**SELECTIVE ANTAGONISM OF THE
ERROR-INCREASING EFFECT OF MORPHINE BY
NALOXONE IN A REPEATED-ACQUISITION TASK**

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Pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of four colors. The response chain was maintained by food presentation under a fixed-ratio schedule. Errors produced a brief timeout but did not reset the chain. When either morphine or naloxone was administered alone, the overall response rate decreased with increasing doses. The rate-decreasing effect was accompanied by an increase in percent errors with morphine but not with naloxone. Both effects of morphine were antagonized by doses of naloxone that were ineffective when given alone. The antagonism was selective in that naloxone (3 mg/kg) completely blocked the error-increasing effect but not the rate-decreasing effect of the higher doses of morphine. The view that naloxone is a specific narcotic antagonist was supported by the finding that naloxone failed to antagonize the rate-decreasing and error-increasing effects of *d*-amphetamine, pentobarbital, and phencyclidine.

Key words: repeated acquisition, response chains, fixed-ratio schedule, drug antagonism, morphine, naloxone, key peck, pigeons

The effects of drug combinations on complex operant behavior have received little experimental attention. In one of the few studies in this area, Thompson (1980) examined the joint effects of *d*-amphetamine and chlorpromazine on behavior in a repeated-acquisition task. Pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of four colors. The response chain was maintained by food presentation under a fixed-ratio (FR) schedule. When *d*-amphetamine was administered alone, the overall response rate decreased and the percent errors increased with increasing doses. When a small dose of chlorpromazine, which was ineffective when given alone, was administered in combination with *d*-amphetamine, the rate-decreasing effect was antagonized. The antagonism was selective, however, in that the error-increasing effect of *d*-amphetamine was augmented by chlorpromazine. The nature of the joint effect of the two drugs thus depended on the behavioral measure: rate vs. accuracy (cf. Branch, 1974).

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The present research examined the possibility that morphine and naloxone would interact in a manner dissimilar to *d*-amphetamine and chlorpromazine in a repeated-acquisition task (Thompson, 1980). Morphine and naloxone were chosen for study because the effects of separate and combined administration of these two drugs on schedule-controlled performance have been investigated extensively in pigeons (see review by McMillan, 1974). For example, when the responding of pigeons is maintained under an FR schedule of food presentation, it has been found that 1) increasing the dose of either morphine or naloxone alone decreases the overall response rate and 2) the rate-decreasing effect of morphine can be antagonized by doses of naloxone that have no effect when given alone (Downs & Woods, 1976; Dykstra, McMillan, & Harris, 1974; Goldberg, Morse, & Goldberg, 1976; Kotersky & Harris, 1973; McMillan, Wolf, & Carchman, 1970; Woods, Downs, & Carney, 1975). Similar results have been obtained with rats (Carney & Rosecrans, 1978; Leander, 1980), squirrel monkeys (Goldberg et al., 1976) and rhesus monkeys (Downs & Woods, 1976; Kelleher & Goldberg, 1979) under FR schedules of reinforcement. In addition to determining the effects of separate and combined administration of morphine and naloxone on behavior

in a repeated-acquisition task, the present research probed the specificity of the obtained morphine-naloxone antagonism by testing *d*-amphetamine, pentobarbital, and phencyclidine alone and in combination with naloxone.

METHOD

Subjects

Three adult male White Carneaux pigeons were maintained at approximately 80% of their free-feeding body weights by food presented during the sessions and by postsession supplemental feeding. The 80% values were 550 g, 450 g, and 450 g for P-788, P-7865, and P-2252, respectively. Water and grit were always available in the home cages. Each subject had an extensive history of repeated acquisition of four-response chains under FR schedules; P-788 had also served in a previous drug study (Thompson & Moerschbaecher, 1980).

Apparatus

The experimental space was a standard three-key pigeon chamber (BRS/LVE model SEC-002). Each translucent response key required a minimum force of .18 N for activation. Each key could be transilluminated by three Sylvania 24ESB indicator lamps, one with a red plastic end cap, one with a green cap, and the third with no cap. To provide a fourth color, "yellow" (actually yellow-orange) was produced by turning on the red and green lights simultaneously. The control equipment consisted of timers, steppers, and associated relay circuitry; recording was by counters, running-time meters, and a cumulative recorder. White noise was continuously present in the chamber to mask extraneous sounds.

