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Differential Modification of Pentobarbital Stimulus Control by *d*-Amphetamine and Ethanol[1]

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KLINE, F. S. AND A. M. YOUNG. *Differential modification of pentobarbital stimulus control by* d-*amphetamine and ethanol*. PHARMACOL BIOCHEM BEHAV **24**(5) 1305–1313, 1986.—The ability of *d*-amphetamine and ethanol to alter discriminative stimulus control by pentobarbital was examined in pigeons. Saline and pentobarbital (5.6 mg/kg) were established as discriminative stimuli for food-maintained responding in six birds. Dose-response functions for stimulus control and response rate were determined for pentobarbital alone and in combination with selected doses of *d*-amphetamine or ethanol. In tests of stimulus generalization, *d*-amphetamine alone did not exert pentobarbital-like stimulus control, while ethanol alone evoked variable degrees of pentobarbital-like stimulus control. *d*-Amphetamine attenuated pentobarbital stimulus control. Doses of 1.0 or 3.2 mg/kg *d*-amphetamine increased the dose of pentobarbital required for stimulus control in five of six birds. Combinations of high *d*-amphetamine and pentobarbital doses yielded less than additive rate suppression. Ethanol produced variable effects on pentobarbital stimulus control, with moderate doses generally decreasing, and high doses increasing, the dose of pentobarbital required for stimulus control. A high ethanol dose decreased the pentobarbital dose required for rate suppression. Taken together, these data demonstrate that pentobarbital stimulus control can be altered by drugs within or without the sedative hypnotic class.

Drug discrimination Pigeons Pentobarbital *d*-Amphetamine Ethanol Drug interactions

CURRENT trends of substance abuse suggest an increased frequency of combined use of stimulant and sedative drugs (e.g., [14, 16, 17, 40]). However, although the individual effects of the prototypic stimulant *d*-amphetamine and of the sedatives pentobarbital and ethanol have been investigated extensively, the effects of combinations of these drugs have received scant attention. Joint effects of drugs are not always predictable from their individual effects, with the result that combinations may display unique behavioral profiles (e.g., [18, 21, 26]). For example, studies of the joint effects of pentobarbital and *d*-amphetamine suggest that the effects of such combinations are dependent on both the doses employed and the dependent measures assessed (e.g., [6, 21, 32]). One specific question of such drug combinations is whether the stimulus effects of a sedative such as pentobarbital are altered by the addition of a stimulant or a second sedative. The present experiment employed a drug discrimination procedure to examine the ability of *d*-amphetamine and ethanol to alter an established pentobarbital discriminative stimulus in pigeons.

Pentobarbital, *d*-amphetamine, and ethanol have been shown to be effective discriminative stimuli in a wide variety of subject populations (for reviews see [3, 10, 35, 38]). Pentobarbital and *d*-amphetamine do not share discriminative effects, each evoking only saline-appropriate responses when administered to subjects trained to discrinate the other (e.g., [29,41]). The exact relationship between pentobarbital and ethanol is not firmly established, but appears to be partly dependent on the training procedures employed [5]. Animals trained to discriminate ethanol from saline display generalization of pentobarbital [7, 27, 28, 30]. However, generalization of ethanol by animals trained to discriminate pentobarbital is more variable (e.g., [4, 19, 27, 30]).

The ability of *d*-amphetamine to alter an established pentobarbital discriminative stimulus is somewhat ambiguous. Amphetamine can enhance, attenuate or leave unaltered the pentobarbital stimulus control evoked by doses of pentobarbital lower than the training dose, that do not in themselves evoke exclusively pentobarbital-appropriate responses [23,41]. For example, Witkin and colleagues [41]

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reported a pattern of interaction dependent on *d*-amphetamine dose, with low doses enhancing stimulus control by low doses of pentobarbital in one of two birds, and a higher *d*-amphetamine dose decreasing such stimulus control in the other bird. No dose of *d*-amphetamine altered stimulus control by doses of pentobarbital higher than the training dose.

The ability of a second sedative-hypnotic to alter stimulus control by pentobarbital has received little attention. The possibility of interesting interactions has been mentioned by Barry [3], who noted that a combination of 5 mg/kg pentobarbital and 500 mg/kg ethanol evoked drug-appropriate responses in rats trained to discriminate either 10 mg/kg pentobarbital and saline, or 1000 mg/kg ethanol and saline, though neither dose alone did so [27]. Further, Jarbe and McMillan [24] have demonstrated that low doses of one sedative-hypnotic may enhance stimulus control by a second sedative-hypnotic. These investigators trained pigeons to discriminate either diazepam and its vehicle, or ethanol and water. In pigeons trained with diazepam, low and moderate doses of ethanol did not engender diazepam-like stimulus control but, when combined with diazepam, progressively decreased the dose of diazepam required for stimulus control. In birds trained with ethanol, diazepam did engender ethanol stimulus control. Sub-threshold doses of ethanol decreased the dose of diazepam required for generalization, such that the investigators concluded that combinations of diazepam and ethanol evoked discriminative control greater than the sum effects of the individual drugs.

