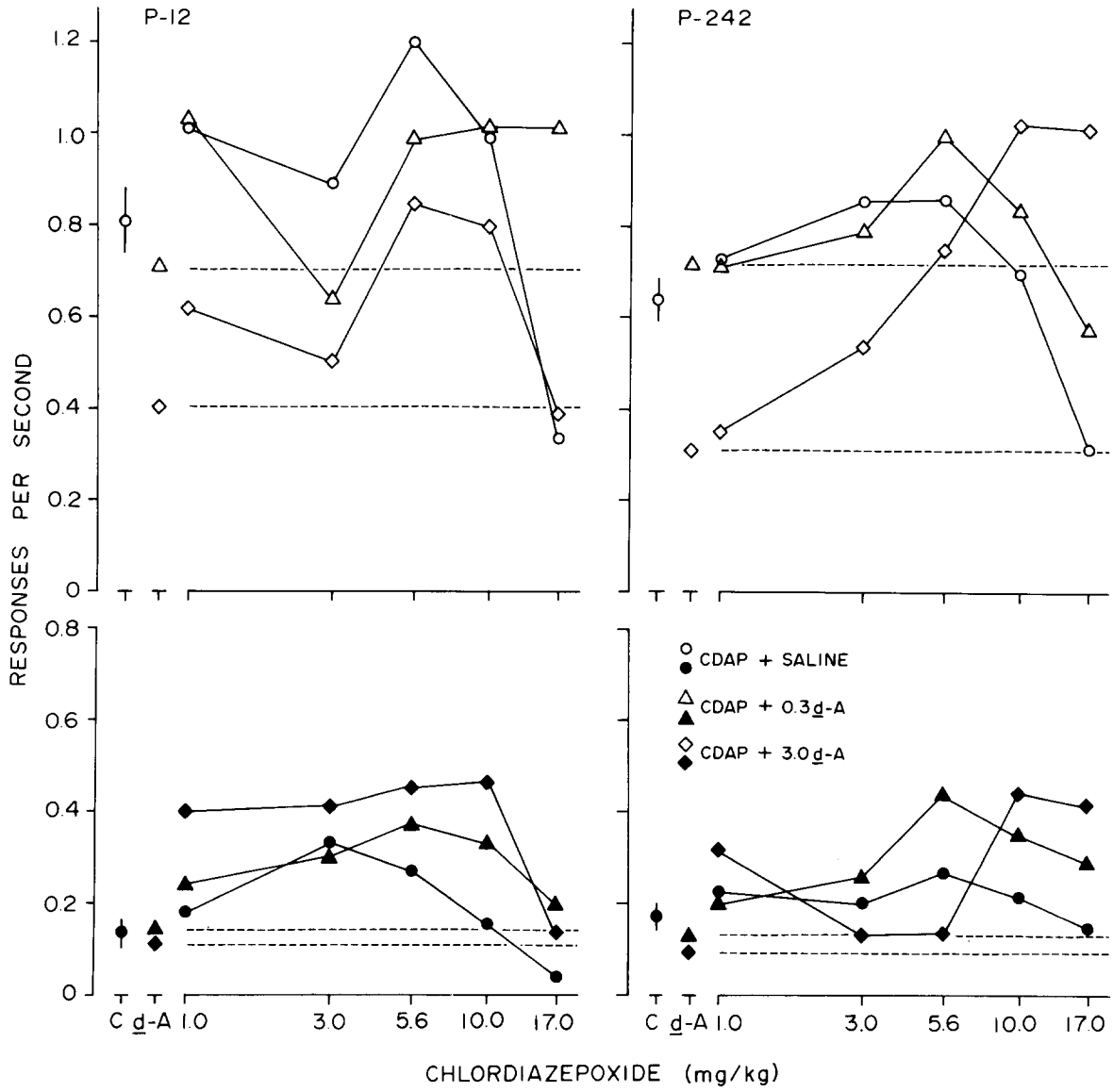

FIG. 3. Effects of d-amphetamine and chlordiazepoxide alone and in combination on punished (bottom, filled symbols) and unpunished (top, open symbols) responding under the multiple schedule with both birds. Vertical lines denote ± 1 SE from the mean, based on at least 14 non-injection or saline control days. Dashed-horizontal lines represent effects of d-amphetamine doses alone. C: control response rates; d-A: effects of d-amphetamine alone.

