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DIFFERENTIAL EFFECTS OF PENTOBARBITAL AND COCAINE ON PUNISHED AND NONPUNISHED RESPONDING

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Similar rates of punished and nonpunished responding, maintained with equated rates of reinforcement, were established in pairs of rats. One subject of each pair was exposed to a random-ratio schedule of food presentation. The interreinforcement intervals for this subject comprised the intervals of a random-interval schedule of reinforcement for the other (yoked) rat. The random-ratio schedule maintained rates of responding higher than those maintained by the same rate of reinforcement schedule according to the yoked random-interval contingency. A random-ratio schedule of electric foot shock added to the random-ratio schedule of food presentation suppressed rates of responding such that similar rates of responding were observed in rats of both groups. Pentobarbital (3.0 to 17.0 mg/kg) increased punished responding at doses that had little effect on or decreased nonpunished responding, whereas cocaine (5.6 to 30 mg/kg) increased nonpunished responding at doses that decreased or did not alter punished responding. Qualitatively different effects of pharmacological agents on punished and nonpunished responding can be obtained using procedures that generate similar rates and temporal patterns of punished and nonpunished responding. The effects of pentobarbital and cocaine on responding can be determined by factors other than simply the baseline rate of responding.

Key words: punishment, pentobarbital, cocaine, random ratio, random interval, yoked schedule, lever press, rats

Behavioral procedures that have been used to compare the effects of drugs on punished and nonpunished responding have contributed to the identification of anxiolytic drugs and the behavioral analysis of their effects. Early work in this area (i.e., Geller, Kulak, & Seifter, 1962; Geller & Seifter, 1960) demonstrated that different drug classes had qualitatively different effects on punished and nonpunished responding. Barbiturates and benzodiazepines, which increased punished responding, could be distinguished reliably from psychomotor stimulants that either had no effect on or decreased punished responding (see reviews by Houser, 1978; McMillan, 1975; McMillan & Leander, 1976). However, because most of the drugs reported to increase punished responding also increased low rates of responding maintained by conditions not using punishment (Dews, 1955; Kelleher & Morse, 1968; Sanger & Blackman, 1976), the punishment-specific effects of these drugs on response rates have been questioned. Early studies that attempted to evaluate the punishment-specific effects of drugs did not control for the general tendency of these drugs to increase low rates of responding regardless of the conditions maintaining or suppressing the rate of responding.

More recently, procedures that generate comparable rates of punished and nonpunished responding have been developed to investigate the punishment-specific effects of drugs. One such procedure assesses the effects of drugs on responding maintained by fixed-interval (FI) schedules in the presence or absence of a punishment contingency. Under FI schedules, low average response rates in the early portions of the interval are followed by higher average rates as the interval progresses. The effect of a drug on low rates of nonpunished responding, obtained during the early segments of an interval, can be compared to comparable rates of punished responding. The use of such procedures has indicated that pentobarbital increased low rates of responding irrespective of how the rates were generated (Spealman, 1979; Wuttke & Kelleher, 1970). However, contrasting data indicated that low rates of punished responding can be increased

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more than similar rates of nonpunished responding (McMillan, 1973), but this effect was restricted mainly to responding during the first 3 s of the FI 5-min schedule. In contrast to the results obtained with barbiturates and benzodiazepines, psychomotor stimulants tested in these procedures have not significantly increased punished responding at doses that increased nonpunished responding (McMillan, 1973; Spealman, 1979).

A second type of procedure eliminates the problem of comparing only local rates of responding under FI schedules (Branch & Gollub, 1974) because it generates nearly equivalent overall rates of punished and nonpunished responding. The procedure generates comparable rates of punished and nonpunished responding by using reinforcement rate to manipulate response rates. These techniques can be used to compare low overall rates of responding maintained by a low rate of reinforcer delivery with comparable rates maintained by a schedule providing more frequent reinforcement with an added punishment contingency (Cook & Catania, 1964). For example, this type of procedure has been used to maintain comparable rates and patterns of punished and nonpunished responding using a multiple random-interval (RI) 6-min food presentation, conjoint RI 1-min food presentation, random-ratio (RR) 3 shock presentation schedule (Branch, Nicholson, & Dworkin, 1977). Pentobarbital was shown to increase punished responding at doses that did not affect nonpunished responding; however, the rate of reinforcement was always higher in the component containing the punishment contingency. Because the rate of reinforcement is typically higher in the punishment component in this type of study, it is possible that the rate of reinforcement may influence the effect of drugs on punished responding.

A third procedure uses somewhat different reinforcement contingencies, during which responding is punished in one component and not punished in a second component, to obtain similar overall rates of responding in both components. The effects of chlordiazepoxide on responding maintained by a multiple schedule of punished and nonpunished responding have been studied using this third type of procedure. In one study of this type (Jeffery & Barrett, 1979), responding was maintained by an FI schedule of food presentation. During one component, responding was also punished by the delivery of electric shock on a fixed-ratio (FR) 30 response schedule. In the other component, only responses occurring at the end of the interval that were preceded by a specified period of no responding were reinforced. This procedure resulted in comparable rates of punished and nonpunished responding. Although chlordiazepoxide increased the equated rates of punished and nonpunished responding, greater increases in punished responding were observed.

In general, procedures that result in comparable overall rates of punished and nonpunished responding are likely to reveal punishment-specific effects of drugs. In addition, most of these studies have evaluated the effects of these drugs using multiple schedules of punished and nonpunished responding by the same subject. Because the environmental context in which behavior occurs can modulate the behavioral effects of drugs (Barrett, 1987), it is important to evaluate the effects of a drug on punished responding in multiple- as well as single-component schedules.

