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Joint Effects of *d*-Amphetamine and Ethanol or Pentobarbital in Pigeons

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HEALEY, M. L. AND L. A. DYKSTRA. *Joint effects of d-amphetamine and ethanol or pentobarbital in pigeons.* PHARMAC. BIOCHEM. BEHAV. 13(3) 349–357, 1980.—Drug interactions were examined in pigeons keypecking under a multiple fixed ratio 30-response, fixed interval 5-minute (mult FR 30, FI 5-min) schedule of food presentation. Low to intermediate doses of *d*-amphetamine attenuated the rate-decreasing effects of ethanol under both components of the multiple schedule; however, these same doses of *d*-amphetamine seldom attenuated the rate-decreasing effects of pentobarbital. Increases in rates of responding produced by ethanol or pentobarbital under FI components were often enhanced following low to intermediate doses of *d*-amphetamine. Higher doses of *d*-amphetamine generally enhanced the rate-decreasing effects produced by either ethanol or pentobarbital alone. Results indicate that the joint effects of two drugs cannot be predicted from a knowledge of either their individual or their rate-dependent effects.

d-Amphetamine Ethanol Pentobarbital Schedule-controlled behavior Drug interactions Pigeons

THE behavioral effects of *d*-amphetamine, ethanol and pentobarbital have been investigated extensively under conditions in which these drugs are administered alone. The examination of interactions between these drugs, however, has received less attention. Both sedative/hypnotic drugs (such as ethanol and pentobarbital) and psychomotor stimulants (such as *d*-amphetamine) are widely used in this country for non-medical purposes [9]. Moreover, these drugs are often used in combination. For example, amphetamines are self-administered frequently in the presence of a barbiturate [2, 8, 9, 10, 21, 26] and there are a number of commercial preparations that combine psychomotor stimulants and barbiturates [4,25]. Psychomotor stimulants are also self-administered in the presence of ethanol [7,23]. Thus, it has become increasingly important to understand the effects of combining a psychomotor stimulant such as *d*-amphetamine with sedative/hypnotic drugs such as ethanol and pentobarbital.

Previous investigations of the behavioral effects of combinations of amphetamine and ethanol or pentobarbital [1, 3, 12, 17, 18, 19, 22, 24] indicate that the behavioral effects observed when these drugs are given in combination are often different from what would be predicted on the basis of the effects of each drug alone. Moreover, the combined effects of two drugs depend on the dose of each drug, as well as the behavior examined (e.g., [1]).

In the present study, the effects of a wide range of doses of *d*-amphetamine were examined alone and in combination with either ethanol (Experiment 1) or pentobarbital (Experiment 2) under a multiple schedule of food presentation in pigeons. Responding in pigeons under similar multiple schedules has been shown to be sensitive to the effects of these drugs when administered alone [13, 14, 15, 16, 19, 20].

In addition, the effects of combinations of *d*-amphetamine and ethanol (Experiment 1) or *d*-amphetamine and pentobarbital (Experiment 2) were examined on local rates of responding under the FI component in order to determine whether the effects of combinations of *d*-amphetamine and ethanol or *d*-amphetamine and pentobarbital could be explained on the basis of the rate-dependent effects of these drugs. *d*-Amphetamine, ethanol and pentobarbital have been shown to produce rate-dependent effects when administered alone to pigeons responding under similar multiple schedules of food presentation [13, 14, 15]. For example, relatively low rates of responding (such as those found in early segments of a fixed interval component) are often increased by doses of these drugs that either increase less, or actually decrease, rates of responding maintained at a higher rate (such as those found in later segments of a fixed interval or throughout a fixed ratio component). It has been suggested that when a drug that alters rate of responding is given in combination with a second drug, the effects of the combination will depend on alterations in rates of responding produced by each drug when administered alone [5]. For example, if the effects observed following combinations of *d*-amphetamine and ethanol or *d*-amphetamine and pentobarbital were rate-dependent, *d*-amphetamine should increase rates of responding decreased by ethanol or pentobarbital proportionately more than it increased the higher control rates of responding. Similarly, if rates of responding were increased by ethanol or pentobarbital, amphetamine should increase these rates proportionately less (or decrease these rates proportionately more) than control rates of responding.

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METHOD

Animals

White male Carneaux pigeons were maintained at 75–80% of their free feeding weights throughout the experiments. Pigeons were housed in a room kept on a 24-hr light cycle with a constant temperature (28°C). Water and oyster grit were freely available in the home cages. Six birds were used, four in each experiment. For the 2 birds that were subjects in both experiments, no drugs were administered for a minimum period of two months between experiments.

Apparatus

The test chambers were Gerbrands no. E3125A-300 sound-attenuating pigeon chambers, similar to those described by Ferster and Skinner [6]. A translucent response key, 2.0 cm in diameter and approximately 21.0 cm above the floor, was mounted on a false wall within each chamber. Closure of the key contacts with a minimal force of approximately 0.15 N defined the keypeck response. Grain was delivered through a 4.5×5.0 cm rectangular opening located approximately 9 cm from the floor. Events within the experimental chamber were programmed and recorded by electromechanical equipment in an adjacent room.