Procedure

Baseline. All three response keys were illuminated at the same time by one of four colors, either yellow, green, red, or white. The pigeon's task was to acquire a four-response chain by pecking the correct key in the presence of each color; e.g., keys yellow—Left correct; keys green—Right correct; keys red—Center correct; keys white—Right correct; reinforcement. The same chain (in this case, Left-Right-Center-Right or LRCR) was repeated throughout a given session. The four-response chain was maintained by food pre-

sensation under an FR 5 schedule; i.e., every fifth completion of the chain was followed by 3-sec (P-2252) or 5-sec (P-788 and P-7865) access to mixed grain. Presentation of the grain magazine was accompanied by the offset of the keylights and the onset of the magazine light. All other completions of the four-response chain produced a .5-sec flash of the magazine light, which was accompanied by the offset of the keylights. When the pigeon pecked an incorrect key (e.g., the left or right key when the center key was correct), the error was followed by a 5-sec timeout. During the timeout, the keys were dark and responses were ineffective. An error did not reset the chain; i.e., the keylights after the timeout were the same color as before the timeout. Each session was terminated after 40 food reinforcements or 3 hr, whichever occurred first. A "blackout" (all lights off) of variable duration preceded and followed each session. Sessions were conducted daily, Monday through Friday.

To establish a steady state of repeated acquisition, the four-response chain was changed from session to session. The chains were carefully selected to be equivalent in several ways and their ordering was restricted across sessions (see Thompson, 1973). An example of a typical set of six chains is as follows: LRCR, CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated colors was always the same: yellow, green, red, white (food on the FR 5 schedule).

As in previous research using repeated-acquisition baselines (e.g., Thompson, 1980), the data for each session were analyzed in terms of 1) the overall response rate (total responses/min, excluding timeouts) and 2) the overall accuracy or percent errors [(errors/total responses) $\times$ 100]. In addition to these measures based on session totals, within-session changes in responding were monitored by a cumulative recorder. For example, acquisition of a response chain was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug testing. Before the drug testing began, the behavior under the baseline schedule was stabilized. The behavior was considered stable when the response rate and the percent errors no longer showed systematic change from session to session. After baseline stabilization (30 to 40 sessions), dose-effect data were ob-

tained for morphine sulfate. The drug was dissolved in saline and injected into the breast muscle 10 min pre-session. The doses of morphine were tested in a mixed order, and there were two determinations for most of the effective doses. Next, 3 mg/kg of naloxone hydrochloride, dissolved in saline, was administered alone (intramuscularly, 10 min pre-session). Varying doses of morphine (in a mixed order) were then administered in combination with the 3 mg/kg dose of naloxone; two determinations were made for most of the doses tested. Both drugs were injected intramuscularly (one on the right side, the other on the left) 10 min pre-session. Next, using the same testing procedure, a lower dose of naloxone, .3 mg/kg, was administered alone and in combination with varying doses of morphine. The dose-effect data for morphine alone were then redetermined. In the next phase of the research, phencyclidine hydrochloride, pentobarbital sodium, and *d*-amphetamine sulfate (each dissolved in saline) were tested, in that order, alone and in combination with 3 mg/kg of naloxone (intramuscularly, 5 min pre-session) in two of the subjects. Before being combined with naloxone, the three drugs were tested at different doses until a dose of each drug was found that clearly decreased the overall response rate and increased the percent errors in each subject; a dose of *d*-amphetamine that eliminated all responding during a 3-hr session was also tested. Finally, higher doses of naloxone were administered alone (intramuscularly, 10 min pre-session) in all three subjects.

Throughout testing, drug sessions were generally conducted on Tuesdays and Fridays, with control sessions (saline alone injected intramuscularly, 5 or 10 min pre-session) occurring on Thursdays, and baseline sessions (no injections) on Mondays and Wednesdays. Approximately one week of baseline sessions intervened between the end of a series of injections with one drug or drug combination and the start of a series with another. The volume of each injection was .1 ml/100 g body weight. All doses are expressed in terms of the salt of each drug.