The present study used a yoked-box procedure (Ferster & Skinner, 1957) to generate similar rates of punished and nonpunished responding. Two rats were placed in individual sound-attenuated enclosures. Responses by 1 rat were reinforced according to an RR schedule. Each reinforcer produced by this rat made the next response by the subject in the second chamber eligible for reinforcement. Thus, responding for the second rat was maintained by an RI schedule in which the successive interreinforcement intervals matched those produced by the first rat. However, response rates were initially higher for the rats exposed to the ratio contingency. A conjoint RR schedule of electric shock presentation was used to decrease the response rates of the subjects on the ratio schedule of food presentation to those obtained with the yoked interval contingency. Thus, different contingencies were used to generate comparable rates and patterns of responding as well as reinforcement rate for punished and nonpunished responding. The effects of pentobarbital and cocaine were then determined.

METHOD

Subjects

Five littermate pairs of male Fischer-344 rats, 75 to 100 days old at the beginning of

the study, were used. The rats were maintained at 80% of their unrestricted feeding weights with postsession and weekend supplemental feeding. They were housed in individual cages with unlimited access to water. The housing cages were located in a temperature- and humidity-controlled room with a reversed 12:12 hr light/dark cycle.

Apparatus

During the experimental session, the rats were placed in standard operant conditioning chambers constructed of aluminum and Plexiglas. These chambers were located in ventilated, sound-attenuating enclosures in a room with white noise. Three feedback relays and a transformer (24 V AC) were mounted on the inside ceiling of these enclosures. Sessions were controlled and data collected and analyzed using Rockwell Aim 65® computers operating under MCS control (Micro Interfaces); the computers were located in an adjacent room. A food receptacle, response lever, and stimulus light (24 V AC) were located on the front wall of the experimental chamber. The food cup was connected to a pellet dispenser (Gerbrands) that delivered 45-mg pellets (BioServ). A force exceeding 0.30 N was required to depress the lever and register a response. Each response operated a feedback relay and darkened the stimulus light for 0.06 s. The floor of the chamber consisted of 0.04-cm diameter stainless steel rods placed 1.2 cm apart parallel with the front wall. The steel rods were individually connected to a 16-pole solid state shocker/distributor (Coulbourn Instruments Model No. E13-16).

Procedure

The five littermate pairs were trained using a yoked-box procedure (Ferster & Skinner, 1957). One rat from each pair was randomly selected to respond on an RR schedule. A food pellet was delivered to this rat after it completed a randomly determined number of responses. The response requirement was generated using the BASIC RND function (RND (x)). The value of x was obtained from the numeric variable of the number of seconds elapsed since the initiation of the program, thus x was a continuously changing variable and resulted in the generation of different random number sequences. The minimum number of responses required was initially set at one and increased to five during the fourth session. The maximum number of responses that could occur before food delivery was initially set at one and increased to 100 by the end of the ninth session.

A littermate of the rat responding under the ratio contingency was placed in another isolated conditioning chamber. Food deliveries to this second subject were presented following the first response emitted by this subject after food was delivered to the subject on the ratio schedule. This resulted in a yoked RI schedule equating the interreinforcement intervals for the subjects on both schedules. A conjoint RR schedule (25 response minimum, 200 response maximum) of electric shock was then added to the ratio food schedule. The 0.4-mA shocks were 100 ms in duration. The shock intensity was occasionally adjusted between drug sessions from 0.4 to 0.8 mA to maintain comparable rates of punished and nonpunished responding. On those occasions when food and shock were scheduled to be delivered following the same response, only a food pellet was delivered, and the shock presentation followed the next response. If more than one reinforcer was delivered to the subject on the ratio schedule before the subject on the yoked schedule responded, only the first presentation was used to arrange food on the yoked schedule. Sessions were initially 90 min in duration but were decreased to 45 min for the drug studies reported. Sessions were conducted Monday through Friday.

During the determination of the pentobarbital dose–effect curve, the RR schedules for food and shock were set to 25 minimum, 400 maximum and 100 minimum, 400 maximum, respectively, for one session that was preceded by the administration of 5.6 mg/kg of pentobarbital.

Drug Procedure

Pentobarbital sodium and cocaine HCl were dissolved in saline and injected intraperitoneally in a volume of 1.0 mL/kg body mass. Doses of pentobarbital, 3.0 to 17 mg/kg (specified in terms of the salt), and saline were administered in an irregular order 30 min prior to selected sessions. Doses of cocaine HCl, 5.6 to 30 mg/kg (expressed in terms of the salt) were investigated following the determination of the effects of pentobarbital. Cocaine was administered using two ascending series and was injected immediately prior to selected sessions. Each dose of both drugs was adminis-

Table 1

Mean obtained schedule values for all subjects. Numbers in parentheses indicate standard deviations.

Condition	Variable	Rat				
Before shock[a]		R1	R5	R6	R7	R9
	RR food schedule	51 (1.64)	51 (3.36)	62 (5.37)	50 (4.77)	52 (1.92)
		Y1	Y5	Y6	Y7	Y9
	Yoked RI schedule (min)	0.83 (0.08)	0.60 (0.05)	0.62 (0.05)	0.57 (0.05)	0.63 (0.03)
Shock[b]		R1	R5	R6	R7	R9
	RR food schedule	51 (8.93)	46 (12.30)	60 (5.31)	72 (20.27)	50 (2.74)
	RR shock schedule	117 (23.76)	110 (17.62)	147 (62.72)	98 (16.32)	109 (18.49)
		Y1	Y5	Y6	Y7	Y9
	Yoked RI schedule (min)	10.31 (3.47)	16.58 (12.45)	21.8 (15.45)	40.07 (30.28)	3.26 (1.80)

[a] Average value for five sessions preceding the addition of shock.
[b] Average value for five sessions preceding drug administration.

tered at least twice to each rat and separated by four or more nondrug sessions. The drug was administered to only one littermate before a selected session. At least two sessions of baseline performance were observed before any drug was administered to either subject.