Drugs

Ethanol was diluted with de-ionized water to a 10% weight/volume solution. *d*-Amphetamine sulfate and sodium pentobarbital were dissolved in de-ionized water and doses were calculated as the salt. Drugs were administered no more frequently than twice a week, usually on Tuesdays and Fridays, with Thursdays and Mondays serving as non-injection control days. Doses of ethanol (0.25 (Experiment 1 only), 0.50, 1.0, 2.0 and 3.0 g/kg) were administered by intubation directly into the proventriculus 15 min prior to test sessions. Doses of *d*-amphetamine (0.1, 0.3, 1.0, 3.0 and 5.6 mg/kg) and pentobarbital (3.0, 5.6, 10.0 and 17.5 mg/kg) were injected intramuscularly 10 min prior to test sessions in a volume of 1.0 ml/kg of body weight. Control injections were de-ionized water administered intramuscularly and/or by intubation. Vehicle intubations were the same volume as the largest dose of ethanol administered to a pigeon. Drugs were administered in ascending order for half of the pigeons and in descending order for the other half.

Procedure

Pigeons were trained to respond under a multiple fixed ratio 30-response, fixed interval 5-min (mult FR 30, FI 5-min) schedule of food presentation. When a blue light illuminated the key, every 30th keypeck produced 4-sec access to grain (FR component). When a red light illuminated the key, the first response after a 5-min interval produced 4-sec access to grain (FI component). The FR and FI components alternated after each presentation of grain. A limited hold was employed, such that if a bird did not make 30 responses in the FR component within 45 sec, the schedule changed to the FI component. If a bird did not respond within 45 sec after the 5-min interval had elapsed in the FI component, the schedule changed to the FR component. Sessions were terminated after the completion of the 24th component; sessions were approximately one-hour long. After stable performance was obtained under the multiple schedule, drug administration began. Dose-effect curves were first determined individually for *d*-amphetamine and ethanol (Experiment 1) or *d*-amphetamine and pentobarbital (Experiment 2) and then for ethanol or pentobarbital in combination with various doses of *d*-amphetamine. After all drug interaction data were collected, individual dose-effect curves were again determined for each drug. Average rates of responding under the FR and FI components were measured for the entire session. In order to be able to analyze the possible rate-dependent effects produced by these drugs, local rates of responding within FI components were also measured. FI components were divided into 10 successive 30-sec bins and average rates of responding within each bin were measured for the entire session. Quarter-life was measured for the FI components in which rates of responding were greater than 0.1 response per second. Quarter-life is the proportion of the FI component during which the first 25% of all FI responses occur. The quarter-life provides a numerical description of the pattern of responding under the FI component.

Control rates of responding gradually shifted in some pigeons over the course of these experiments; however, rates of responding were stable on successive non-drug days. Therefore, all data are expressed as percent of control performance with the day previous to each drug (or vehicle) injection serving as a control.

TABLE 1

MEAN VALUES (± ONE STANDARD DEVIATION) OF CONTROL RATES OF RESPONDING UNDER THE FR AND FI COMPONENTS OF A MULTIPLE FR 30, FI 5-MIN SCHEDULE OF FOOD PRESENTATION AND MEAN QUARTER-LIFE VALUES (± ONE STANDARD DEVIATION) DURING THE FI 5-MIN COMPONENT FOR THE FOUR BIRDS IN EXPERIMENT 1

Bird	89	876	626	711
Fixed ratio (responses per second)	1.72 ± 0.26	2.17 ± 0.22	3.46 ± 0.31	4.29 ± 0.45
Fixed interval (responses per second)	0.59 ± 0.14	0.64 ± 0.08	0.37 ± 0.15	0.79 ± 0.19
Quarter-life (proportion of the FI)	0.63 ± 0.07	0.53 ± 0.05	0.59 ± 0.06	0.59 ± 0.06

EXPERIMENT 1: *d*-AMPHETAMINE AND ETHANOL

RESULTS

Table 1 presents mean control rates of responding (±one standard deviation) under the FR and FI components, as well as mean quarter-life values (±one standard deviation) under the FI component, of the multiple FR 30, FI 5-min schedule of food presentation in individual birds over the course of Experiment 1. In general, rates of responding under the FR component were relatively high with minimal pausing after reinforcement whereas rates of responding under the FI component were lower; the quater-life values indicate that rates of responding under the FI component were positively accelerated.

Figure 1 presents the effects of low to intermediate doses of *d*-amphetamine (0.1, 0.3, and 1.0 mg/kg) alone and in combination with various doses of ethanol in individual