responding appeared offset by the occurrence of shock. Despite the failure of d-amphetamine alone to increase overall rates of punished responding under the present schedule conditions, the combination of d-amphetamine with either pentobarbital or chlordiazepoxide often produced increases in punished responding that exceeded the rate increases obtained when either of these two drugs were administered separately. This synergistic effect on punished behavior is especially noteworthy since the combined drug effects could not be predicted on the basis of the effects produced by the drugs when given separately.

In the present study, certain doses of d-amphetamine (e.g., 3.0 mg/kg) decreased unpunished responding maintained under the VI schedule. These decreases with d-amphetamine were antagonized by both chlordiazepoxide and pentobarbital. Certain dose combinations of d-amphetamine with either pentobarbital or chlordiazepoxide also resulted in increases in unpunished responding that were larger than those obtained with these drugs alone. These results reemphasize the point that drug interactions can result in both synergism or antagonism depending on the schedule of reinforcement, the resultant ongoing behavior and on the particular dosage combinations. As such, these findings are comparable to those of Rutledge and Kelleher [18], Branch [2] and Richelle [14] on the effects of amphetamine-barbiturate and amphetamine-benzodiazepine interactions on unpunished responding.

In the present experiment the rate-increasing effects of pentobarbital and chlordiazepoxide on punished responding were enhanced by doses of d-amphetamine which, when administered separately, did not increase low punished response rates. Davidson and Cook [5] have also reported

