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Pentazocine, Cyclazocine, and Nalorphine as Discriminative Stimuli

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Abstract. Pentazocine, cyclazocine, and nalorphine are narcotic antagonists that also have analgesic activity of their own. The present investigation compared the stimulus properties of these three drugs in rats. Each drug was used as a discriminative stimulus for a separate group of rats. Depression of one lever resulted in food reinforcement following the administration of drug, and the opposite lever was reinforced after saline. Each drug readily acquired control of discriminated responding. The specific narcotic antagonist, naloxone, which antagonizes many of the effects of pentazocine, cyclazocine, and nalorphine, also antagonized the discrimination of these drugs. Stimulus generalization tests to each other narcotic antagonist, *d*-amphetamine, morphine, and LSD, showed that each narcotic antagonist has highly specific stimulus properties. Clear generalization occurred only to pentazocine and cyclazocine in the nalorphine-saline group, but neither cyclazocine nor pentazocine generalized to nalorphine.

Key words: Drug discrimination – Narcotic antagonist – Pentazocine – Cyclazocine – Nalorphine – Naloxone

A large body of literature indicates that a variety of centrally acting drugs can serve as discriminative stimuli for laboratory animals (see reviews by Overton, 1971; Barry, 1974). The list of centrally acting drugs that have been used as discriminative stimuli is still growing. Narcotic analgesics are among the more recent additions, the first report being morphine in 1971 (Hill et al.).

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In humans morphine produces subjective effects that are generally perceived as strongly pleasant. Morphine has a high liability for abuse, as do other narcotic analgesics that produce morphinelike subjective effects (Fraser et al., 1961). Some narcotic antagonist, besides having the ability of antagonizing the pharmacological effects of morphine and other narcotic analgesics, also have narcotic analgesic activity of their own. Certain of these narcotic antagonist analgesics produce subjective effects dissimilar to those of morphine and have a low abuse potential. Examples are nalorphine, which produces subjective effects characterized by dysphoria and psychotomimetic effects (Lasagna and Beecher, 1954), and cyclazocine, which produces similar subjective effects (Haertzen, 1970). Although effective analgesics, the unpleasant subjective effects of nalorphine and cyclazocine diminish the clinical utility of these drugs. Pentazocine is an antagonist analgesic that produces subjective effects that more closely resemble those of morphine (Jasinski et al., 1970).

The present investigation compared the stimulus properties of three narcotic antagonist analgesics, pentazocine, cyclazocine, and nalorphine. Of these three drugs, only pentazocine has been reported to be an effective discriminative stimulus (Kuhn et al., 1976). However, all three drugs have been tested for their ability to substitute for morphine in animals previously trained to discriminate morphine from saline (Hirschhorn and Rosecrans, 1976; Shannon and Holtzman, 1976). In both studies pentazocine, but not the others, could substitute for morphine. In addition, cyclazocine, but not the others, could substitute for lysergic acid diethylamide (LSD) in animals previously trained to discriminate LSD from saline, although the generalization was only partial (Hirschhorn and Rosecrans, 1976).

The specific objectives of the present investigation were to determine (1) whether cyclazocine, nalor-

phine, and pentazocine can serve as discriminative stimuli, as previously reported for pentazocine in a different procedure, (2) whether the stimulus properties of these three drugs would generalize to each other, *d*-amphetamine, morphine, and LSD, and (3) whether naloxone, a specific narcotic antagonist (Blumberg et al., 1966), would antagonize the stimulus properties of these drugs. Although naloxone reportedly antagonizes the stimulus properties of pentazocine (Kuhn et al., 1976), these investigators tested only a single dose of naloxone and obtained only a partial antagonism.

MATERIALS AND METHODS

Subjects. The subjects were 21 cesaerian delivered Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) approximately 6 weeks of age when obtained from the supplier. They were housed in individual home cages where water was freely available and exposed to a 12-h light-dark cycle. They were maintained at approximately 85% of their free-feeding weights with adjusted feedings of a commercial rat chow following each experimental session (mean experimental weight = 416 g).

