

DISCRIMINATIVE STIMULUS, ANTAGONIST, AND RATE-DECREASING EFFECTS OF CYCLORPHAN:  
MULTIPLE MODES OF ACTION<sup>1</sup>

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Summary

The discriminative effects of cyclorphan were studied in pigeons trained to discriminate 0.32 mg/kg ethylketazocine, 1.8 mg/kg cyclazocine, or 32 mg/kg naltrexone from saline. A fourth group of pigeons was administered 100 mg/kg/day morphine and trained to discriminate 0.1 mg/kg naltrexone from saline. Cyclorphan produced dose-related ethylketazocine-appropriate responding that reached a maximum of 83% of the total session responses at 0.3 mg/kg. Higher cyclorphan doses produced less ethylketazocine-appropriate responding. In pigeons trained to discriminate cyclazocine from saline, maximum drug-appropriate responding of greater than 90% occurred at 5.6-10.0 mg/kg cyclorphan. In narcotic-naive pigeons trained to discriminate 32 mg/kg naltrexone from saline, cyclorphan produced a maximum of less than 50% drug-appropriate responding. In contrast, in pigeons chronically administered morphine and trained to discriminate 0.1 mg/kg naltrexone from saline, 1.0 mg/kg cyclorphan resulted in 100% drug-appropriate responding. In pigeons responding under a multiple fixed-interval, fixed-ratio schedule of food delivery, cyclorphan produced a complete dose-related reversal of the rate-decreasing effects of 10 mg/kg morphine, the maximally effective antagonist doses being 1.0-3.2 mg/kg. Higher cyclorphan doses (10 mg/kg) resulted in response rate decreases that were not reversed by naloxone (1 mg/kg). Thus, cyclorphan has discriminative effects that are similar to those of both ethylketazocine and, at 20-fold higher doses, cyclazocine. In addition, in morphine-treated pigeons, cyclorphan, across the same range of doses that produce ethylketazocine-appropriate responding, has discriminative effects that are similar to those of naltrexone, an effect that is probably related to the antagonist action of the drug.

Cyclorphan ((-)-3-hydroxy-N-cyclopropylmethyl-morphinan) is a mixed narcotic agonist-antagonist which has also been reported to produce psychotomimetic activity in man (1). As an analgesic in man, cyclorphan is about 60 times more

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potent than morphine (1); as an antagonist of the effects of morphine and meperidine in animals, cyclorphan is 3-5 times more potent than nalorphine and about 1.5 times less potent than cyclazocine (2), an N-cyclopropylmethyl derivative in the benzomorphan series. In contrast to the well-described analgesic and antagonist effects of cyclorphan, the psychotomimetic effects of the drug in man are not well documented (see e.g., 1,2,3).

In unanesthetized dogs and monkeys, cyclorphan produces behavioral effects similar to those produced by cyclazocine. These include: sedation, loss of postural reflexes, ataxia, and muscular incoordination (cf. 2,4,5). Like cyclazocine, cyclorphan has little or no effect on response to painful stimuli in a variety of analgesic tests in rats, dogs, or monkeys (e.g., 2,5). However, both are potent analgesics in man (1). Thus, in many respects, the pharmacology of cyclorphan resembles that of cyclazocine, a compound with well-documented sedative, dysphoric, and psychotomimetic effects in man (6,7).

The discriminative effects of cyclorphan in laboratory animals have yet to be fully characterized, although in the rhesus monkey, both cyclorphan and cyclazocine have discriminative effects in common with ethylketazocine (ethylketocyclazocine), the 5-ethyl, 8-keto analogue of cyclazocine (8). Cyclazocine, on the other hand, has been more extensively studied in a number of animal species (9-13), and has been shown in rats and pigeons to have discriminative effects similar to those of phencyclidine and ketamine (12-14). Also, since these effects of cyclazocine are relatively resistant to blockade by narcotic antagonists (12-16), it has been suggested that the discriminative effects of cyclazocine in these species include an important non-opiate component (12,13), and that these effects of the drug may be analogous to the psychotomimetic and sedative effects that are known to be produced by cyclazocine and phencyclidine in man (6,7,17).