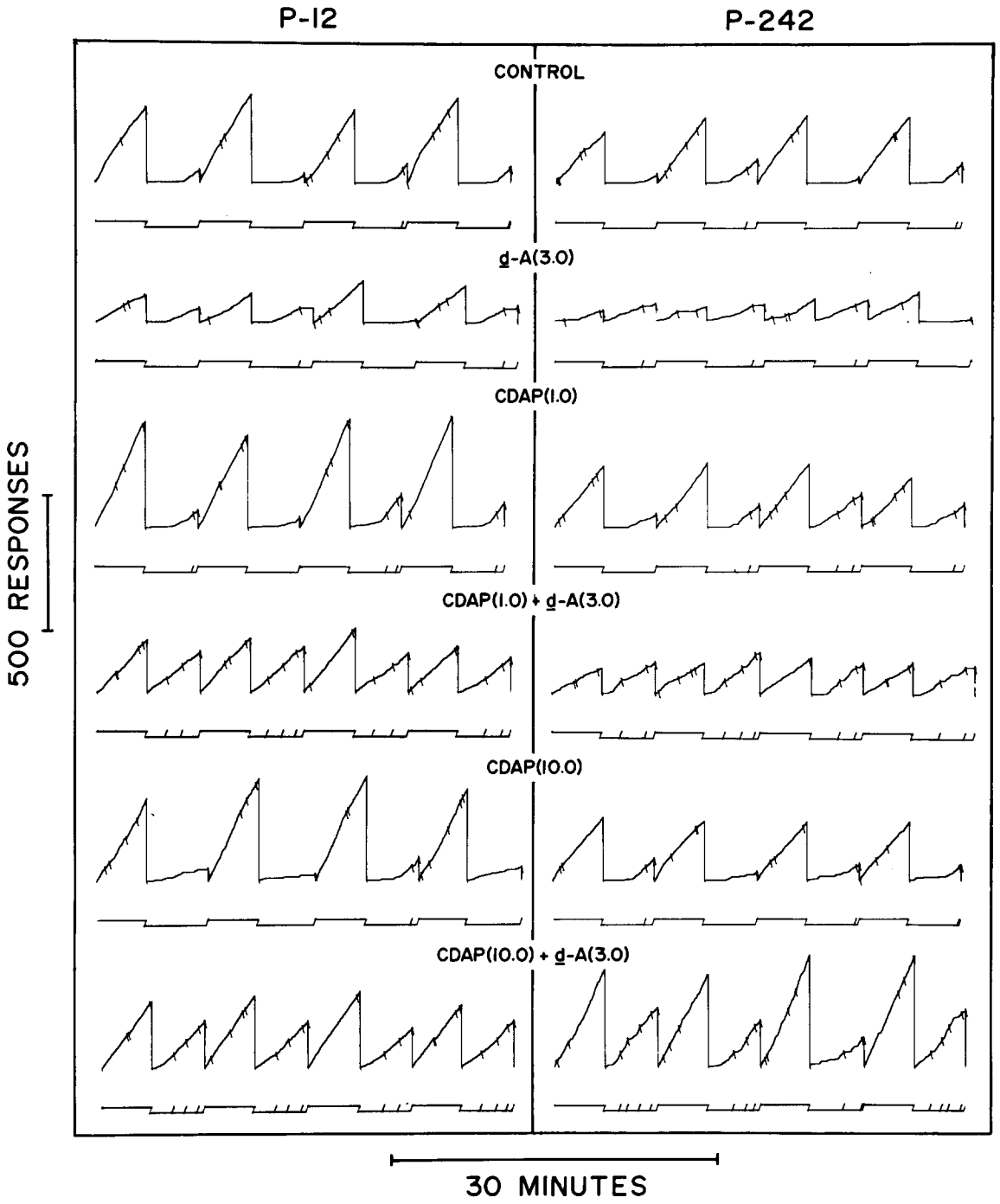

FIG. 4. Cumulative response records for both pigeons under the multiple schedule showing control rates and patterns of responding and the effects of d-amphetamine or chlordiazepoxide alone and in combination. Abscissa: time; ordinate: cumulative responses. Recording as in Fig. 1.

greater increases in punished responding with drug combinations under conditions where, at a given dose level, one of the drugs alone had no effect. In that study Davidson and Cook found that a combination of a non-effective dose of trifluoperazine with an effective dose of amobarbital produced greater increases in punished responding than those of amobarbital alone. At certain dose combinations in the Davidson and Cook experiment, as well as in the present study, the combined drug administration increased punished responding while, at the same time, only decreasing responding that was not punished.

In most studies on drug interactions with amphetamines, increases in behavior greater than those obtained with the individual drugs have been reported. In these studies,

however, increases in behavior were typically produced with certain doses of each of the individual drugs. In the present study d-amphetamine never produced increases in overall rates of punished behavior. When given in combination with either pentobarbital or chlordiazepoxide, however, increases in punished responding were greater than those produced by these drugs in isolation. Cooper, Joyce and Summerfield [4] reported increases in unpunished responding with amphetamine-amobarbital combinations that were larger than those produced by either drug alone. This was true even though amphetamine increased and amobarbital decreased responding. Thus, under some conditions, the combined effects of amphetamines with other drugs cannot be predicted on the basis of the individual agonistic effects of the drugs as was suggested by Rutledge and Kelleher [18] and Branch [2].

The broad range of effects obtained in the present experiment make it difficult to easily characterize the effects of drug interactions on behavior. Both antagonism and synergism of the effects of d-amphetamine on behavior were observed at the same dose combinations of either pentobarbital or chlordiazepoxide. For example, the rate-decreasing effects of 17.0 mg/kg of pentobarbital on unpunished responding were antagonized by 0.3 mg/kg d-amphetamine which, alone, had little effect. These same dose combinations, however, increased punished responding well above the level obtained with pentobarbital alone even though the 0.3 mg/kg dose of d-amphetamine did not affect the rate of punished responding.

These findings suggest that combinations of d-amphetamine with pentobarbital or chlordiazepoxide are capable of generating behaviors substantially different from those obtained with either drug alone. The manner and extent to which any particular behavior is modified by drug interactions appears to depend on the schedule under which that behavior is maintained rather than upon any specific effects of the drugs.

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