Behavioral Methods. The training and testing procedures were similar to those previously described (Hirschhorn and Winter, 1971). The apparatus was two standard operant test chambers (Lehigh Valley Electronics) each housed in a larger sound-insulated and light-proof box with an exhaust fan. Conventional electro-mechanical programming equipment was used to control and record the sessions.

The rats were divided into three equal groups: (1) pentazocine (10 mg/kg)-saline, (2) nalorphine (20 mg/kg)-saline, and (3) cyclazocine (0.5 mg/kg)-saline. Training doses were selected on the basis of observations in previous stimulus generalization experiments (Hirschhorn and Rosecrans, 1976), to sufficiently serve as stimuli without causing obvious behavioral impairment. The rats were first trained to press both levers to obtain reinforcement (45 mg standard formula Noyes pellets), and then discrimination training began. Each daily session was preceded by one of two treatments. Following the injection of the assigned narcotic antagonist, depression of one lever resulted in the delivery of reinforcement. When saline was given, responses on the opposite lever were reinforced. For four animals in each group, the right lever was reinforced after drug and the left lever was reinforced following saline; these conditions were reversed for the other three animals. Experimental sessions lasted 15 min. In the first four sessions drug and saline administration were alternated daily and each correct bar press resulted in delivery of reinforcement. Subsequent sessions began with an initial 2.5-min period during which no responses were reinforced, followed by a 12.5-min period during which a variable interval of 15 s (VI-15 s) schedule was in effect. Discrimination accuracy was calculated on the basis of responses during the initial unreinforced 2.5-min period. During these sessions, 2 days of drug treatment were followed by 2 days of saline treatment (double alternation).

Stimulus generalization and drug interaction experiments were performed in test sessions. These were 2.5-min sessions in which no responses were reinforced. They were interposed among the double alternation sequence of the regular training sessions beginning after the first 36 discrimination training sessions. At least one, usually three, regular training sessions were given between any two test sessions. When an animal made fewer than three responses during a test session, the test sessions was extended for an additional 25 min. If fewer than three responses were made for the total 5 min, the session was excluded from the calculations of lever choices. In general, drugs were tested in increasing doses until stimulus generalization was obtained or until a severely depressed response rate prevented testing a higher dose. Stimulus generalization was considered to have occurred when the rats made at least as high a percentage of their total responses on the drug-correct lever as when given the training drug.

Drugs. The drugs used in these experiments follow: pentazocine base, cyclazocine base, nalorphine hydrochloride, morphine sulfate, *d*-amphetamine sulfate, naloxone hydrochloride, and lysergic acid diethylamide tartrate. All drug doses are expressed in terms of these bases and salts. Pentazocine and cyclazocine were dissolved in 1.0 N hydrochloric acid and the pH was adjusted with 0.5 N sodium hydroxide to between 5.0 and 6.0. The other drugs were dissolved in 0.9% sodium chloride. All drugs were injected s.c. in a volume of 1 ml/kg body weight, 30 min prior to the start of the experimental session. When two drugs were administered on the same day, in the naloxone antagonism experiments, injections were made in rapid succession into different s.c. sites.

RESULTS

In all three groups of rats, discriminated responding was evident after only two to four sessions with each training treatment. By the end of the 36 discrimination training sessions preceding stimulus generalization tests, a discrimination accuracy of at least 80–90% was attained. During the last eight of these sessions (sessions 28–36), the pentazocine-saline rats made a mean of 93% of their total responses in the initial 2.5-min nonreinforced period on the pentazocine lever in sessions preceded by the injection of pentazocine, and 10% of their responses on the same lever on saline days. The cyclazocine-saline rats responded 81% on the cyclazocine lever following cyclazocine and 15% on this lever on saline days, and the nalorphine-saline rats, 89% on the nalorphine lever after nalorphine and 11% following saline. With the exception of one in the nalorphine-saline group, all of the rats reached this high level of discriminated responding and continued to respond with high accuracy throughout the experiments. The one nalorphine-saline animal did not maintain stable discriminated responding and was eliminated from the study. The rate of responding varied among animals within each group, but the rates under the two training conditions in each group were similar. Responses/min on both levers combined in the first 2.5 min for sessions 28–36 follow: pentazocine 27, saline 32; cyclazocine 57, saline 46; nalorphine 12, and saline 13. Although no responses were reinforced in the first 2.5 min of each daily session (training and test) throughout these experiments, the response rate in this period remained high even in the final stages of the experiments after over 100 regular training sessions. The mean responses/min on both levers combined under both training conditions in the first 2.5 min of the final four training