The present study examined the combined effects of pentobarbital and *d*-amphetamine, and of pentobarbital and ethanol, on established stimulus control by pentobarbital in pigeons. Pentobarbital (5.6 mg/kg) was established as a discriminative stimulus for food-maintained operant behavior in six pigeons. The ability of selected doses of *d*-amphetamine and ethanol to alter both the discriminative stimulus and the rate-altering effects of pentobarbital was examined.

METHOD

Subjects

Six adult male White Carneaux pigeons were housed individually in a moderately sized colony room maintained at 20–22°C and lit on a 12 hr light/dark cycle. Each bird was maintained at approximately 85–90% of its free-feeding body weight by restricted access to Purina Pigeon Chow. Water and grit were freely available in the home cage. Prior to this experiment, all birds had been trained over approximately three months to peck a lit response key in order to gain 4 second access to Purina Pigeon Chow.

Apparatus

Experimental sessions were conducted in sound-attenuating commercial test chambers (Small Universal Cubicles; BRS/LVE, Beltsville, MD) equipped with a panel containing three response keys (2.5 cm diameter). The two outer keys were mounted 16.5 cm apart horizontally and 25 cm above the chamber floor. The center response key remained dark at all times. During experimental sessions, the two outer keys and a houselight above the keys were dimly lit white. Opening of the key contact with a minimum force of 0.15 N defined the response. Purina Pigeon Chow could be presented from a hopper accessible through a rectangular opening located 10 cm above the floor in the middle of the front panel. During food presentation, a white light above the hopper was lit and the response key lights were extinguished. Each chamber was ventilated by an exhaust fan and supplied with white noise to mask extraneous sounds. Rockwell Aim 65 microcomputers located in an adjacent room were used for programming and data collection.

Procedure

Initial discrimination training. Pentobarbital (5.6 mg/kg) and saline were established as discriminative stimuli for food-maintained key pecks using the method described by Herling *et al.* [19]. Birds were injected intramuscularly with either 5.6 mg/kg pentobarbital or saline 15 minutes prior to the start of daily experimental sessions and placed in the dark experimental chamber. Illumination of the left and right keys and the house lamp signaled the start of the experimental session. At the beginning of training, each bird was required to emit a single peck on one of the lit keys to gain 4 sec access to food. Following administration of pentobarbital, responses on the left key produced food; following administration of saline, responses on the right key produced food. The number of responses required for food delivery was gradually increased to 30 (fixed ratio 30) over successive sessions. Responses had to occur in succession on the injection-appropriate key, with responses on the inappropriate key resetting the ratio requirement on the appropriate key. Sessions ended after 50 food deliveries or 30 minutes, whichever occurred first. Pentobarbital and saline injections were alternated from one session to the next. Training continued for each bird until the criteria of emitting less than 60 pecks before the first reinforcer and distributing at least 90% of the total responses on the correct key were met during 5 consecutive sessions. Then, pentobarbital and saline training sessions were conducted in a double alternation sequence (e.g., pentobarbital, pentobarbital, saline, saline) until performance criteria were met for 4 consecutive sessions.

Stimulus control tests. After performance criteria were met during the double alternation sequence, stimulus control tests were conducted. Test sessions ended after 50 food deliveries or 30 minutes, whichever occurred first. During tests, 30 consecutive responses on either key produced food. The ratio counter reset if the subject changed keys before completing the 30 response requirement. In general, test sessions alternated with training sessions, unless a bird did not meet the criteria for stimulus control during a training session. In such cases, testing was postponed until the criteria were met in at least two consecutive sessions. The stimulus administered during a training session was independent of that given during a preceding test session. Multiple consecutive training sessions were occasionally conducted even in the absence of performance errors. Response distribution data from tests of stimulus control were analyzed only if a bird earned at least two reinforcers or emitted more than 150 responses during a test session.

Initially, two pentobarbital dose-response functions were established for each subject. First, a complete range of doses was tested in an unsystematic order. Then, each dose was re-examined one, two, or three times during a second determination of the pentobarbital function.