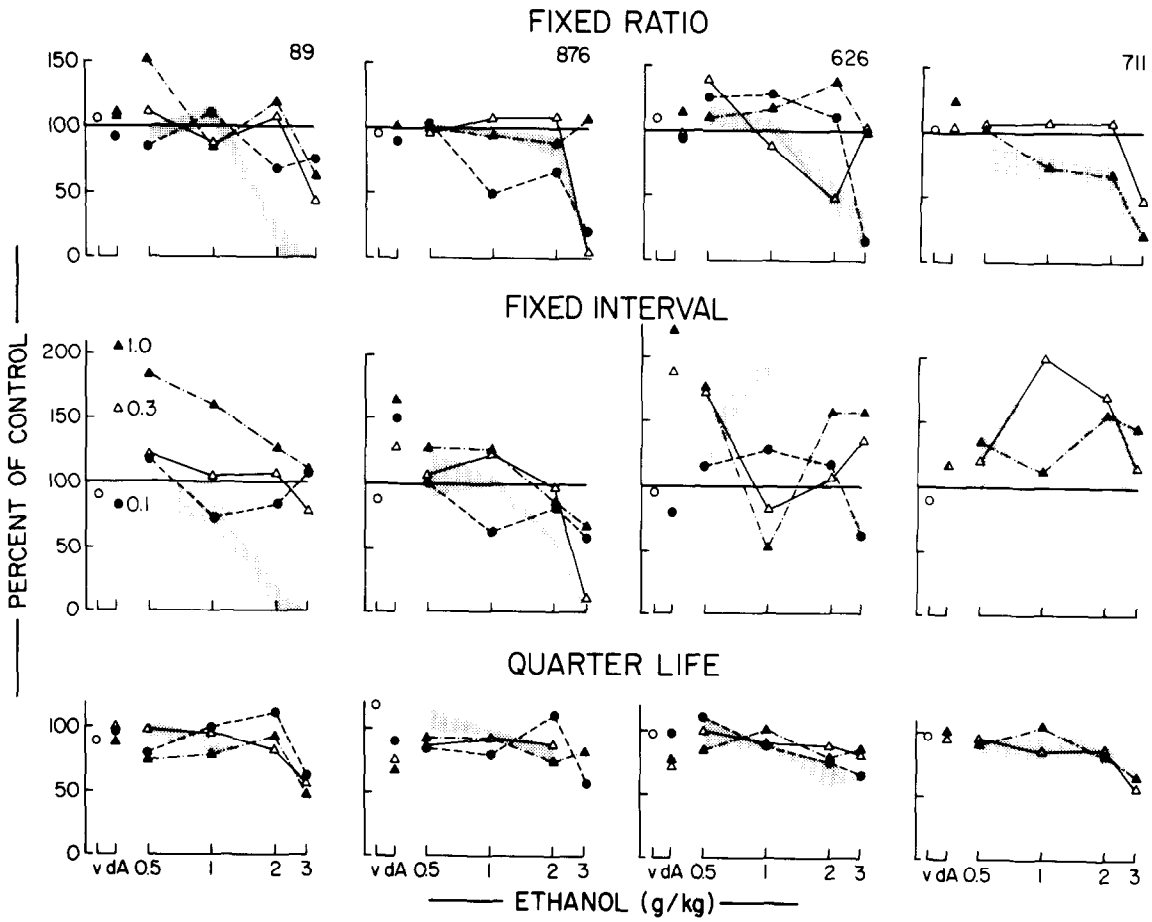

FIG. 1. Effects of *d*-amphetamine and ethanol, alone and in combination, on rates of responding under the FR and FI components of a multiple FR 30, FI 5-min schedule of food presentation and on quarter-life values during the FI 5-min component in four birds. Abscissa: Dose of ethanol, log scale. Ordinate: Mean rates of responding during the entire session (top and middle panels) and mean quarter-life as a proportion of the FI component (bottom panels) presented as percent of control performance. Quarter-life values were not calculated when mean rates of responding were less than 0.1 response per second. The point (○) above V in each panel represents the mean of two double vehicle (oral and intramuscular) injections. Points (●, △ and ▲) above dA represent the mean of two administrations of 0.1, 0.3 and 1.0 mg/kg *d*-amphetamine, respectively, administered alone. The shaded area is the range of values of two administrations of each dose of ethanol administered alone, with one administration prior to and one administration following the collection of all interaction data. ●— —●, △——△ and ▲— — —▲ are dose-effect curves for ethanol in the presence of 0.1, 0.3 and 1.0 mg/kg *d*-amphetamine, respectively. Each combination was administered once. (Note: no dose-effect curve is presented for the ethanol in the presence of 0.1 mg/kg *d*-amphetamine for bird 711 as this bird died before this interaction was examined).

birds. The effects of *d*-amphetamine alone (mean of two determinations) are shown as individual points to the far left of each panel (above dA). These low to intermediate doses of *d*-amphetamine generally increased rates of responding under the FI component of the multiple schedule whereas rates of responding under the FR component were unaffected. Higher doses of *d*-amphetamine (3.0 and 5.6 mg/kg) which generally decreased rates of responding under both components of the multiple schedule when administered alone are not shown as these doses in combination with ethanol either did not affect the ethanol dose-effect curve or increased the rate-decreasing effects of ethanol. Doses of *d*-amphetamine which increased rates or responding under the FI component generally decreased quarter-life values, i.e., a greater proportion of total responding under the FI component occurred in earlier segments of individual components.

The effects of ethanol alone (0.5, 1.0, 2.0 and 3.0 g/kg) are shown in Fig. 1 as the shaded area: this area indicates the range of two administrations of ethanol alone, one administration prior to and one administration following the collection of all interaction data. The dose of 0.25 g/kg of ethanol is not shown as this dose did not alter behavior either when administered alone or when given in combination with *d*-amphetamine in any of the four birds. Ethanol produced a dose-related decrease in rates of responding under the FR component in all birds. Rates of responding under the FI component were decreased in a dose-realted manner in two birds (89 and 876); increased and then decreased in a dose-related manner in one bird (626) and increased inconsistently following all doses in one bird (711). (Note: bird 711 died before a rate-decreasing dose of ethanol could be determined). Doses of ethanol that decreased rates of responding under the FI component also decreased quarter-life values slightly.

The effects of *d*-amphetamine in combination with

ethanol are also shown in Fig. 1. *d*-Amphetamine attenuated ethanol-induced decreases in rates of responding, but the degree to which *d*-amphetamine attenuated these effects differed across birds and between components of the multiple schedule. Selective doses of *d*-amphetamine attenuated ethanol-induced decreases in rates of responding under the FR component in all birds. *d*-Amphetamine also attenuated decreases in rates of responding produced by ethanol under the FI component in all birds in which ethanol alone decreased rates of responding (i.e., all except bird 711). When *d*-amphetamine attenuated ethanol-induced decreases in rates of responding under the FI component, decreases in quarter-life values were generally attenuated, but seldom returned to control values. In those cases in which ethanol alone increased rates of responding under the FI component, the effects of combinations of low to intermediate doses of *d*-amphetamine and ethanol were inconsistent.