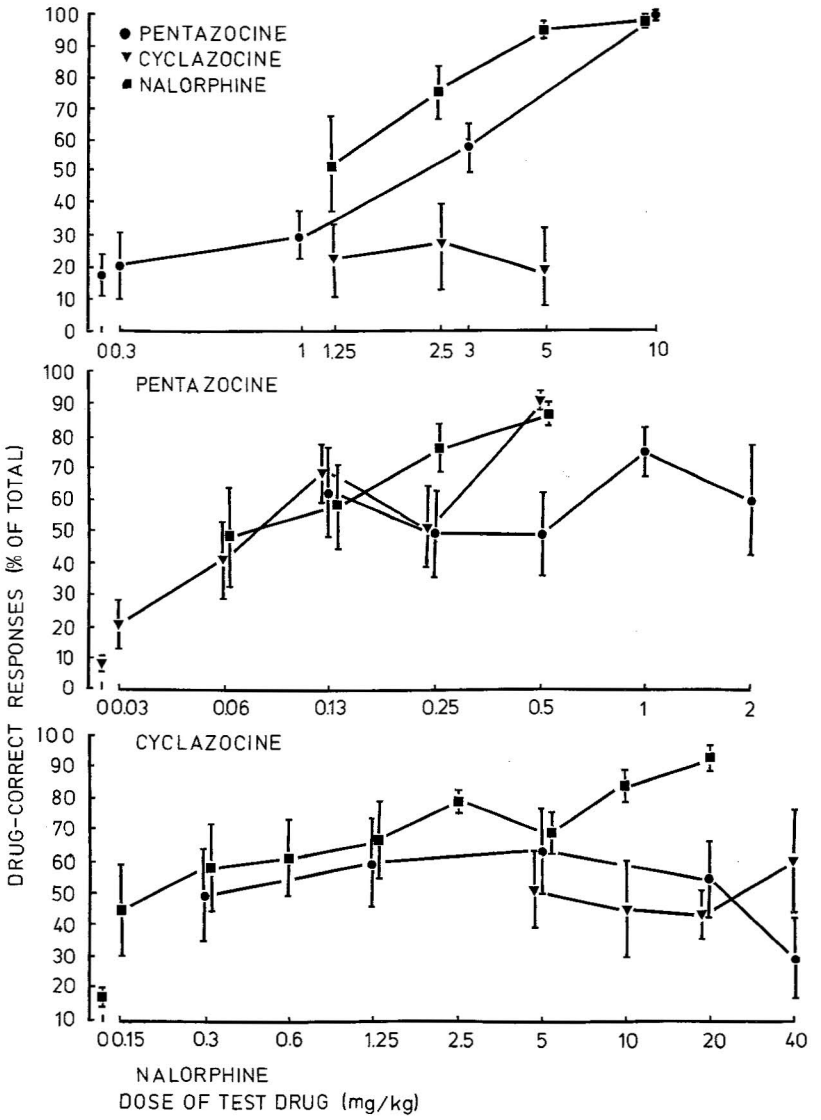

Fig. 1
Generalization tests with pentazocine, cyclazocine, and nalorphine. Three different groups of rats were trained to discriminate pentazocine (10 mg/kg), cyclazocine (0.5 mg/kg), and nalorphine (20 mg/kg) from saline. Then, test sessions of 2.5 min duration, during which no responses were reinforced, were interposed among the regular training sessions. The rats received various doses of pentazocine, cyclazocine, and nalorphine in test sessions. *Ordinate:* number of responses on the drug-correct lever expressed as a percentage of total responses. *Abscissa:* dose of test drug plotted on a log scale. Each point is the mean of at least one determination in each of 7 animals ± SEM or 6 animals ± SEM for the nalorphine group. The points at zero (saline) and the training dose of drug for each group represent the means of regular saline and drug training sessions during the period of testing lower doses of the training drug (number of sessions under each condition for each group: pentazocine, 6; cyclazocine, 6; nalorphine, 10)

sessions follow: pentazocine group 28, cyclazocine group 33, and nalorphine group 25.

During the stimulus generalization tests and the naloxone experiment, all groups maintained stable discriminated responding. The mean percent drug-correct responses following each training treatment in the first 2.5 min of the regular training sessions during this period follow: pentazocine 95, saline 8; cyclazocine 87, saline 5; and nalorphine 92, saline 16.