After pentobarbital dose-response functions were established, a range of *d*-amphetamine doses was tested once in each subject. *d*-Amphetamine was administered 30 minutes before the session, followed by saline 15 minutes before the session. Control procedures included administration of saline 30 minutes before the session, followed by either saline or 5.6 mg/kg pentobarbital 15 minutes before the ses-

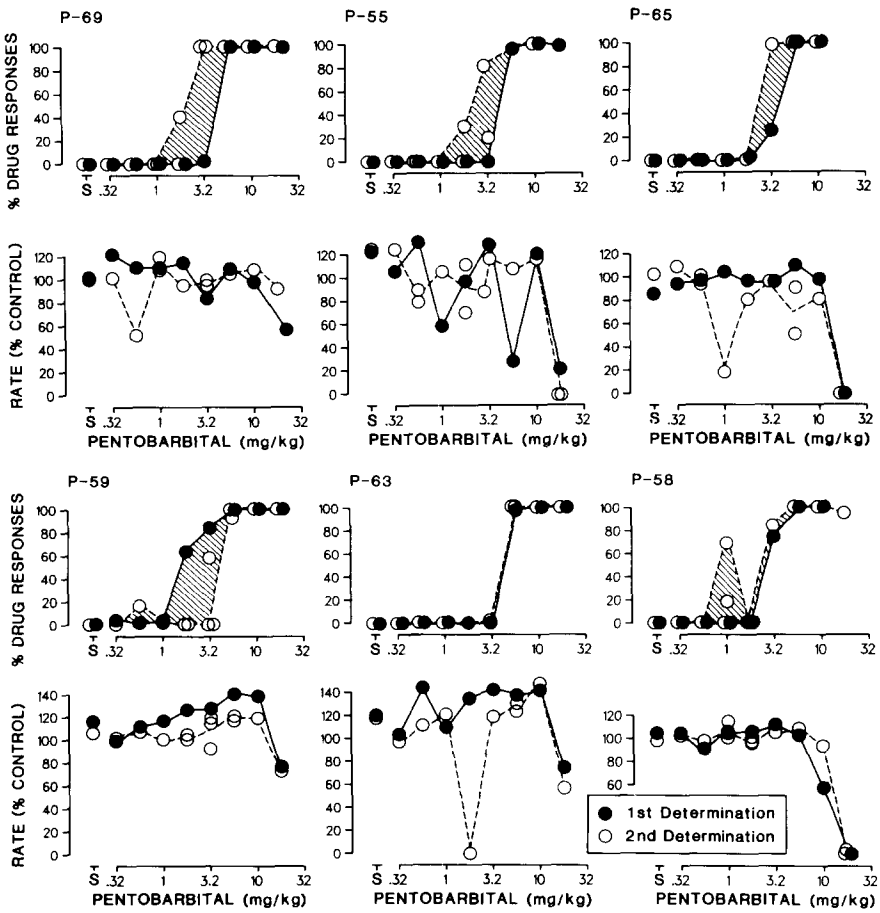

FIG. 1. Dose-response curves for the stimulus and rate-altering effects of pentobarbital in six pigeons trained to discriminate between 5.6 mg/kg pentobarbital and saline. Closed circles connected by solid lines represent data obtained during the first determination. Open circles represent all observations obtained during the second determination. Dotted lines connect the range of stimulus control values and the average rate values from all observations during the second determination. Abscissae: mg/kg dose of pentobarbital, log scale. Ordinate, upper panel: percentage of total session responses emitted on the pentobarbital-appropriate key. Ordinate, lower panel: response rate, expressed as a percentage of the individual subject's average rate during saline training sessions conducted during the period of testing. Points at 'S' represent tests with saline alone. During the period of pentobarbital tests, average rates during saline training sessions were: P-69, 1.58 (first determination) and 1.43 (second determination); P-55, 1.47 and 1.53; P-65, 1.37 and 1.56; P-59, 1.35 and 1.57; P-63, 1.09 and 1.09; P-58, 2.08 and 2.09 responses/sec.

sion. Two doses of *d*-amphetamine that did not evoke pentobarbital-appropriate responses were tested in combination with a range of doses of pentobarbital. *d*-Amphetamine was administered 30 minutes before the session, followed by pentobarbital 15 minutes before the session. All combinations were tested at least once.