Data Analysis

Responses by each subject were recorded and used to calculate the mean response rates for the session. Mean control response rates were calculated from sessions that directly preceded sessions during which a drug or saline was administered.

RESULTS

Control Performance

The mean schedule values obtained during the last 5 days before the introduction of the punishment contingency and the 5 days preceding the initial dose–effect curve determinations are presented in Table 1. The mean RR schedule ranged from 51 to 62, and the mean RI schedule ranged from 0.57 to 0.83 min. There was very little variability in the obtained schedule parameters during control sessions. Additionally, both the RR and yoked RI schedule values were similar for all subjects. The RR shock contingency decreased the rate of responding by the rats on the punishment schedule, and the decrease in response rate significantly increased the mean interreinforcement interval. Specifically, the punishment contingency resulted in a considerable increase in the yoked RI value, which ranged from a mean of 3.26 to 40.07 min after shock was added. The programmed RR shock contingency resulted in a mean ratio ranging between 98 and 147.

Figure 1 shows the mean response rates that were obtained by the schedule values presented in Table 1. Responding maintained by the ratio schedule, before the addition of shock, was at least 2.5 times greater than the rate maintained by the interval contingency (left panel). The increased interreinforcement interval decreased rates of responding maintained by the yoked RI schedule (Figure 1, right), thereby resulting in similar response rates maintained by the schedules with and without the punishment contingency. Figure 2 contains representative cumulative records from one pair of subjects (R9, Y9) before and after the introduction of electric shock. Responding under the RR schedule before shock was added was characterized by a relatively high and constant rate of responding. Although brief pauses occasionally followed food presentations, the yoked RI contingency resulted in a fairly constant but lower rate of responding (Figure 2, left panels). The right panels contain representative records, from the same pair of rats, after the shock contingency was added. The

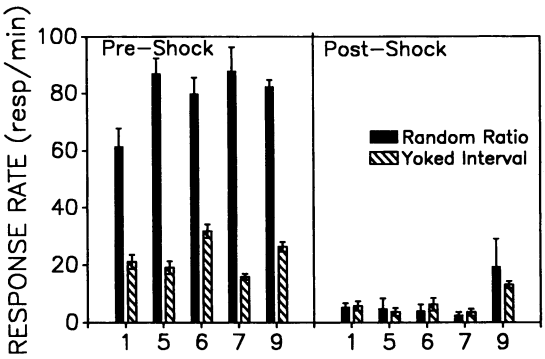

Fig. 1. Mean response rates for the five pairs of rats (R1-Y1, R5-Y5, R6-Y6, R7-Y7, R9-Y9) on the ratio (filled bars) and yoked interval (slashed bars) schedule. The bars to the left of the center vertical line represent the data collected during the last five sessions before the introduction of the punishment contingency. The data shown to the right of this line were collected the last five sessions before any drug was administered. Vertical lines indicate 1 *SD*.

top record shows that individual shocks did not consistently increase or decrease responding that occurred immediately after a shock but resulted in an overall decrease in responding. Similar response patterns were obtained by both schedules.

Effects of Pentobarbital

The cumulative records in Figure 3 show the effects of a dose of pentobarbital on punished and nonpunished responding for a pair of subjects (R9, Y9). The cumulative records presented in the top panels illustrate control performance and were collected from two different sessions immediately preceding the administration of 10 mg/kg pentobarbital. The records displayed in the bottom panels show that the drug significantly increased punished responding and resulted in a consequential increase in both food deliveries and shock pre-