RESULTS

Effects of morphine alone and in combination with naloxone. Figure 1 shows the effects of varying doses of morphine alone and in

combination with two doses of naloxone on the overall response rate and percent errors for each subject. When morphine was administered alone, the response rate decreased and the percent errors increased with increasing doses. When morphine was administered in combination with .3 mg/kg of naloxone, the dose-effect curves for both rate and accuracy were shifted to the right, an indication of surmountable antagonism (Fingl & Woodbury, 1975). The shift in the dose-effect curves cannot be attributed to the development of behavioral tolerance to morphine since the effects of morphine alone replicated after the morphine-naloxone combinations were tested (see the unconnected triangles). In the presence of .3 mg/kg of naloxone, it was necessary to increase the dose of morphine to 10 mg/kg (P-788), 17 mg/kg (P-7865), or 30 mg/kg (P-2252) in order to obtain rate-decreasing effects that were comparable to those obtained with morphine alone at 3 mg/kg, 5.6 mg/kg, and 5.6 mg/kg, respectively. As was the case with morphine alone, doses of morphine in combination with .3 mg/kg of naloxone that decreased response rate generally increased the percent errors. This was not the case, however, when morphine was combined with 3 mg/kg of naloxone. Although this dose of naloxone antagonized both the rate-decreasing and error-increasing effects of morphine across a broad range of doses, the antagonism was selective in that naloxone completely blocked the error-increasing effect but not the rate-decreasing effect of the higher doses of morphine. For example, when 30 mg/kg of morphine was administered in combination with 3 mg/kg of naloxone, rate-decreasing effects were consistently produced (both determinations) in P-788 and P-7865. In P-2252, the first determination at this dose combination produced a small rate-decreasing effect; i.e., the minimum value of the range at this dose combination was below the minimum control rate. In contrast to these rate-decreasing effects, the percent errors remained within the control range at the same dose combination (both determinations) in all three subjects. Both the .3 mg/kg and 3 mg/kg doses of naloxone were ineffective when given alone (Figure 4).

Figure 2 shows the pattern of responding during a representative saline session (one that approximated the mean for both overall response rate and overall accuracy) and during

Fig. 1. Effects of varying doses of morphine alone and in combination with two doses of naloxone on the overall response rate and overall accuracy for each pigeon. The points and vertical lines at C indicate the mean and range for 30 control (saline) sessions. The points with vertical lines in the dose-effect curves indicate the mean and range for two determinations; the points without vertical lines indicate either a single determination or, occasionally, an instance in which the range is encompassed by the point. Points for percent errors have been omitted in cases where the overall response rate was virtually zero. The unconnected triangles show a redetermination of the dose-effect data for morphine alone after morphine was tested in combination with naloxone.

several drug sessions for P-7865. As can be seen in the saline record, errors decreased in frequency as the session progressed; i.e., acquisition occurred. After the first 5 min of the session, there were frequent runs of correct responses emitted at a high rate and relatively few errors were made. The runs of correct responses were often preceded by brief pauses. When 3 mg/kg of morphine was administered alone, there was an initial period during which errors were emitted at a high frequency, and then an extended pause occurred. After the pause, errors continued to occur at a higher frequency than during the saline session. When 10 mg/kg of morphine was administered alone, there was no responding for a long period of time, after which errors occurred at a high frequency. There was vir-

tually no acquisition (error reduction) during this 3-hr session. In contrast, when 10 mg/kg of morphine was administered in combination with .3 mg/kg of naloxone, the pattern of responding was similar to that obtained after 3 mg/kg of morphine alone; i.e., there was an initial error-increasing effect followed by an extended pause. Finally, when 10 mg/kg of morphine was administered in combination with 3 mg/kg of naloxone, the pattern of responding was similar to that seen in the saline session.