Next, a range of ethanol doses were tested at least once in each subject. Ethanol was delivered by gastric gavage 30 min before the session, followed by a saline injection 15 minutes before the session. Control procedures included administering de-ionized water 30 minutes before the session, followed by injection of either saline or 5.6 mg/kg pentobarbital 15 minutes before the session. Then, two or three doses of ethanol that did not evoke complete pentobarbital-appropriate responding were tested in combination with a range of doses of pentobarbital. Ethanol was administered by gavage 30 minutes before the session, followed by pentobarbital 15 minutes before the session. Combinations were generally tested once.

Data Analysis

Stimulus control data are presented as two functions of dose. First, the number of responses emitted on the pentobarbital-appropriate key is given as a percentage of the total responses emitted during the session. Second, the overall rate of responding on both keys is presented as a percentage of the average rate for the saline training sessions conducted during each phase of stimulus control tests.

Drugs and Vehicles

Sodium pentobarbital (Henry Schein, Inc., prepared in propylene glycol (30%) and benzyl alcohol (2%) in water) and *d*-amphetamine sulfate (gift of Smith Kline & French Labora-

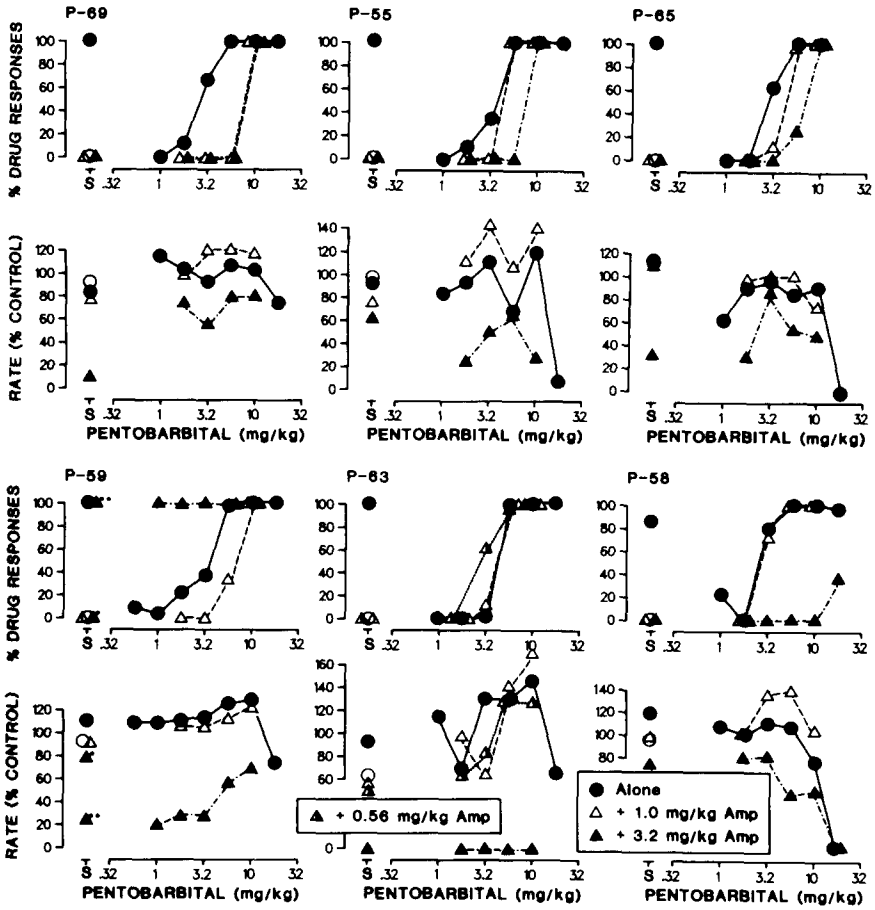

FIG. 2. Comparison of the dose-related effects of pentobarbital administered alone (closed circles) or in combination with 0.56 mg/kg (half-closed triangles, P-63 only), 1.0 mg/kg (open triangles), or 3.2 mg/kg (closed triangles) *d*-amphetamine in six pigeons trained to discriminate between 5.6 mg/kg pentobarbital and saline. Abscissae and ordinates as in Fig. 1. Points for pentobarbital alone represent the mean of all observations conducted before tests of drug combinations. Points for drug combinations represent one or two observations in each bird. Points at 'S' represent the effects of a saline injection administered concomitantly with a second injection of saline (open circle), 5.6 pentobarbital (closed circle), or each *d*-amphetamine dose. For P-59, the closed triangle with one asterisk represents the initial effects of 3.2 mg/kg *d*-amphetamine, and the closed triangle with two asterisks represents the effects of this dose after testing all pentobarbital and *d*-amphetamine combinations. During the period of amphetamine tests, average rates during saline training sessions were: P-69, 1.32; P-55, 1.33; P-65, 1.50; P-59, 1.46; P-63, 0.95; P-58, 1.87 responses/sec.