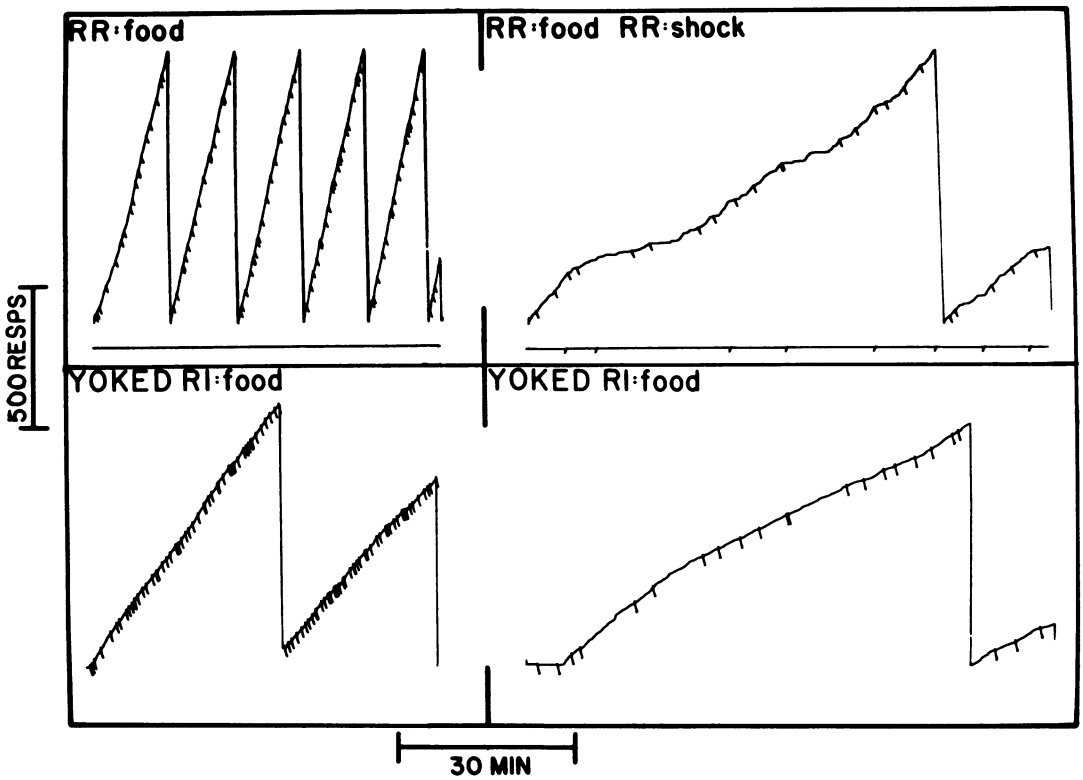

Fig. 2. Cumulative records of responding before (left) and after (right) the introduction of the punishment contingency. Records in the top panels are from a subject (R9) studied on the ratio food contingency, and the records on the bottom are from a subject (Y9) placed on the yoked interval contingency. The records presented are from the same session for each subject. Each response stepped the top pen; deflections of this pen indicate food presentations. Deflections of the bottom pen indicate shock presentations. These control records were selected from sessions that were terminated after either 90 min or 100 food presentations.

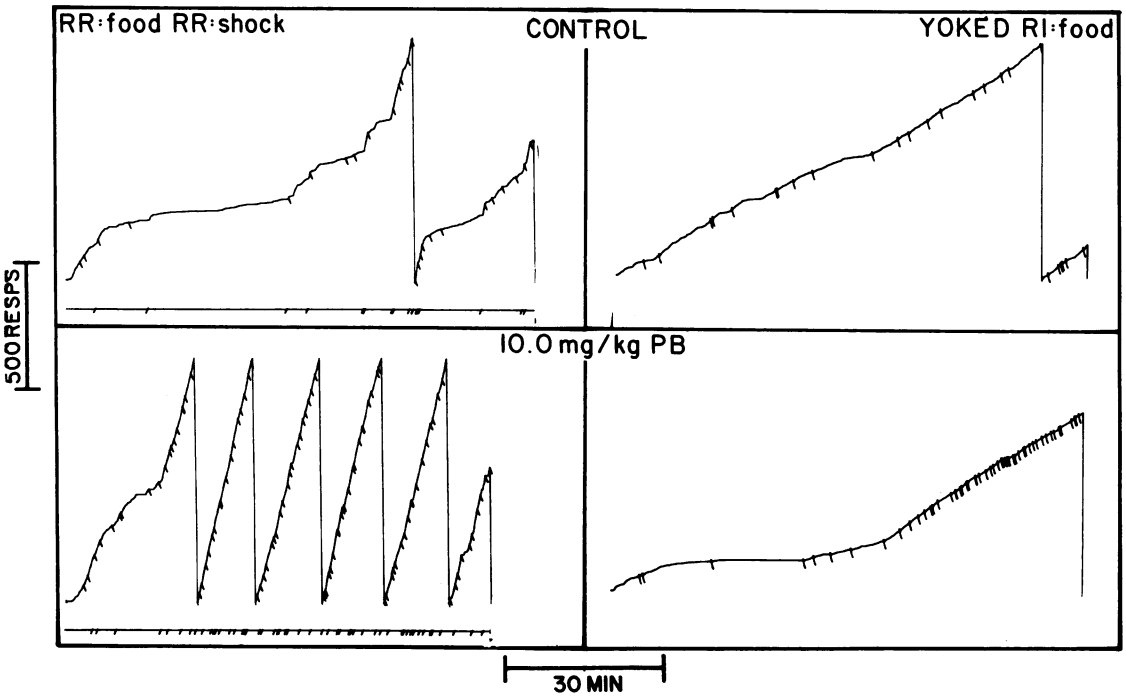

Fig. 3. Cumulative records of control performance and the effects of 10.0 mg/kg pentobarbital on responding maintained by the two schedule contingencies. Control records were obtained from a day that immediately preceded a drug injection and are not from the same experimental session. Other details are the same as for Figure 2 except that the sessions were terminated after 45 min or 100 food presentations.

sentations during the session. Moreover, the pattern of responding obtained was very similar to the cumulative records collected before the addition of the punishment contingency. Nonpunished responding was not appreciably altered by this dose.

Pentobarbital produced substantial increases in punished responding at doses that had little effect on or decreased nonpunished responding in all subjects (Figure 4). The lowest dose evaluated produced either no effect on or a slight increase in punished responding. In all 5 rats, the 5.6 mg/kg dose produced a substantial rate-increasing effect. Punished responding by the fifth rat was significantly increased by both the 5.6 and 10 mg/kg dose. The largest dose of pentobarbital evaluated decreased responding in all but 1 rat on the punishment schedule and 3 rats on the yoked interval schedule. The rate-increasing effects of pentobarbital on punished responding resulted in a substantial increase in the reinforcement frequency for the rats on the yoked interval contingency; however, response rates increased slightly in 3 subjects.