Figure 3 shows the within-session effects of 17 mg/kg of morphine in combination with .3 mg/kg and 3 mg/kg of naloxone on the responding of P-7865. For comparison, cumulative records for sessions testing these doses of naloxone alone are also shown; the pattern of

Fig. 2. Cumulative records for P-7865 showing the pattern of responding during a representative control session and during sessions preceded by injections of morphine alone (3 mg/kg and 10 mg/kg) and morphine (10 mg/kg) in combination with naloxone (.3 mg/kg and 3 mg/kg). Each record represents a complete session (either 40 reinforcements or 3 hr), except at morphine 3 mg/kg, where only the first two excursions of the response pen are shown. Long periods of no responding (115 min, 128 min, and 77 min) have been omitted at the points indicated. The response pen stepped upward with each correct response and was deflected downward each time the four-response chain was completed. Errors are indicated by the event pen (below each record), which was held down during each timeout.

responding during these sessions was similar to that seen in saline sessions (Figure 2). When 17 mg/kg of morphine was administered in combination with .3 mg/kg of naloxone, there was substantial pausing throughout the session, and when responding did occur, errors were

frequent. In contrast, when this dose of morphine was administered in combination with 3 mg/kg of naloxone, there was no extended pausing during the session, although the rate of correct responding was decreased somewhat; the pattern of acquisition in terms of error

Fig. 3. Cumulative records for P-7865 showing the pattern of responding during sessions preceded by injections of naloxone alone (.3 mg/kg and 3 mg/kg) and morphine (17 mg/kg) in combination with naloxone (.3 mg/kg and 3 mg/kg). Each record represents a complete session. A long period of no responding (130 min) has been omitted at the point indicated. The recording details are the same as in Figure 2.

reduction was similar to that seen with naloxone (or saline) alone. In general, the within-session effects of morphine alone and in combination with naloxone in P-7865 (Figures 2 and 3) were replicated with the other two subjects, although the particular doses of morphine were different.

Effects of phencyclidine, pentobarbital, and d-amphetamine alone and in combination with naloxone. Table 1 shows the effects of phencyclidine, pentobarbital, and d-amphetamine alone and in combination with naloxone on the overall response rate and percent errors for P-788 and P-7865. When phencyc-

lidine (1 mg/kg), pentobarbital (10 or 17 mg/kg), and d-amphetamine (1 or 1.7 mg/kg) were administered alone, each drug produced disruptive effects that were similar to those of morphine (Figure 1), namely, the overall response rate decreased and the percent errors increased. Unlike morphine, however, the disruptive effects of these three drugs were not antagonized by naloxone (3 mg/kg). This was also true at a higher dose of d-amphetamine (5.6 mg/kg), which eliminated all responding during the 3-hr session.

Effects of naloxone alone. Figure 4 shows the effects of varying doses of naloxone alone

Table 1

Effects of phencyclidine, pentobarbital, and *d*-amphetamine alone and in combination with naloxone on the overall response rate and overall accuracy.

Pigeon	Drug	Mg/Kg	Resp/Min	% Errors
P-788	Control range ^a		34.57-51.65	5.21-15.52
	Phencyclidine	1	18.41	27.07
	Phencyclidine	1	17.26	26.19
	+			
	Naloxone	3		
	Pentobarbital	17	7.72	23.73
	Pentobarbital	17	8.03	24.45
	+			
	Naloxone	3		
	<i>d</i> -Amphetamine	1	10.76	18.70
	<i>d</i> -Amphetamine	1	7.06	20.71
	+			
	Naloxone	3		
	<i>d</i> -Amphetamine	5.6	0	---
	<i>d</i> -Amphetamine	5.6	0	---
	+			
	Naloxone	3		
P-7865	Control range ^a		39.96-59.29	8.56-19.75
	Phencyclidine	1	20.40	34.21
	Phencyclidine	1	15.95	30.25
	+			
	Naloxone	3		
	Pentobarbital	10	32.70	33.17
	Pentobarbital	10	26.73	30.06
	+			
	Naloxone	3		
	<i>d</i> -Amphetamine	1.7	16.35	22.48
	<i>d</i> -Amphetamine	1.7	11.67	23.29
	+			
	Naloxone	3		
	<i>d</i> -Amphetamine	5.6	0	---
	<i>d</i> -Amphetamine	5.6	0	---
	+			
	Naloxone	3		

^a Based on 30 saline sessions.

on the overall response rate and percent errors for each subject. Unlike morphine (Figure 1), naloxone had no effect on either behavioral measure at doses ranging from .3 mg/kg to 10 mg/kg. At 17 mg/kg of naloxone, there was a small decrease in the overall rate in P-788 and a larger decrease in P-7865. At 30 mg/kg of naloxone, there was a substantial rate-decreasing effect in all three subjects. In general, these higher doses of naloxone had no effect on overall accuracy, the only exception being a small increase in percent errors at the 30 mg/kg dose in P-2252.