The effects of combinations of *d*-amphetamine and ethanol were also examined on local rates of responding under the FI component in order to determine whether the effects of combinations of *d*-amphetamine and ethanol could be predicted on the basis of their individual rate-dependent effects. Doses of *d*-amphetamine and ethanol which produced rate-dependent effects when administered alone were selected for analysis. For example, 1.0 mg/kg *d*-amphetamine produced rate-dependent effects in bird 876, e.g., it increased low rates of responding maintained during early segments of the FI component whereas higher rates of responding maintained in latter segments of the FI component were increased less or not altered. Similarly, 2.0 g/kg of ethanol produced rate-dependent effects in bird 876, i.e., it did not affect low rates of responding maintained during early segments of the FI component whereas it decreased higher rates of responding maintained in latter segments of the FI component. When these doses of *d*-amphetamine and ethanol were given in combination, rates of responding were not changed in a way which could be predicted from the rate-dependent effects of each drug alone.

Figure 2 presents the effects in bird 876 of 1.0 mg/kg of *d*-amphetamine and 2.0 g/kg ethanol alone and in combination on rates of responding in the 10 successive 30-sec bins of the FI 5-min component. In bird 876, vehicle (or control) rates of responding in the 5th, 30-sec bin of the FI were approximately 0.45 response per second. Following 1.0 mg/kg of *d*-amphetamine alone rates of responding in the 5th bin were 0.83 response per second, i.e., *d*-amphetamine alone increased rates of responding by 84%. Comparable rates of responding following 2.0 g/kg ethanol alone were observed during the 8th, 30-sec bin of the FI. When *d*-amphetamine and ethanol were given in combination, rates of responding during the 8th bin were 0.61 response per second, i.e., rates of responding were only increased by 36%. Similarly, control rates of responding in the 4th, 30-sec bin of the FI which were approximately 0.34 response per sec were increased to 0.73 response per sec (or by 115%) following 1.0 mg/kg *d*-amphetamine alone. A similar rate of responding was observed in the 6th, 30-sec bin of the FI following 2.0 g/kg ethanol alone. When ethanol and *d*-amphetamine were given in combination, rates of responding were only 0.48 response per second (a 41% increase) in the 6th bin. Similar rate-dependent analysis of the joint effects of various doses of *d*-amphetamine and ethanol in all four birds also indicated that rates of responding were not changed in a way which could be predicted from the rate-dependent effects of each drug alone.

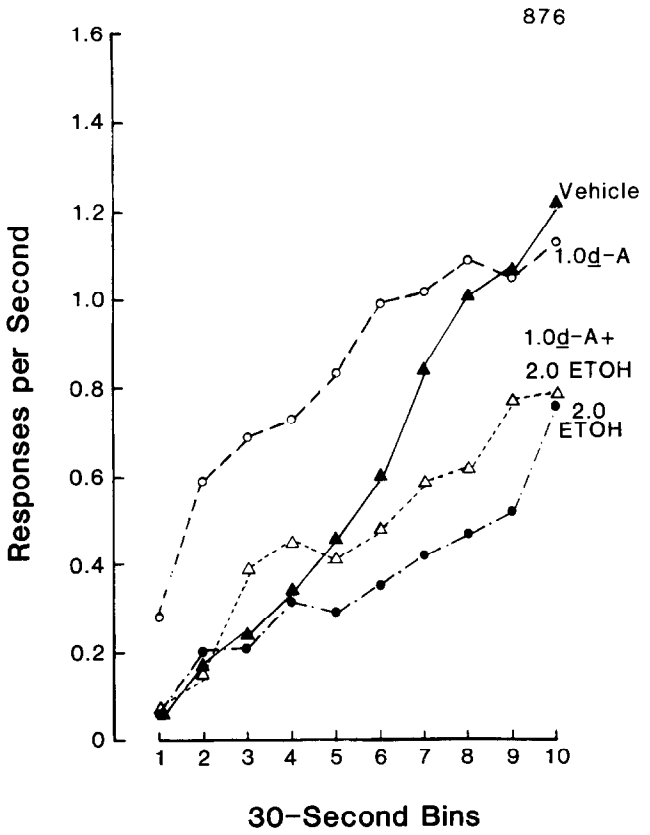

FIG. 2. Effects of *d*-amphetamine and ethanol, alone and in combination, on local rates of responding under the FI component of a multiple FR 30, FI 5-min schedule of food presentation in bird 876. Abscissa: Successive 30-second bins of the FI 5-min component. Ordinate: Mean local rates of responding. ▲——▲, ○— —○, ●—·—● and △— — —△ represent data following the administration of vehicle, 1.0 mg/kg *d*-amphetamine alone, 2.0 g/kg ethanol alone and a combination of 1.0 mg/kg *d*-amphetamine and 2.0 g/kg ethanol, respectively. Each point represents the mean of two drug or vehicle administrations, except those representing the combination of *d*-amphetamine and ethanol, which was administered once.