tories) were dissolved in physiological saline. Doses were calculated as the salts. Injections of these drugs were administered in a volume of 1 ml/kg body weight into the left or right pectoral muscles, the muscle in which the bird received the injection varying unsystematically over days. When two injections were administered, one was given into one muscle, and the other was given into the opposite muscle. Ethanol solutions were prepared by diluting 95% ethanol to a 10% weight/volume solution with de-ionized water. Ethanol solutions and de-ionized water were intubated by gavage down the esophagus into the proventriculus with a 15.2 cm stainless steel animal tube. Doses of all drugs and combinations were tested in unsystematic order, with the restriction that all tests of amphetamine-pentobarbital combinations were completed before examination of ethanol-pentobarbital combinations.

RESULTS

Stimulus Control by Pentobarbital

Five of the six pigeons acquired the pentobarbital-saline discrimination in 24 to 27 sessions, the sixth requiring 80 sessions. Over the period of testing, average response rates for individual birds during saline training sessions ranged from 0.77 to 2.09 responses/sec. Response rates during pentobarbital training sessions were typically higher, ranging from 1.17 to 2.44 responses/sec.

Stimulus control by pentobarbital was dependent on dose (Fig. 1, upper panels). Doses of 1.0 mg/kg and below generally evoked only saline-appropriate responses. Some variability was observed around intermediate doses (1.78 to 3.2 mg/kg), suggesting these may represent threshold intensities. The training dose and higher doses of pentobarbital (5.6 to

TABLE 1

EFFECTS OF *d*-AMPHETAMINE ALONE IN INDIVIDUAL PIGEONS

Dose (mg/kg)	P-69	P-55	P-65	P-59	P-63	P-58
			Percentage of responses to the pentobarbital-appropriate key*			
0.32	0	0, 0	0.1	0	0	0
0.56	0	0	0	0.1	0	0
1.0	0	0	0, 0	0	0	0
1.78	0	0	0	0	*	0
3.2	0	0	*, 0, 0	0.1	*	0
			Response rate (% of control values†)			
0.32	103	80,109	105	95	119	97
0.56	96	96	82	90	50	93
1.0	77	76	82,134	92	57	98
1.78	89	97	66	91	0	96
3.2	12	62	0,76, 21	79	0	74

*Data from all test sessions are presented. Failure to respond during a test session is indicated by an asterisk.

†Control values were the average response rates during saline training sessions conducted during the period of *d*-amphetamine tests.

17.8 mg/kg) evoked responses almost solely on the drug-appropriate key. Comparisons of the first and second gradients for individual birds showed shifts to the left upon redetermination in 4 birds, no shift in 1 bird, and a shift to the right in the final bird. At the end of all interaction experiments, 1.78 and 3.2 mg/kg were re-tested for stimulus control. The intra- and inter-subject variability observed in these final tests was similar to that in Fig. 1.

Response rates were more variable than discriminative control (Fig. 1, lower panels). Generally, low to moderate doses of pentobarbital slightly increased or did not alter rate, while higher doses decreased rate.

Ability of d-*Amphetamine to Alter Stimulus Control by Pentobarbital*

d-Amphetamine (0.32 to 3.2 mg/kg) did not evoke pentobarbital-appropriate responding in any pigeon (Table 1, upper panel). Low to intermediate doses slightly lowered response rates, while moderate to high doses markedly decreased rates (Table 1, lower panel).

d-Amphetamine-pentobarbital interactions are presented in Fig. 2. *d*-Amphetamine doses of 1.0 or 3.2 mg/kg increased the dose of pentobarbital required for stimulus control in five of six birds (Fig. 2, upper graphs for each bird). In the presence of *d*-amphetamine, even the training dose of pentobarbital, and in one case higher doses (P-58: 10.0 and 17.8 mg/kg), evoked primarily saline key responses. Increasing the pentobarbital dose to 10.0 mg/kg was sufficient to surmount the *d*-amphetamine challenge in all birds except P-58.

Two subjects showed unique effects of *d*-amphetamine. For P-63, combinations of 3.2 mg/kg *d*-amphetamine and pentobarbital repeatedly suppressed responding, with the result that stimulus effects of the combination could not be assessed. The second subject, P-59, began to display generalization of 3.2 mg/kg *d*-amphetamine during combined administration of 3.2 mg/kg *d*-amphetamine and pentobarbital. Such generalization had not occurred during earlier tests of *d*-amphetamine alone (cf. Table 1) or in combination with pentobarbital.