Figure 5 shows the pattern of responding during a representative saline session (one that approximated the mean for both overall re-

sponse rate and overall accuracy) and during two naloxone sessions (17 mg/kg and 30 mg/kg) for P-7865. At both doses of naloxone, there were noticeable periods of pausing during the first part of the session. The 30 mg/kg dose also produced a small decrease in the running rate of correct responding (e.g., compare the second excursion of the response pen under drug vs. saline). Apart from the rate-decreasing effects, the pattern of acquisition in terms of error reduction during the naloxone sessions was similar to that seen during the saline sessions. In general, the within-session effects of naloxone alone in P-7865 were replicated with the other two subjects.

DISCUSSION

In the present study, morphine produced a dose-related decrease in the overall response rate of pigeons in a repeated-acquisition task, where sequential responding on three keys was maintained under an FR schedule. The rate-decreasing effect of morphine was antagonized by doses of naloxone that had no effect when given alone. The morphine dose-effect curve for rate shifted progressively to the right as the dose of naloxone was increased. These results are similar to those previously obtained with morphine and naloxone in pigeons (Downs & Woods, 1976; Dykstra et al., 1974; Goldberg et al., 1976; Kotersky & Harris, 1973; McMillan et al., 1970; Woods et al., 1975), rats

Fig. 4. Effects of varying doses of naloxone alone on the overall response rate and overall accuracy for each pigeon. The points and vertical lines at C indicate the mean and range for 30 control (saline) sessions. Each point in the dose-effect curves represents a single determination, except at 30 mg/kg. At this dose, the mean and range (vertical lines) for two determinations are shown, except where the range is encompassed by the point.

Fig. 5. Cumulative records for P-7865 showing the pattern of responding during a representative control session and during sessions preceded by injections of naloxone alone (17 mg/kg and 30 mg/kg). Each record represents a complete session. The recording details are the same as in Figure 2.

(Carney & Rosecrans, 1978; Leander, 1980), and monkeys (Downs & Woods, 1976; Goldberg et al., 1976; Kelleher & Goldberg, 1979) responding under FR schedules on a single key. The generality of the previous findings is therefore extended by the present research, which involved more complex operant behavior.

Another behavioral measure in the repeated-acquisition task affected by morphine was overall accuracy (percent errors). When morphine was administered alone, the percent errors generally increased with increasing doses. Additionally, doses of morphine that decreased response rate generally increased the percent errors. Similar results have been obtained with rats in a discrete-trial two-choice discrimination procedure (Hernandez & Appel, 1979). The relationship between response rate and accuracy was also found when morphine was

administered in combination with .3 mg/kg of naloxone. At 3 mg/kg, however, naloxone completely blocked the error-increasing effect but not the rate-decreasing effect of the higher doses of morphine. This morphine-naloxone antagonism is in striking contrast to the previously reported interaction between *d*-amphetamine and chlorpromazine in the same repeated-acquisition task (Thompson, 1980). Chlorpromazine, at a dose that was ineffective when given alone, antagonized the rate-decreasing effect of *d*-amphetamine, but potentiated *d*-amphetamine's error-increasing effect.

The selective nature of the obtained morphine-naloxone antagonism might be questioned on the following grounds. Figure 1 indicates that when morphine was administered alone, percent errors increased substantially only when response rate was markedly decreased. The response rate after the mor-