The increase in punished responding following the administration of pentobarbital resulted in an increased number of food presentations to both subjects and shock deliveries to the rats on the punishment schedule (see Table 2). Although only 1 subject in each pair received the drug during selected sessions, the yoked-box procedure was always in effect. Therefore, doses of pentobarbital that substantially increased or decreased punished responding also significantly altered the mean interreinforcement interval for both subjects (see Table 2). Accordingly, the effects of the resulting schedule change for the rats on the yoked schedule, during sessions prior to which pentobarbital was administered to the rats on the ratio schedule, were evaluated. The decrease in the mean interval value, following the peak rate-increasing effect of pentobarbital, resulted in a small but reliable increase in responding maintained by the interval schedule in 2 rats (Figure 4, squares), whereas doses of the drug that decreased punished responding also decreased responding by the nondrugged yoked subjects.

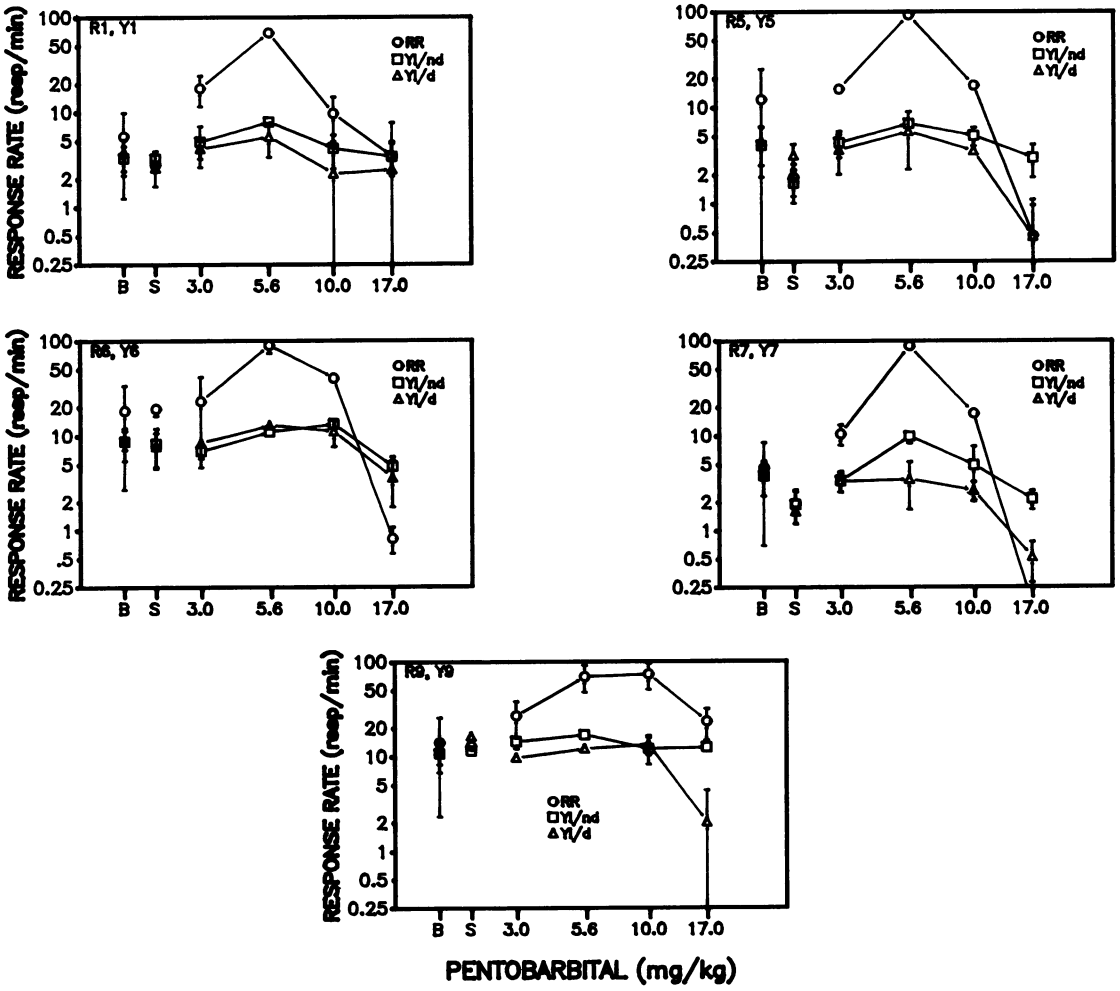

Fig. 4. Dose-response curves depicting the effects of pentobarbital on response rates maintained by the schedule contingencies. The open circle (RR) and triangles (YI/d) indicate the effects of the drug on punished and nonpunished responding, respectively. The points indicated by the squares (YI/nd) show the response rates observed from the nondrugged rats on the yoked interval contingency during sessions preceded by the administration of the drug to the rats on the punishment schedule. The points displayed above B are from control sessions the day prior to drug administration, and the points above S indicate the effects of saline administration. Vertical lines above the points represent 1 *SD*. The point for the 17.0 mg/kg dose given to R7 was 0.17 ± 0.15.