Analysis of the joint effects of pentobarbital and *d*-amphetamine on response rate showed that 1.0 mg/kg *d*-amphetamine slightly enhanced the rate-increasing effect of pentobarbital in some birds, while combinations of 3.2 mg/kg *d*-amphetamine and pentobarbital produced less than additive decreases in response rates (Fig. 2, lower panels of graphs).

Ability of Ethanol to Alter Stimulus Control by Pentobarbital

Ethanol (0.3 to 3.0 g/kg, orally) evoked variable levels of pentobarbital-appropriate responding (Table 2). In one bird (P-69), no ethanol dose evoked pentobarbital-appropriate responding, while in other birds doses of 0.56 to 3.0 g/kg ethanol evoked intermediate or high levels of pentobarbital-appropriate responding. In bird P-59, while both low and high doses of ethanol evoked few pentobarbital-appropriate responses, 1.0 g/kg did on occasion evoke 100% pentobarbital-appropriate responding. Low to moderate doses of ethanol tended to slightly increase response rates (Table 2, lower panel). Higher doses decreased or completely suppressed response rates.

During tests with ethanol, some birds distributed responses to both keys to a greater degree than during all other phases of the study. Chi-square analyses revealed that this pattern of responding occurred significantly more often during tests with ethanol than during all other phases of the study combined in birds P-65, $\chi^2(1)=12.4$, $p\leq 0.01$, P-59, $\chi^2(1)=22.6$, $p\leq 0.01$, and P-63, $\chi^2(1)=6.5$, $p\leq 0.05$; results in the other three birds were not significant.

Ethanol doses that did not in themselves evoke pentobarbital generalization were tested in combination with pentobarbital, with one exception (P-55, 1.0 g/kg). Ethanol doses of 0.32 or 1.0 g/kg decreased by 2 to 3-fold the dose of pentobarbital required for stimulus control in two or three birds, respectively (Fig. 3, upper graphs for each bird). In

TABLE 2
EFFECTS OF ETHANOL ALONE IN INDIVIDUAL PIGEONS

Dose (g/kg)	P-69	P-55	P-65	P-59	P-63	P-58
			Percentage of responses to the pentobarbital-appropriate key*			
0.30	0	0, 0	0	18, 0.1	0, 24	0
0.56	0	94, 0, 54	0, 0	0.1	44	0.2
1.0	0, 0	100, 98	0.1,0.1	100, 2, 18	28	88, 0.7, 0, 28
2.0	*, *	92	98, 1	15, 16, 8	51	99,100
3.0	*	100	75	10, 10	100	95
			Response rate (% of control values†)			
0.30	126	102,108	92	99,106	115, 93	107
0.56	100	117, 97, 10	105,93	98	125	108
1.0	108,102	115,113	88,92	102,109,108	98	113,106,104,106
2.0	0, 0	10	66,62	92,100, 94	52	86,105
3.0	0	12	50	91, 89	8	77

*Data from all test sessions are presented. Failure to respond during a test session is indicated by an asterisk.
†Control values were the average response rates during saline training sessions conducted during the period of ethanol tests.

contrast, a yet higher dose of ethanol, 2.0 g/kg, increased the dose of pentobarbital required for stimulus control in three birds (P-65, P-59, and P-63). Thus, in some subjects, lower doses of ethanol enhanced and a higher dose attenuated pentobarbital stimulus control.

Combinations of ethanol and pentobarbital also exerted variable effects on response rate (Fig. 3, lower graphs for each bird). In bird P-69, 1.0 g/kg ethanol slightly increased response rate when combined with pentobarbital. No predictable interactions of pentobarbital and low to moderate ethanol doses emerged in other birds. A high dose of ethanol (2.0 g/kg) decreased response rates in a greater than additive manner when combined with 5.6 or 10 mg/kg pentobarbital (e.g., P-63 and P-65).

DISCUSSION

d-Amphetamine and ethanol differentially modified pentobarbital stimulus control in pigeons. At certain doses, *d*-amphetamine attenuated stimulus control by pentobarbital doses lower than, equal to, or higher than the training dose. In contrast, low doses of ethanol enhanced stimulus control by pentobarbital doses lower than the training dose, whereas a higher ethanol dose attenuated stimulus control by that training dose.