phine-naloxone (3 mg/kg) combination was never reduced as much as the response rate after morphine alone. Had that been the case, it could be argued that an error-increasing effect would have occurred. Although this argument cannot be refuted on the basis of the present data, there are other aspects of the data in Figure 1 that support the conclusion that the morphine-naloxone antagonism was selective in all three subjects. In P-788, 30 mg/kg of morphine in combination with 3 mg/kg of naloxone produced a greater rate-decreasing effect than that obtained at 1.7 mg/kg of morphine alone. Nevertheless, there was no error-increasing effect after the morphine-naloxone combination, whereas the error levels after 1.7 mg/kg of morphine alone were consistently above the control range. In P-7865, the same morphine-naloxone combination (both determinations) produced a very large decrease in response rate but the percent errors remained within the control range. The decrease in rate was comparable to the rate-decreasing effects obtained at 3 and 5.6 mg/kg of morphine alone in this subject, yet both of these doses produced error-increasing effects. In P-2252, the first determination at 1 mg/kg of morphine alone and the first determination at 30 mg/kg of morphine in combination with 3 mg/kg of naloxone both produced a small rate-decreasing effect; i.e., the minimum value of the range in each case was below the minimum control rate. However, 1 mg/kg of morphine alone produced a small but consistent error-increasing effect in this subject, whereas the morphine-naloxone combination had no effect on errors.

The present research also probed the specificity of the obtained morphine-naloxone antagonism by testing *d*-amphetamine, pentobarbital, and phencyclidine alone and in combination with naloxone. When administered alone, these drugs were similar to morphine in that each decreased response rate and increased percent errors. This finding replicates the results obtained with *d*-amphetamine (e.g., Thompson & Moerschbaeher, 1979), pentobarbital (Harting & McMillan, 1976; Moerschbaeher & Thompson, 1980b), and phencyclidine (Moerschbaeher & Thompson, 1980a, 1980b) in previous repeated-acquisition studies. Unlike morphine, however, when these drugs were administered in combination with 3 mg/kg of naloxone, their disruptive effects

were not antagonized. This finding complements the results reported by Holtzman (1979). In that study, naloxone failed to modify the effects of two nonopiate drugs, *d*-amphetamine and chlorpromazine, on avoidance behavior in squirrel monkeys. The possibility that naloxone might antagonize the behavioral effects of *d*-amphetamine, pentobarbital, or phencyclidine in the repeated-acquisition task if other doses were tested remains to be investigated.

The present finding that 30 mg/kg of naloxone alone produced substantial rate-decreasing effects is consistent with previous reports that high doses of naloxone affect the responding of pigeons and monkeys under FR schedules in a manner similar to morphine (Downs & Woods, 1976; Goldberg et al., 1976; Kelleher & Goldberg, 1979; McMillan et al., 1970). Unlike morphine, however, the rate-decreasing effects of naloxone were generally not accompanied by error-increasing effects. This was true even in cases where naloxone decreased response rate to a greater extent than morphine (e.g., in P-788, compare the effects of 30 mg/kg of naloxone in Figure 4 to the effects of 1.7 mg/kg of morphine in Figure 1). It is interesting that 30 mg/kg of naloxone alone produced selective effects that were similar to those obtained when 30 mg/kg of morphine was administered in combination with 3 mg/kg of naloxone (compare Figures 1 and 4). The possibility exists, of course, that doses of naloxone higher than 30 mg/kg would have disrupted accuracy. Such doses were not tested in the present study because it had previously been observed that 56 mg/kg of naloxone produced gross disturbances such as severe tremors and vomiting in pigeons (Goldberg et al., 1976). Although the rate-decreasing effects of naloxone alone are noteworthy, it should be emphasized that naloxone did function as a morphine antagonist at far lower doses (.3 and 3 mg/kg).

In summary, like the Thompson (1980) study of *d*-amphetamine-chlorpromazine combinations, the present study of morphine-naloxone combinations examined a classic drug antagonism in behavioral pharmacology. In both studies, a complex behavioral baseline (repeated acquisition) was used and a selective, albeit different, antagonism was obtained. Chlorpromazine antagonized the rate-decreasing but not the error-increasing effects of *d*-amphetamine, whereas naloxone (3 mg/kg)

completely blocked the error-increasing but not the rate-decreasing effects of morphine. It is important to note that neither of the two types of selective antagonism could have been predicted on the basis of results obtained with less complex schedule-controlled behavior (e.g., Davis, 1965; McMillan, 1974). The selective nature of the antagonism in both cases also raises questions about the putative neurotransmitter-receptor interactions involved.

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