DISCUSSION

Low to intermediate doses of *d*-amphetamine (0.1, 0.3 and 1.0 mg/kg) attenuated decreases in rates of responding produced by ethanol in pigeons responding under a multiple FR 30, FI 5-min schedule of food presentation, but the degree to which *d*-amphetamine attenuated these effects differed across birds and between components of the multiple schedule. Under the FR component, low to intermediate doses of *d*-amphetamine generally attenuated the rate-decreasing effects of ethanol in all birds. Under the FI component, these same doses of *d*-amphetamine, when given in combination with ethanol often increased rates of responding over those observed following ethanol alone. In those birds in which ethanol consistently decreased rates of responding under the FI component, low to intermediate doses of *d*-amphetamine attenuated these decreases. Doses of *d*-amphetamine which best attenuated the rate-decreasing effects of ethanol under both components of the multiple schedule were doses which generally increased rates of responding under the FI component when administered alone but which did not alter rates of responding under the FR component. Nevertheless, the dose of *d*-amphetamine which

TABLE 2

MEAN VALUES (± ONE STANDARD DEVIATION) OF CONTROL RATES OF RESPONDING UNDER THE FR AND FI COMPONENTS OF A MULTIPLE FR 30, FI 5-MIN SCHEDULE OF FOOD PRESENTATION AND MEAN QUARTER-LIFE VALUES (± ONE STANDARD DEVIATION) DURING THE FI 5-MIN COMPONENT FOR THE FOUR BIRDS IN EXPERIMENT 2

Bird	89	6801	712	876
Fixed ratio (responses per second)	1.56 ± 0.22	2.85 ± 0.62	2.61 ± 0.24	2.26 ± 0.23
Fixed interval (responses per second)	0.56 ± 0.11	0.41 ± 0.09	0.69 ± 0.13	0.69 ± 0.15
Quarter-life (proportion of FI)	0.68 ± 0.04	0.60 ± 0.08	0.60 ± 0.04	0.54 ± 0.05

would be most effective in attenuating the rate-decreasing effects of ethanol could not be predicted by the extent to which rates of responding under the FI component were increased by d-amphetamine. Similarly, those doses of d-amphetamine most likely to enhance the rate-increasing effects of ethanol could not be predicted on the basis of the effects observed when d-amphetamine was administered alone. Higher doses of d-amphetamine (3.0 and 5.6 mg/kg) which decreased rates of responding under both components of the multiple schedule when administered alone either did not affect the ethanol dose-effect curve or enhanced the rate-decreasing effects of ethanol under both components. Moreover, the joint effects of d-amphetamine and ethanol could not be predicted on the basis of the rate-dependent effects of these drugs when administered alone.

The effects observed when ethanol and d-amphetamine were administered, alone and in combination, to pigeons responding under a multiple FR 30, FI-5 min schedule of food presentation are similar to those reported by Katz and Barrett [12] in pigeons responding under single FR 30 or FI 5-min schedules of food presentation. Katz and Barrett also reported that low doses of d-amphetamine, which increased rates of responding under the FI schedule when administered alone, attenuated decreases in rates of responding produced by ethanol under both schedules, and that higher doses of d-amphetamine either did not affect the ethanol dose-effect curve or shifted these curves to the left in most birds under both schedules. In their study, combinations of ethanol and d-amphetamine often produced increases in rates of responding under the FI schedule that were greater than those produced by either drug alone. Only in one bird in this study (711) were rates of responding under the FI component greater following the joint administration of ethanol and d-amphetamine than following d-amphetamine alone. It should be noted, however, that the rate-increasing effects of d-amphetamine on rates of responding under the FI component were more pronounced in this study than under the FI schedule in the Katz and Barrett Study.

In other studies examining the joint effects of ethanol and amphetamine, amphetamine has been shown to enhance the ethanol-induced decrement on rotorod performance in rodents [17,18] and on a cumulative response duration task in dogs [24]. None of these studies reported any attenuation of ethanol-induced disruption by amphetamine; however, these investigators generally did not examine doses of amphetamine as low as those which were effective in attenuating the rate-decreasing effects observed in pigeons responding under either a multiple FR 30, FI 5-min schedule of food presentation (in present study) or single FR 30 or FI 5-min schedules of food presentation [12]. It should be noted that ethanol-induced disruption of the pattern of responding under the FI component of a multiple FR 30, FI 5-min schedule of food presentation as reflected by decreases in quarter-life value was not always attenuated by doses of d-amphetamine which attenuated ethanol-induced decreases in rates of responding. It is possible, therefore, that while low doses of amphetamine can counteract ethanol-induced decreases in rates of responding, behavior following the administration of ethanol alone or in combination with amphetamine is different from behavior maintained under control conditions.

EXPERIMENT 2: d-AMPHETAMINE AND PENTOBARBITAL

RESULTS

Table 2 presents mean control rates of responding (± one standard deviation) under the FR and FI components, as well as mean quarter life values (± one standard deviation) under the FI component, of the multiple FR 30, FI 5-min schedule of food presentation in individual birds over the course of Experiment 2. Rates and patterns of responding under control conditions were similar to those reported in Experiment 1.

Figure 3 presents the effects of d-amphetamine (0.3, 1.0 and 3.0 mg/kg) alone and in combination with various doses of pentobarbital in individual birds. The effects of d-amphetamine alone (mean of two determinations) are shown as individual points to the far left of each panel (above dA). Low to intermediate doses of d-amphetamine (0.3 and 1.0 mg/kg) generally increased rates of responding slightly under the FI component while not altering rates of responding under the FR component. Doses of d-amphetamine which increased rates of responding under the FI component when administered alone generally decreased quarter-life values. In bird 712 only, low to intermediate doses of d-amphetamine decreased rates of responding under the FR component. A higher dose of d-amphetamine (3.0 mg/kg) decreased rates of responding under both components of the multiple schedule. In addition, a dose of 5.6 mg/kg of d-amphetamine (not shown) was administered to two birds; this dose decreased rates of responding under both schedule components.