The results of stimulus generalization tests with other drugs are shown in Figures 1 and 2. For all three drugs the percentage of responses on the drug-correct lever varies directly with the dose of drug in a typical dose-effect relationship (Fig. 1). For pentazocine and cyclazocine the decrease in drug-correct responding with decreasing dosage is rapid. Nalorphine has a much shallower dose-response relationship; i.e., relatively small changes in nalorphine discrimination result from relatively large changes in dosage.

Stimulus generalization to a test drug is unambiguous when the test drug produces an orderly dose-related increase in drug-correct responses up to as high a percentage of the total responses as produced by the training drug. There are only two clear stimulus generalizations in these results. These were pentazocine and cyclazocine in the nalorphine group (Fig. 1), where the nalorphine-correct responses (97% for 10 mg/kg of pentazocine and 87% for 0.5 mg/kg of cyclazocine) are similar to the 92% obtained with 20 mg/kg of nalorphine. Each of the individual animals in both cases made a high percentage of its total responses on the nalorphine lever.

In some instances one or more doses of a test drug yielded a majority of responses on the drug-correct

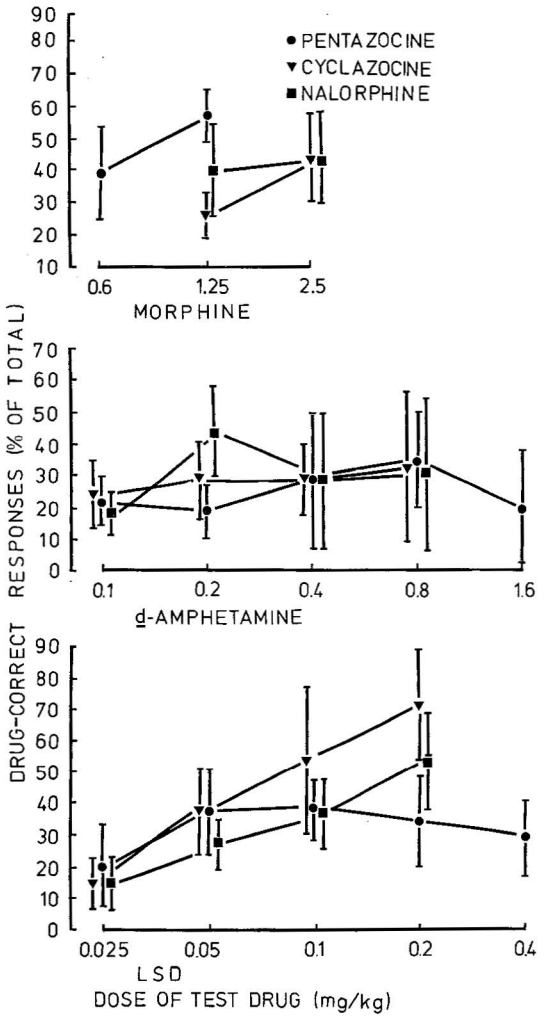

Fig. 2. Generalization tests with morphine, *d*-amphetamine, and LSD. The three groups of rats trained to discriminate pentazocine, cyclazocine, and nalorphine from saline were given various doses of morphine, *d*-amphetamine, and LSD in test sessions. Other details are as in Figure 1