An established pentobarbital discriminative stimulus retains stimulus control in the presence of behaviorally active doses of many drugs that lie outside the sedative-hypnotic class (e.g., [31]). One striking exception is the attenuation of pentobarbital stimulus control by the analeptics bemegride and pentylenetetrazol [20, 22, 25, 29]. Studies of the pharmacological specificity of this attenuation have demonstrated that the behavioral stimulants cocaine and caffeine do not alter stimulus control by a pentobarbital training dose [22,25]. In previous studies, *d*-amphetamine also left stimulus control by a pentobarbital training dose unaltered, but did modify control by lower doses [23,41]. In contrast, in the present study *d*-amphetamine induced a clear attenuation of pentobarbital stimulus control. At appropriate doses, *d*-amphetamine increased the dose of pentobarbital required for stimulus control in five of six birds, with the excluded bird failing to respond at *d*-amphetamine doses higher than 1.0 mg/kg. Importantly, certain doses of *d*-amphetamine attenuated stimulus control by the training dose of pentobarbital, and in one bird, control by higher doses. Thus, the group of drugs able to attenuate pentobarbital stimulus control under at least some experimental conditions appears to include bemegride, pentylenetetrazol, and *d*-amphetamine.

Although the experimental design does not allow unambiguous conclusions about the factors underlying the different patterns of *d*-amphetamine-pentobarbital stimulus interactions reported by us and others, the present pattern of attenuation may have resulted from our use of a 30-min test session, which allowed a longer sample of behavior after high dose combinations than in previous studies. Discrimination task variables may also control the interaction patterns obtained. *d*-Amphetamine can attenuate control by a pentobarbital training stimulus in subjects trained to discriminate pentobarbital from amphetamine ([41], but see [34]).

Ethanol produced a different pattern of alterations in pentobarbital stimulus control. Ethanol alone evoked variable degrees of pentobarbital-appropriate responding in individual birds, in agreement with previous studies (e.g., [4, 19, 27, 30]). When combined with pentobarbital, low doses of ethanol, which did not in themselves evoke substantial pentobarbital generalization, enhanced stimulus control by low pentobarbital doses in individual birds. These results extend to pentobarbital the observation [24] that ethanol can enhance stimulus control by low doses of other sedative-hypnotics. Jarbe and McMillan [24] reported that in pigeons trained with diazepam, low and moderate doses of ethanol did not engender diazepam-like stimulus control but, when combined with diazepam, progressively decreased the dose of diazepam required for stimulus control. As in the present study, a dose of 1.0 g/kg ethanol decreased by 3-fold the dose of diazepam required for stimulus control. The present observation that low to moderate doses of ethanol enhanced stimulus control by pentobarbital is congruent with results of previous studies and general beliefs about barbiturate-alcohol interactions (e.g., [3, 8, 9, 27, 37, 39]).