The effects of pentobarbital alone (3.0, 5.6, 10.0 and 17.5 mg/kg) are shown in Fig. 3 as the shaded area: this area indicates the range of two administrations of pentobarbital alone, one administration prior to and one administration following the collection of all interaction data. Most doses of pentobarbital examined (3.0, 5.6 and 10.0 mg/kg) increased rates of responding under the FI component. Only in bird 876 did 10.0 mg/kg pentobarbital decrease rates of responding under the FI component; no dose of pentobarbital consistently increased rates of responding under either component for bird 876. The highest dose of pentobarbital administered (17.5 mg/kg) decreased or eliminated responding in all birds under both components of the multiple schedule. Lower doses of pentobarbital either did not affect or slightly increased rates of responding under the FR component.

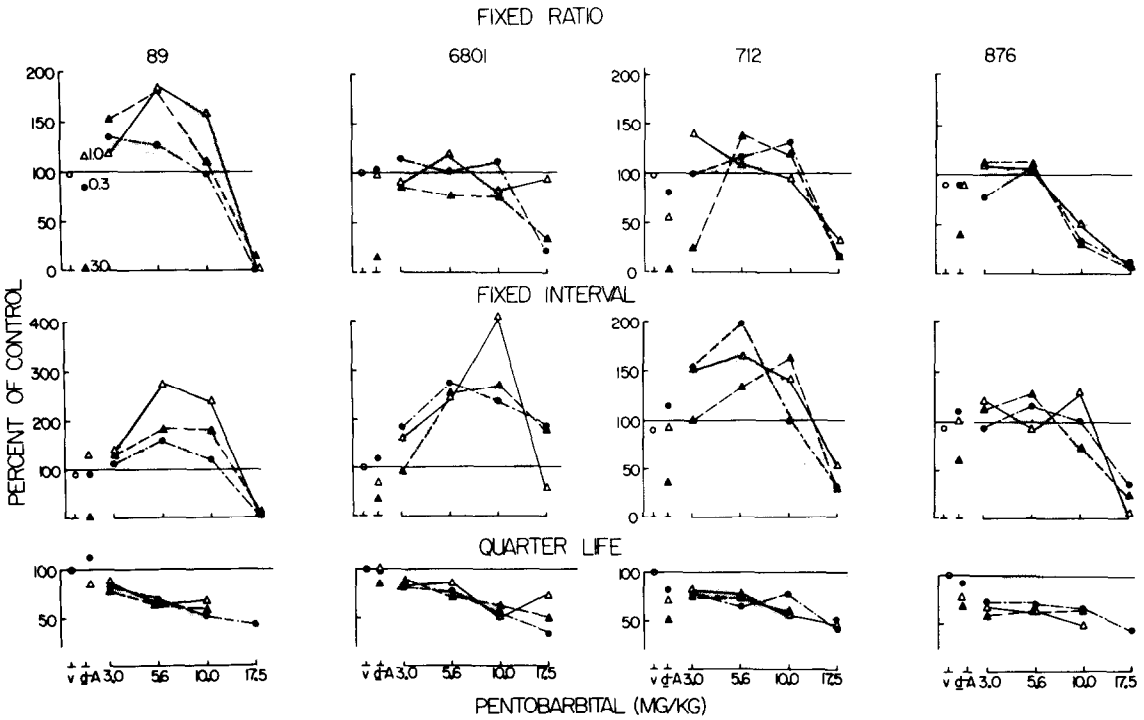

FIG. 3. Effects of *d*-amphetamine and pentobarbital, alone and in combination, on rates of responding under the FR and FI components of a multiple FR 30, FI 5-min schedule of food presentation and on quarter-life values during the FI 5-min component in four birds. Abscissa: Dose of pentobarbital, log scale. Ordinate: Mean rates of responding during the entire session (top and middle panels) and mean quarter-life as a proportion of the FI component (bottom panels) presented as percent of control performance. Quarter-life values were not calculated when mean rates of responding were less than 0.1 response per second. The point (○) above V in each panel represents the mean of two double vehicle (intramuscular in each breast muscle) injections. Points (●, △ and ▲) above dA represent the mean of two administrations of 0.3, 1.0 and 3.0 mg/kg *d*-amphetamine, respectively, administered alone. The shaded area is the range of values of two administrations of each dose of pentobarbital administered alone, with one administration prior to and one administration following the collection of all interaction data. ●— —●, △—— —△ and ▲— —▲ are dose-effect curves for pentobarbital in the presence of 0.3, 1.0 and 3.0 mg/kg *d*-amphetamine, respectively. Each combination was administered once.

The effects of *d*-amphetamine in combination with pentobarbital are also shown in Fig. 3. The effects of *d*-amphetamine/pentobarbital combinations differed under the two components of the multiple schedule. Under the FR component, the rate-increasing effects of low doses of pentobarbital (3.0 and 5.6 mg/kg) were enhanced in bird 89 by doses of *d*-amphetamine that did not increase rates of responding when administered alone; in bird 712, doses of *d*-amphetamine which actually decreased rates of responding when administered alone sometimes increased rates of responding above those produced by pentobarbital alone when administered in combination with pentobarbital. Decreases in rates of responding produced by pentobarbital were only attenuated by one dose of *d*-amphetamine in one bird (6801). On the other hand, when 3.0 mg/kg *d*-amphetamine was given in combination with doses of pentobarbital which either did not affect or slightly increased rates of responding when administered alone, the rate-decreasing effects of 3.0 mg/kg *d*-amphetamine were attenuated. Decreases in rates of responding produced by a higher dose of *d*-amphetamine (5.6 mg/kg) in one of two birds tested were also attenuated when 5.6 mg/kg *d*-amphetamine was given in combination with 3.0, 5.6 or 10.0 mg/kg pentobarbital (not shown).