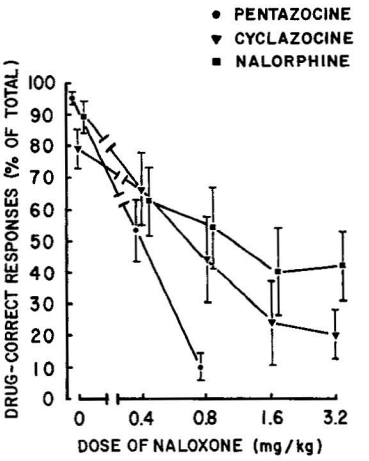

Fig. 3. Effect of naloxone on the discrimination of pentazocine, cyclazocine, and nalorphine. The three groups of rats trained to discriminate pentazocine, cyclazocine, and nalorphine from saline were given various doses of naloxone hydrochloride in combination with the respective training drug in test sessions. Other details are as in Figure 1

lever, but the percentage was lower than that produced by the training drug. Cyclazocine at 1 mg/kg produced 75% pentazocine-correct responses in the pentazocine group (Fig. 1). A lower dose of 0.5 mg/kg should have been sufficient to produce stimulus generalization, since this is an effective stimulus dose (cyclazocine group), but yielded only 49% pentazocine-correct responding. A higher dose (2.0 mg/kg) resulted in a very low rate of responding (2.8/min) and the five animals responding made all of their responses on either the pentazocine lever (three animals) or saline lever (two animals). In the cyclazocine animals, 0.20 mg/kg of LSD produced 70% cyclazocine-correct responses (Fig. 2) but also a low rate of responding (2.0/min). Again, a lower dose (0.10 mg/kg) should have been sufficient to produce generalization (Hirschhorn and Rosecrans, 1976). A higher dose of LSD (0.40 mg/kg) virtually abolished responding (0.2/min). In all of the other stimulus generalization tests the rats responded either mostly on the saline lever or they divided their responses approximately equally between the saline and the drug levers.

In most of the stimulus generalization tests the rate of responding was supressed by the highest dose tested. Since the dose of test drugs was increased until either stimulus generalization occurred or responding was markedly suppressed, this result is not surprising for those drugs in which relatively high doses were tested (cyclazocine, nalorphine, *d*-amphetamine, and LSD). However, some drugs markedly suppressed the response rate at doses lower than might have been anticipated. Pentazocine at 10 mg/kg reduced the mean responses/min for all seven rats of the cyclazocine group to 5.6, abolished responding for four animals, and reduced the mean rate per minute in the nalorphine group to 4.3 with one animal not responding. Morphine reduced response rate in all three groups at relatively low doses. In the pentazocine group the mean responses/min for all seven animals decreased from 8.5 with one animal not responding at 0.6 mg/kg to 0.8 with four animals not responding at 2.5 mg/kg. In the cyclazocine group the rate per minute was 9.3 with one animal not responding at 1.25 mg/kg and 4.4 with three animals failing to respond at 2.5 mg/kg, and in the nalorphine group the rate decreased from 12.3 with one animal not responding at 1.25 mg/kg to 1.3 with four animals not responding at 5.0 mg/kg.

The effect of naloxone on the discrimination of pentazocine, cyclazocine, and nalorphine is shown in Figure 3. For each drug the percentage of drug-correct responses was lower when naloxone was given with the training drug than when the training drug was given alone. In all cases this effect is directly proportional to the dose of naloxone. Although the curve is steepest for pentazocine and shallowest for nalorphine, this may simply reflect the relative steepness of the discrimination dose-response curves as presented in Fig. 1. Doses of naloxone that blocked discrimination produced saline-appropriate responding when given alone: pentazocine group, 0.8 mg/kg, 20% pentazocine-correct responses; cyclazocine group, 3.2 mg/kg, 36% cyclazocine-correct responses; nalorphine group, 3.2 mg/kg, 31% nalorphine-correct responses.