Since cyclorphan appears to have a complex set of different pharmacological actions in man, it was of interest to characterize more completely the discriminative stimulus effects of the drug. Thus, cyclorphan was administered to separate groups of pigeons trained to discriminate cyclazocine, ethylketazocine, or naltrexone (32 mg/kg) from saline. In addition, cyclorphan was tested in pigeons that were chronically administered morphine, 100 mg/kg/day, and trained to discriminate 0.1 mg/kg naltrexone from saline. In pigeons, cyclazocine has discriminative effects that are similar to those of phencyclidine (13), but which differ from those of morphine (18). In contrast, ethylketazocine produces discriminative effects in the pigeon which are similar to those of morphine (18). The effects of high doses of naltrexone in narcotic-naive pigeons represent yet another distinct set of discriminative effects in that neither ethylketazocine nor cyclazocine results in naltrexone-appropriate responding (19,20, unpublished observations). However, in pigeons that are chronically treated with morphine (100 mg/kg/day) and trained to discriminate low doses of naltrexone from saline, cyclazocine and a number of other narcotic antagonists produce naltrexone-appropriate responding (20), whereas ethylketazocine, which is devoid of any narcotic antagonist activity (21,22), does not produce naltrexone-like discriminative effects (unpublished observations). Thus, the discriminative effects of cyclorphan were assessed for their similarity to four very different sets of discriminative stimuli. In addition, the effects of cyclorphan, administered alone or in combination with morphine or naloxone, were studied in pigeons responding under a multiple fixed-interval, fixed-ratio schedule of food presentation. Cyclazocine has previously been shown to be a potent antagonist of the rate-decreasing effects of morphine in the pigeon, but the response rate-decreasing effects of cyclazocine are not reversed by naloxone (23).

### Methods

Subjects. Sixteen White Carneaux pigeons (Veterinary Animal Science Unit, Bowman-Gray Medical School, Winston-Salem, NC) were reduced to approximately 80% of their free-feeding weights. Sufficient mixed grain and Purina Pigeon Checkers supplemented the mixed grain earned during experimental sessions to maintain these reduced weights. Water and grit were freely available in each pigeon's home cage. Results of previous experiments in some of these pigeons are described elsewhere (13,24).

Apparatus. Each experimental chamber contained two translucent response keys (2 cm diameter and 5 cm apart), located 25 cm above the floor of the chamber, either one of which or both could be transilluminated with red or green 7-W lights. Mixed grain from a hopper could be made available through a rectangular opening located directly below the keys and approximately 10 cm above the chamber floor. A white light illuminated the hopper during food delivery. Each chamber was ventilated by an exhaust fan, and white noise was present to mask extraneous sounds. A more detailed description of the experimental chambers has been reported elsewhere (18). Programming, recording, and data collection were accomplished with a Texas Instruments 960A computer and cumulative recorders.

Drug discrimination studies. Each of 12 pigeons was trained to peck one of two red-lit keys by reinforcing successive approximations of the key-peck response with 4 sec access to mixed grain. Following the acquisition of the response, the appropriate key to be pecked to produce grain was determined by the injection the pigeon received before the session, i.e., drug (left key) or saline (right key). Across sessions, the number of consecutive responses required for grain delivery was increased to 20. Responses on the inappropriate key reset the response requirement on the appropriate key. Sessions ended after 32 deliveries of mixed grain or 1 hr, whichever occurred first.

Training sessions were usually conducted six days per week. Initially, drug and saline injections alternated from one session to the next. Drug discriminations were established with either ethylketazocine (0.32 mg/kg, 4 pigeons), cyclazocine (1.8 mg/kg, 2 pigeons), or naltrexone (32 mg/kg, 3 pigeons). In addition, a fourth group of 3 pigeons was chronically administered morphine, 100 mg/kg/day, approximately 8 hr before the session, and trained to discriminate 0.1 mg/kg naltrexone from saline. In these pigeons, 100 mg/kg morphine was administered daily for approximately 1 week before the start of drug discrimination training and continued to be administered throughout the course of the experiment. In the ethylketazocine-trained pigeons, ethylketazocine or saline was injected 5 min before the session. In each of the other pigeons, the training drug or saline was administered 10 min before the session.