Under the FI component, doses of *d*-amphetamine which either did not increase or increased slightly the rates of responding when administered alone, enhanced the rate-increasing effects of pentobarbital in all birds except 712. As under the FR component, decreases in rates of responding following 3.0 mg/kg *d*-amphetamine (or 5.6 mg/kg *d*-amphetamine in one of two birds tested) alone were attenuated when given in combination with doses of pentobarbital which either did not affect or increased rates of responding when administered alone. Decreases in rates of responding produced by 17.5 mg/kg pentobarbital were attenuated in two birds (6801 and 876) by doses of *d*-amphetamine which either did not affect, or actually decreased, rates of responding when administered alone.

As in Experiment 1, the effects of combinations of *d*-amphetamine and pentobarbital on local rates of responding in the FI component were examined to determine whether the effects of combinations of *d*-amphetamine and pentobarbital could be predicted on the basis of their individual rate-dependent effects. Figure 4 is representative of the effects in bird 89 of a dose of *d*-amphetamine which produced rate-dependent effects when administered alone in combination with a dose of pentobarbital which produced rate-dependent effects when administered alone. Analysis of rates of responding in the 10 successive 30-sec bins of the FI 5-min component following combinations of *d*-amphetamine and pentobarbital indicated that rates of responding were not changed in an way which could be predicted from the rate-dependent effects of each drug alone. For example, in bird

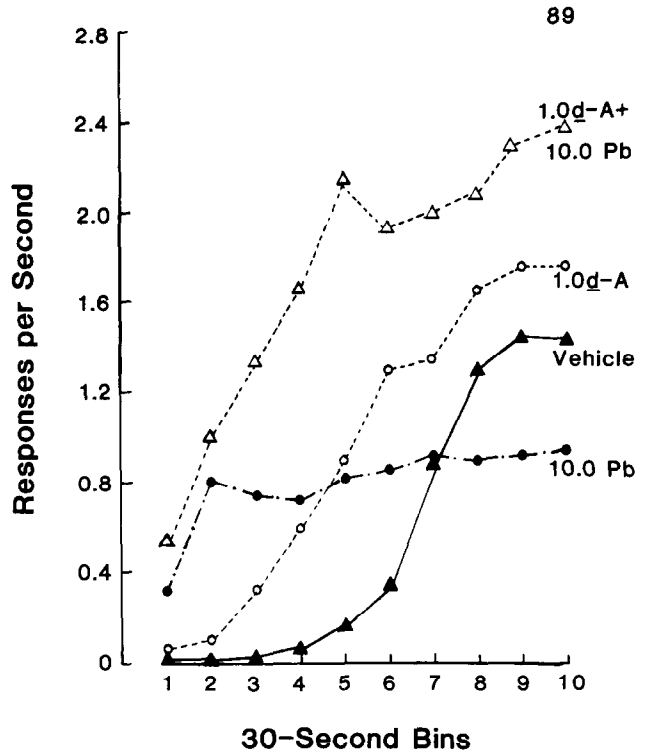

FIG. 4. Effects of *d*-amphetamine and pentobarbital, alone and in combination, on local rates of responding under the FI component of a multiple FR 30, FI 5-min schedule of food presentation in bird 89. Abscissa: Successive 30-sec bins of the FI 5-min component. Ordinate: Mean local rates of responding. ▲——▲, ○— —○, ●— · —● and ^— —^ represent data following the administration of vehicle, 1.0 mg/kg *d*-amphetamine, 10.0 mg/kg pentobarbital and a combination of 1.0 mg/kg *d*-amphetamine and 10.0 mg/kg pentobarbital, respectively. Each point represents the mean of two drug or vehicle administrations, except those representing the combination of *d*-amphetamine and pentobarbital, which was administered once.

89, vehicle (or control) rates of responding in the 7th, 30-sec bin of the FI were approximately 0.89 responses per second. Following 1.0 mg/kg *d*-amphetamine alone, rates of responding in the 7th bin were 1.36 responses per sec, i.e., *d*-amphetamine alone increased rates of responding by 53%. Comparable rates of responding (0.93 responses per second) following 10.0 mg/kg pentobarbital alone were observed in the 7th, 30-sec bin of the FI. When *d*-amphetamine and pentobarbital were given in combination, rates of responding during the 7th bin were approximately 2.01 responses per sec, i.e., rates of responding were increased 116% over pentobarbital alone. Whereas it was often the case when *d*-amphetamine and pentobarbital were given in combination that *d*-amphetamine increased rates of responding following vehicle administration less than similar rates of responding following pentobarbital administration, this was not a consistent finding. For example, control rates of responding in the 6th, 30-sec bin were approximately 0.37 response per sec. Following 1.0 mg/kg *d*-amphetamine alone, rates of responding in the 6th bin were 1.30 response per sec, i.e., *d*-amphetamine alone increased rates of responding by 251%. Comparable rates of responding (0.33 response per sec) following 10.0 mg/kg pentobarbital alone were observed during the 1st, 30-sec bin of the FI. When *d*-amphetamine and pentobarbital were given in combination rates of responding in the 1st bin were approximately 0.55 response per sec, i.e., rates of responding were increased by only 67%. Whereas the effects observed when *d*-amphetamine or pentobarbital were administered were rate-dependent in all birds, the effects observed following *d*-amphetamine/pentobarbital combinations could not be adequately explained on the basis of these rate-dependent effects.