Interestingly, a higher ethanol dose, 2 g/kg, attenuated

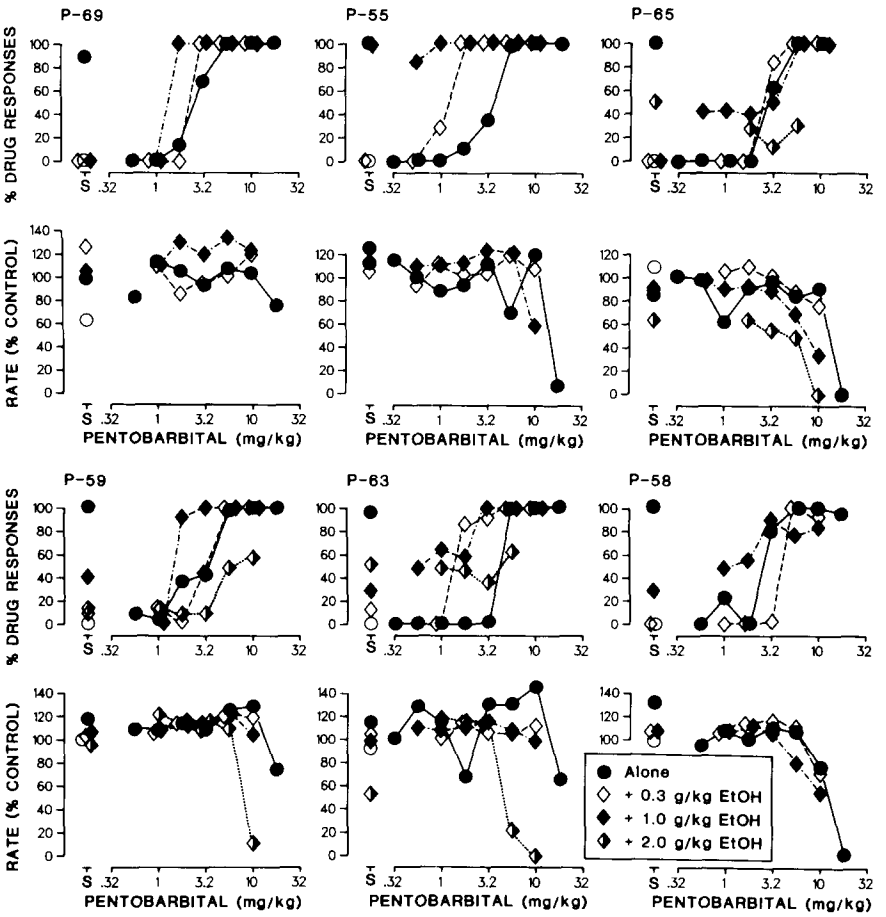

FIG. 3. Comparison of the dose-related effects of pentobarbital administered alone (closed circles) or in combination with 0.3 g/kg (open diamonds), 1.0 g/kg (closed diamonds), or 2.0 g/kg (half-closed diamonds; P-65, P-59, and P-63 only) ethanol in six pigeons trained to discriminate between 5.6 mg/kg pentobarbital and saline. Abscissae and ordinates as in Fig. 1. Points for pentobarbital alone represent the mean of all observations conducted before tests of drug combinations. Points for drug combinations represent one or two observations in each bird. Points at 'S' represent the effects of distilled water intubations administered concomitantly with an injection of saline (open circle) or 5.6 pentobarbital (closed circle), or of an injection of saline administered concomitantly with intubations of each ethanol dose. During the period of ethanol tests, average rates during saline training sessions were: P-69, 1.31; P-55, 1.49; P-65, 1.65; P-59, 1.48; P-63, 1.16; P-58, 1.87 responses/sec.

stimulus control by the pentobarbital training dose in three birds that did not display unambiguous generalization to this dose of ethanol. Thus, stimulus control by pentobarbital was attenuated not only by *d*-amphetamine, a drug from a different pharmacological class, but also by high doses of ethanol, a second sedative-hypnotic. In the presence of appropriate doses of either drug, pentobarbital did not exert its usual stimulus control, so that responses were distributed to the saline key or to both keys. This pattern may indicate (1) that the drug combinations exerted distinctive stimulus effects, or (2) that the *d*-amphetamine or ethanol stimuli overrode the pentobarbital stimulus, so that behavior reflected stimulus control by the challenge drug itself. The latter outcome may reflect an interaction that parallels the masking phenomena observed among exteroceptive stimuli (cf. [31]), in which presentation of a second stimulus in a defined spatial or temporal relation to a target stimulus can occlude perception of that target. Since the drug-saline discrimination procedure we employed does not allow one to assign stimulus profiles to drugs on the basis of saline-appropriate responding, further experiments will be required to evaluate these possibilities. However, these results highlight the possibility that drug stimulus control can be attenuated by drugs other than specific antagonists. The present data suggest that the possibility of stimulus interactions such as masking should be considered when interpreting the results of drug stimulus interaction studies.

The rate-altering effects of pentobarbital, ethanol, and *d*-amphetamine alone were similar to those reported under fixed-ratio schedules under other conditions (e.g., [2, 12, 13]). The combined effects of *d*-amphetamine and pentobarbital on response rate were not predictable from their individual effects, in agreement with previous reports (e.g., [1, 6, 18, 33]). Intermediate doses of *d*-amphetamine enhanced slightly the rate-increasing effect of pentobarbital, while a higher dose produced less than additive decreases in re-

sponse rate when combined with various doses of pentobarbital. The combined effects of pentobarbital and low doses of ethanol were indistinguishable from the effects of either drug alone. The highest dose of ethanol decreased rate of responding in a greater than additive manner when combined with pentobarbital.

It should be noted that, at certain doses, both amphetamine and ethanol attenuated stimulus control by pentobarbital without producing a parallel alleviation of pentobarbital's rate-altering effects. These results thus extend to new pairs of drugs the observation that a challenge drug can attenuate stimulus control by a drug stimulus without altering other effects of that drug [15]. Such selective attenuation of a drug's stimulus effects may underlie the untoward clinical outcomes of combinations of stimulants and sedatives, or of two sedatives (e.g., [11, 14, 37]). Attenuation of stimulus or subjective effects may be accompanied by unchanged or exaggerated deficits in coordinated motor activity. Such disparate interactions encourage the examination of drug combinations over a wide range of doses and behavioral endpoints.

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