The effects of increasing the RR requirements during a session immediately preceded by an injection of 5.6 mg/kg of pentobarbital were determined for each rat. This manipulation, the results of which are shown in Table 3, was intended to keep the number of food presentations and shock deliveries similar to control values during the drug session when response rates were increased. Thus, this change in schedule contingencies was used to evaluate the influence of the increased rate of reinforcement and shock delivery that occurred following the administration of the 5.6 mg/kg dose under the usual schedule contingencies in maintaining higher rates of responding during drug sessions. The ratio contingency for food was increased from the 5 response minimum, 100 response maximum to a minimum of 25 and a maximum of 400 responses. The RR for shock was increased from a 25 response minimum, 200 response maximum to 100 minimum and 800 maximum. The administration of 5.6 mg/kg of pentobarbital to the rats placed on this altered schedule resulted in

Table 2

Number of food and shock presentations during the pentobarbital dose–effect curve determination. Data in parentheses are standard deviations. Control data are means of sessions for the day before a drug was administered.

Dose	Food	Shock	Food	Shock	Food	Shock	Food	Shock	Food	Shock
	R1		R5		R6		R7		R9	
Control	4 (3)	2 (1)	10 (10)	5 (6)	17 (16)	7 (6)	4 (4)	1 (2)	15 (13)	8 (7)
3.0 mg/kg	16 (8)	7 (1)	15 (1)	2 (3)	22 (15)	5 (2)	8 (2)	4 (1)	25 (8)	17 (11)
5.6 mg/kg	60 (5)	25 (1)	76 (9)	37 (4)	75 (8)	37 (3)	83 (11)	35 (10)	69 (27)	26 (7)
10 mg/kg	8 (4)	4 (2)	18 (3)	9 (3)	31 (2)	18 (2)	13 (1)	7 (0)	64 (19)	29 (9)
17 mg/kg	3 (4)	1 (1)	0	1 (1)	1 (1)	0	0	0	35 (25)	14 (11)
	Y1		Y5		Y6		Y7		Y9	
Control	4 (3)		10 (10)		17 (16)		4 (4)		15 (13)	
3.0 mg/kg	16 (8)		15 (1)		22 (15)		8 (2)		25 (8)	
5.6 mg/kg	59 (4)		74 (8)		74 (8)		83 (11)		60 (27)	
10 mg/kg	8 (4)		18 (3)		31 (2)		13 (1)		64 (19)	
17 mg/kg	3 (4)		0		1 (1)		0		35 (25)	

similar increases in punished responding as were observed when the standard schedule values were used. However, the number of foods and shocks delivered were similar to those values observed after the 3.0 mg/kg dose was administered during the standard schedule contingencies, which resulted in only a modest increase in response rates (see Table 3). Thus, the rate-increasing effects of the 5.6 mg/kg dose were not simply a result of changes in the number of food deliveries or shock presentations.

Effects of Cocaine

The cumulative records displayed in Figure 5 show the effects of cocaine on punished and nonpunished responding for one pair of rats (R9, Y9). The control records in the top panel were obtained from two different sessions. The largest dose of cocaine investigated resulted in a uniform increase in nonpunished responding and a decrease in punished responding. Cocaine resulted in dose-related increases in responding by the rats on the yoked RI schedule and consistent decreases in responding by the rats on the punishment schedule (Figure 6). Increasing doses of the drug resulted in increases in nonpunished responding, whereas the lowest dose of cocaine did not significantly alter punished responding and larger doses of the drug resulted in further decreases in punished responding.

Table 3

Number of food and shock presentations and response rates from the single control and drug session using the higher ratio contingencies.

	R1	Y1	R5	Y5	R6	Y6	R7	Y7	R9	Y9
Control										
Number of foods	8	8	5	5	26	26	3	3	16	16
Number of shocks	2	—	0	—	12	—	0	—	4	—
Response rate (resp/min)	9.19	2.3	2.9	3.7	32.8	8.6	2.8	2.5	14.93	13.7
5.6 mg/kg pentobarbital										
Number of foods	8	8	17	17	25	25	20	20	23	23
Number of shocks	5	—	8	—	11	—	8	—	9	—
Response rate (resp/min)	43.1	3.7	77.4	5.1	110.7	8.7	96.0	7.1	82.7	12.2

Note. Food ratio was set at 25 minimum, 400 maximum, and shock ratio was set at 100 minimum, 800 maximum. 5.6 mg/kg pentobarbital was administered before the session.