DISCUSSION

When *d*-amphetamine and pentobarbital are administered in combination to pigeons responding under a multiple FR 30, FI 5-min schedule of food presentation, the effects observed depended on the component of the multiple schedule. In general, under the FR component, the pentobarbital dose-effect curve was not substantially altered by the addition of *d*-amphetamine. Under the FI component, however, increases in rates of responding following *d*-amphetamine/pentobarbital combinations were greater in all pigeons than those observed following either drug alone. Moreover, these increases were greater than would be expected if the effects of *d*-amphetamine and pentobarbital were additive.

Rutledge and Kelleher [19] examined combinations of amphetamine and pentobarbital in pigeons responding under a multiple FR 31, FI 5-min schedule of food presentation and reported that these drugs produced additive effects under the FR component and produced greater than additive, or synergistic, effects under the FI component. Synergistic increases in rates of responding following *d*-amphetamine/pentobarbital combinations were also observed in pigeons responding under a FI 5-min component of a multiple VI 3-min, FI 5-min schedule of food presentation in which every 50th keypeck during the FI 5-min component was punished by a brief electric shock [1]. While additive effects were not observed under the FR 30 component in this study, synergistic increases in rates of responding were observed under the FI component. Since rates of responding under control conditions were similar under the FR components across the two studies and the effects of amphetamine and pentobarbital, when administered alone, were similar, it is not clear why the joint effects of amphetamine and pentobarbital differ. On the other hand, synergistic effects between pentobarbital and amphetamine have also been reported in dogs responding under a cumulative response duration task [24]. Responding under FI 5-min schedules of food presentation, punished and unpunished, and responding under a cumulative response duration task are all behaviors that are maintained at a relatively low rate. Therefore, synergistic increases in rates of responding are probably more likely to be observed following the joint administration of amphetamine and pentobarbital when the behavior being examined occurs at a relatively low rate. For example, higher local rates of responding at the end of FI components were not increased in a synergistic manner following combinations of pentobarbital and *d*-amphetamine. In general it would appear that amphetamine generally increases the behavioral disruption produced by pentobarbital and does not attenuate it.

GENERAL DISCUSSION

When *d*-amphetamine is administered in combination with ethanol or pentobarbital to pigeons responding under a multiple FR 30, FI 5-min schedule of food presentation, the effects cannot be predicted on the basis of existing theories. Two suggestions have been offered to account for the effects observed following the joint administration of behaviorally active drugs:

(1) The joint effects of two drugs can be predicted on the basis of the effects of the drugs when administered individually [3].

(2) The joint effects of two drugs can be predicted on the basis of rate-dependency, i.e., the effects of combining two drugs will depend on rates of responding produced by one of the drugs and not on rates of responding in the absence of a drug [5].

The experiments reported here do not support either of these suggestions. The effects observed following combinations of *d*-amphetamine and ethanol or pentobarbital could not be predicted by simply adding together the effects of each drug when administered individually. Moreover, analysis of the effects of *d*-amphetamine with ethanol or pentobarbital indicated that the effects of combinations of these drugs could not be attributed to rate-dependent interactions.

The results reported here following the administration of ethanol or pentobarbital alone to pigeons responding under a multiple FR 30, FI 5-min schedule of food presentation are not in complete agreement with other findings. Katz and Barrett [12] reported that the effects of ethanol and pentobarbital on behavior were similar under a wide range of conditions and, furthermore, that the effects of *d*-amphetamine were similar when combined with either of these drugs. In the experiments reported here, the effects of ethanol and of pentobarbital alone were different in a number of ways. In pigeons responding under a multiple FR 30, FI 5-min schedule of food presentation, a high dose of pentobarbital (17.5 mg/kg) produced decreases in rates of responding that were more consistent across animals and components of the multiple schedule than were decreases in rates of responding produced by the highest dose of ethanol examined (3.0 g/kg). Furthermore, low doses of pentobarbital consistently increased rates of responding under both components of the multiple schedule whereas ethanol produced inconsistent increases in rates of responding under FI components. In addition, the effects of combinations of ethanol and *d*-amphetamine were different from those of pentobarbital and *d*-amphetamine. For example, *d*-amphetamine attenuated ethanol-induced decreases in rates of responding under FR components more effectively than it attenuated pentobarbital-induced decreases in rates of responding under FR components. On the other hand, the effects of combinations of *d*-amphetamine and ethanol or pentobarbital were more similar under FI components.

In general, doses of *d*-amphetamine were more likely to alter the shape of the ethanol dose-effect curve than the pentobarbital dose-effect curve. This difference may be due to the fact that pentobarbital alone produced more consistent effects across birds and schedule components than did ethanol alone. This relative resistance of the pentobarbital dose-effect curve has also been observed when pentobarbital and ethanol dose-effect curves, alone and in combination with various doses of caffeine, nicotine, or a mixed local anesthetic, were compared in birds responding under a similar multiple schedule of food presentation (Healey, unpublished Dissertation).

In summary, whereas the joint effects observed following the administration of ethanol or pentobarbital in combination with *d*-amphetamine could not be accounted for on the basis of individual drug effects or on the basis of rate-dependent effects of these drugs, these two variables were still important factors in determining joint drug effects. For example, lower rates of responding maintained under FI components of the multiple schedule were not only more likely to be increased by the administration of individual drugs, but enhancement of rate-increasing effects were more often observed under FI components than under FR components, where rates of responding were generally maintained at a higher rate. Doses of *d*-amphetamine that increased rates of responding under FI components when administered alone were more likely to enhance both ethanol- and pentobarbital-induced increases in rates of responding under either component of the multiple schedule than were doses of *d*-amphetamine which either did not alter or decreased rates of responding under the FI component. In addition, the effects of a dose of pentobarbital which eliminated responding were less likely to be attenuated than the effects of doses of pentobarbital or ethanol which markedly decreased, but did not eliminate responding.

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