DISCUSSION

The present results add cyclazocine and nalorphine to the list of drugs that can serve as discriminative stimuli and confirm the recent report that pentazocine can serve as a discriminative stimulus (Kuhn et al., 1976). The rate of acquisition and the final accuracy of discrimination for pentazocine, caclazocine, and nalorphine are similar to those observed with several other drugs tested in a similar procedure (e.g., Hirschhorn and Winter, 1971; Hirschhorn and Rosecrans, 1974). As with other drugs in previous studies, the accuracy of discrimination was related to dosage with all three drugs in the present study. The dose-response curve obtained with nalorphine is considerably more shallow than that obtained for any other drug we have studied. An explanation for this is not at hand. However, this phenomenon does not seem to be unique for the stimulus properties of nalorphine. Extremely shallow dose-response relationships with nalorphine have also been reported for increase in locomotor activity and avoidance responding (Holtzman, 1974).

A general limitation of drug discrimination research is that the specific discriminative effect of a drug is not usually known (Barry, 1974). Nevertheless, by the use of stimulus generalization tests to other drugs and specific antagonists it is possible to characterize drug stimuli to some extent. The present results indicate that each drug has highly specific stimulus properties. In stimulus generalization tests with each of the three groups of rats to pentazocine, cyclazocine, nalorphine, morphine, *d*-amphetamine, and LSD, only two clear stimulus generalizations occurred, to pentazocine and cyclazocine in the nalorphine group. Even in these two cases the reverse generalization tests, from pentazocine and cyclazocine to nalorphine, did not result in generalization but rather in approximately equal responding on both levers. The stimulus properties of each of these drugs, then, are unique, but the generalization from nalorphine to pentazocine and cylcazocine indicates that there is some overlap in these properties. No generalization occurred to *d*-amphetamine, although pentazocine (Holtzman and Jewett, 1972), cyclazocine (Holtzman and Jewett, 1973), and nalorphine (Holtzman, 1974), in the dose ranges of the present study, produce increased locomotor activity. In the present investigation, this effect was not objectively measured but was observed, especially with pentazocine and cyclazocine. Increased locomotor activity, therefore, is unlikely to be the basis for the discrimination of these drugs. One characteristic that all three drug stimuli have in common is that they are all antagonized by naloxone. This characteristic is shared with most effects of these drugs in animals and humans (e.g., Holtzman, 1974; Holtzman and Jewett, 1973; Jasinski et al., 1968; Fink et al., 1973), as well as with most effects of all narcotic analgesics.

Some of the present results are relevant to those of Hirschhorn and Rosecrans (1976), in which pentazocine, cyclazocine, and nalorphine were tested for stimulus generalization in rats previously trained to discriminate morphine from saline and LSD from saline. In that study generalization was observed from morphine to pentazocine and from LSD to cyclazocine, although this latter generalization was only partial. The generalization from pentazocine to morphine in the present investigation was inconclusive because of the unexpected decrease in response rate in all three groups of rats with doses lower than those that have been demonstrated to be effective stimuli. A partial generalization similar to that which occurred from LSD to cyclazocine was observed in the present study from cyclazocine to LSD, again indicating that these two drugs are similar but not interchangeable in terms of stimulus properties. Because different results were obtained in generalization tests from LSD to nalorphine and cyclazocine in the earlier investigation, we suggested that nalorphine and cyclazocine have differentiable stimulus properties. The direct comparisons of these two drugs in the present study support this suggestion. In agreement with these results, Gilbert and Martin (1976) have recently reported that nalorphine only partially suppresses cyclazocine withdrawal in the dog and is, therefore, only a partial agonist compared with cyclazocine.

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