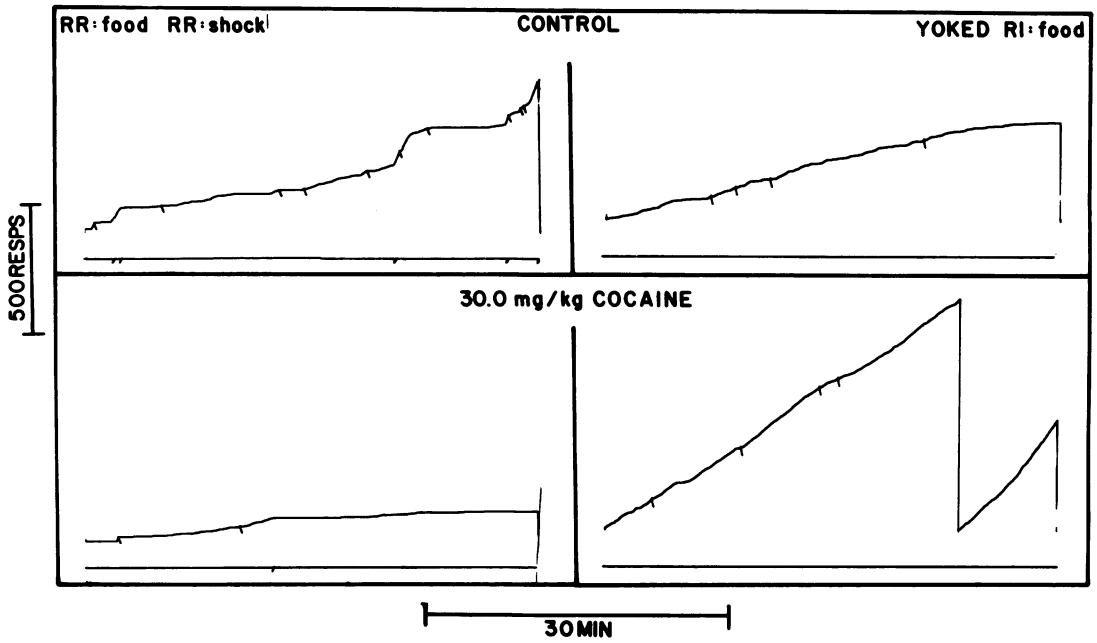

Fig. 5. Cumulative records showing the effects of cocaine on temporal patterns of responding. Details are the same as for Figures 2 and 4. Sessions were terminated after 45 min or 100 food presentations.

DISCUSSION

Pentobarbital selectively increased punished responding maintained by an RR schedule at doses that either had no effect on or decreased similar rates of nonpunished responding maintained by a yoked RI schedule. Thus, the rate-increasing effect of pentobarbital was not simply a rate-dependent effect. The results of previous studies investigating the effects of pentobarbital or benzodiazepines on comparable rates of punished and nonpunished responding have been discrepant. McMillan (1973), Branch et al. (1977), and Jeffery and Barrett (1979) reported that these drugs selectively increased responding punished by electric shock, whereas Spealman (1979) and Wuttke and Kelleher (1970) found that compounds in these classes increased similarly low rates of both punished and nonpunished responding. In the first and two latter studies, however, the mean overall rates of punished and nonpunished responding were different. Moreover, the punishment procedures used in several of these studies resulted in large differences in the density of reinforcement in the components with and without the punishment contingencies. Thus, the differences in overall rate of responding or in the density of reinforcement could be important determinants of the differential effects of drugs on punished responding. The procedures used in the present study resulted in similar rates and patterns of responding and density of reinforcement and, therefore, minimized the influence of these two factors.

Two of the studies mentioned above (Branch et al., 1977; Jeffery & Barrett, 1979) demonstrated qualitatively different effects of pentobarbital or benzodiazepine on comparable rates and patterns of punished and nonpunished responding. Three other studies (McMillan, 1973; Spealman, 1979; Wuttke & Kelleher, 1970) equated control rates of responding by analyzing local rates during FI schedules (specifically by dividing the interval into 10 equal segments and collecting average rates in each segment) with and without a conjoint FR punishment contingency. That is, the effect of the drug during the initial segment of the intervals not containing the additional punishment contingency was compared to roughly equated low rates that occurred during later segments of the intervals containing the conjoint shock schedule. These studies showed that barbiturates and benzodiazepines increase both punished and nonpunished responding,

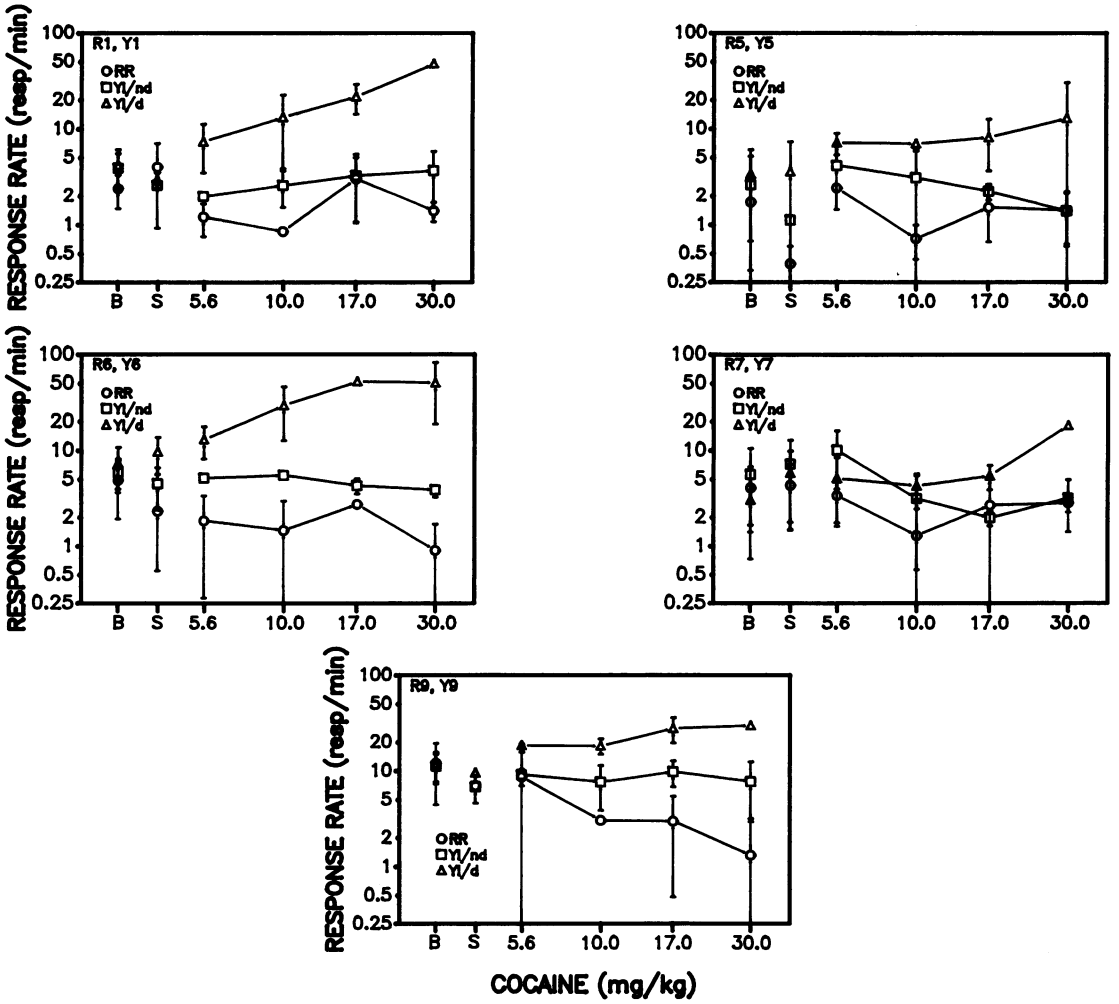

Fig. 6. Mean response per minute as a function of dose of cocaine for responding by the rats on the conjoint RR food and shock schedule (circles) and yoked interval schedule (triangles). Nondrugged performance by the rats on the interval contingency yoked to the intervals generated during sessions prior to which the rats on the ratio schedule received the drug are represented by squares. Other details are the same as in Figure 4.

although larger increases in punished responding are sometimes seen (Foree, Moretz, & McMillan, 1973). The increases in nonpunished responding, however, are usually seen in early parts of the FI, whereas increases in punished responding often occur in later segments. Comparison of such rates, therefore, entails the assumption that controlling variables are the same early and late in FI schedules. Studies comparing local rates of responding during different segments of a fixed interval also have been criticized for their reliance on local rates that may not be indicative of actual rates obtained (Branch & Gollub, 1974). Different temporal segments of an FI schedule most likely reflect very different patterns of responding even when the rates are similar. The low rates obtained during early segments are the result of averaging zero rates of responding (i.e., postreinforcement pause) with actual low rates that occur early in the interval, whereas the low rates obtained during terminal segments of an interval containing a punishment contingency most likely reflect a constant low rate of responding.

The present study showed that nonpunished responding was either unaffected or decreased by doses of pentobarbital that increased punished responding. This suggests that the effect of the drug on equated local rates may be very

different from the effects of the drug in procedures that are designed to produce comparable overall rates of punished and nonpunished responding.

This study also resulted in equal reinforcement rates for both punished and nonpunished responding. In general, studies that have determined the effects of drugs on punished responding by equating punished responding during schedules with a high rate of reinforcement with responding maintained by schedules with a low rate of reinforcement are potentially confounded by the rate-of-reinforcement difference. The present study, which also shows a qualitative difference in the effects of the drug on punished responding, controlled for reinforcement rate.

Only a few studies comparing the effects of cocaine on punished and nonpunished responding by rats have been reported. One of these studies presented preliminary data that indicated equivocal effects of the drug on responding maintained by a multiple variable-interval (VI) 2 min (food), conjoint FR 1 food and shock schedule (Geller, Hartmann, & Blum, 1972). In 3 of 6 rats, both punished (FR 1) and nonpunished (VI 2) responding were decreased by the administration of moderate doses of cocaine. Responding was slightly increased in 2 subjects, and 1 rat showed a selective effect. A second study that investigated the effects of several doses of cocaine on responding maintained by a similar multiple schedule reported decreases in both punished and nonpunished responding (Wilson, 1977). Thus, these studies suggest that cocaine may not have selective effects on punished responding. However, response rates were not reported for the punished component in the first study, and in the second, response rates were considerably higher in the nonpunished component. Data from the present study are in agreement with those reported in squirrel monkeys (Spealman, 1979) and indicate that cocaine can increase rates of nonpunished responding at doses that decrease comparable rates of punished responding.

The failure of cocaine to increase punished responding at doses that increased comparable rates of nonpunished responding is in agreement with other literature on the effects of stimulants on punished behavior (McMillan, 1975). Although *d*-amphetamine can increase punished responding in certain situations depending on the schedule context and the subject's history (Barrett, 1977, 1985; Barrett & Witkin, 1986; McKearney & Barrett, 1975, 1978), these enabling conditions did not occur in the present study.

There is increasing evidence that cocaine and *d*-amphetamine have dissimilar neurobiological and behavioral actions. Cocaine binds to specific receptors that block presynaptic dopamine reuptake (Kennedy & Hanbauer, 1983; Schoemaker et al., 1985), whereas amphetamine results in the release of dopamine and direct postsynaptic activation (Cooper, Bloom, & Roth, 1982). Moreover, the contingent administration of amphetamine but not cocaine into the nucleus accumbens has been shown to be reinforcing (Goeders & Smith, 1983). However, these two stimulants appear to exert similar effects on punished responding and either have no effect on or further decrease responding.

The procedure used in the present study has several advantages for investigating the specificity of the rate-increasing and -decreasing effects of pharmacological agents as well as the neurobiological mechanisms of punishment. This procedure results in comparable overall rates of punished and nonpunished repsonding, thus eliminating the necessity for comparing statistically equated rates that may be influenced by additional factors. The procedure also controls for reinforcement rate for both punished and nonpunished responding. There were, however, at least two differences between the two groups. The schedule contingencies were different (RR and yoked RI), and one group of rats was never exposed to electric shock. Furthermore, some of the definitiveness resulting from within-subject designs was forgone by the use of a yoked design. However, the procedure used in the present study may be more suitable for neurobiological investigations of the behavioral effects of drugs and provides a unique method for investigating the punishment-specific effects of pharmacological agents.

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