Training continued in each pigeon until the pigeon met the criteria of emitting fewer than 40 responses before the first grain presentation of the session and of distributing at least 90% of the total session responses on the appropriate key. Each pigeon was required to meet these criteria for five consecutive sessions during which saline and drug injections alternated, and then on four consecutive sessions prior to which drug or saline was administered in a double alternation sequence (e.g., saline, saline, cyclazocine, cyclazocine).

Once these criteria were met, test sessions were conducted in each bird with a range of doses of cyclorphan. Cyclorphan was always injected 10 min before the session. Throughout an entire test session, 20 consecutive responses on either the drug-appropriate or saline-appropriate key produced access to grain; in all other respects, test sessions were identical to

training sessions. In general, test sessions alternated during the week with training sessions. If during a training session an animal failed to meet the training criteria, further testing was postponed until the criteria were met on at least two consecutive training sessions.

Cyclorphan effects on schedule-controlled responding. The effects of cyclorphan, administered alone or in combination with morphine (10 mg/kg) or naloxone (1 mg/kg), were assessed in 4 pigeons responding under a multiple fixed-interval 5-min (FI 5), fixed-ratio 30-response (FR 30) schedule of food delivery (4-sec access to mixed grain). In these studies only a single key was lit. When the key was transilluminated by a green light, the first response after 5 min resulted in food delivery (FI 5); alternately, 30 responses when the key was lit red also resulted in food delivery (FR 30). A 1-min limited-hold was in effect for both components of the schedule; if a response was not emitted within 1 min of the end of the FI or if 30 responses were not emitted within 1 min of the onset of the FR component, the schedule advanced into the next component. Each session consisted of 10 FI and 10 FR components presented in alternation. Sessions were conducted 5 days per week, Monday through Friday. Drugs or saline were administered immediately before the start of the session, no more frequently than twice per week, usually on Tuesdays and Fridays.

Data analyses. Data for the drug discrimination studies are presented as the average number of responses emitted on the drug-appropriate key throughout the session, expressed as a percentage of the total session responses. In addition, the overall rate of responding on both keys after an injection of cyclorphan is presented as a percentage of the rate of responding during the saline training sessions that immediately preceded test sessions.

Results of the studies of drug effects on schedule-controlled responding are presented as response rates during the FI and FR components of the schedule, expressed as a percentage of the rate of responding in these components during sessions prior to which saline was administered. In addition, the effects of the drugs on the fixed-interval quarter-life, which provides a measure of the temporal pattern of responding within the interval (see e.g., 25), are also expressed as a percentage of the quarter-life values for saline control sessions.

Drugs. Cyclorphan hydrochloride (kindly provided by Dr. M. D. Gates, Univ. of Rochester, Rochester, NY and Hoffmann-La Roche Inc., Nutley, NJ), morphine sulfate (Mallinckrodt Chemical Works, St. Louis, MO), naloxone hydrochloride, and naltrexone hydrochloride (both generously supplied by Endo Laboratories, Garden City, NY) were dissolved in 0.9% sterile saline. Ethylketazocine methane sulfonate and cyclazocine base (kindly supplied by Dr. W. Michne, Sterling-Winthrop Research Institute, Rensselaer, NY) were dissolved in sterile water to which a small amount of lactic acid was added; sodium hydroxide was then used to adjust the pH of these solutions to above 4. Drug doses refer to the forms described. Injections of all drugs and saline were made into the pectoral muscle in a volume of 1 ml/kg. The order of cyclorphan doses administered and drug combinations was unsystematic. When drug combinations were studied, an injection of one drug was made into the pectoral muscle on one side of the pigeon, followed immediately by an injection into the muscle on the opposite side.

## Results

Drug Discrimination Studies. Each of the 12 pigeons in these experiments acquired a drug-saline discrimination. The average number of sessions to reach criterion level performance in each group of pigeons was: 38 for pigeons

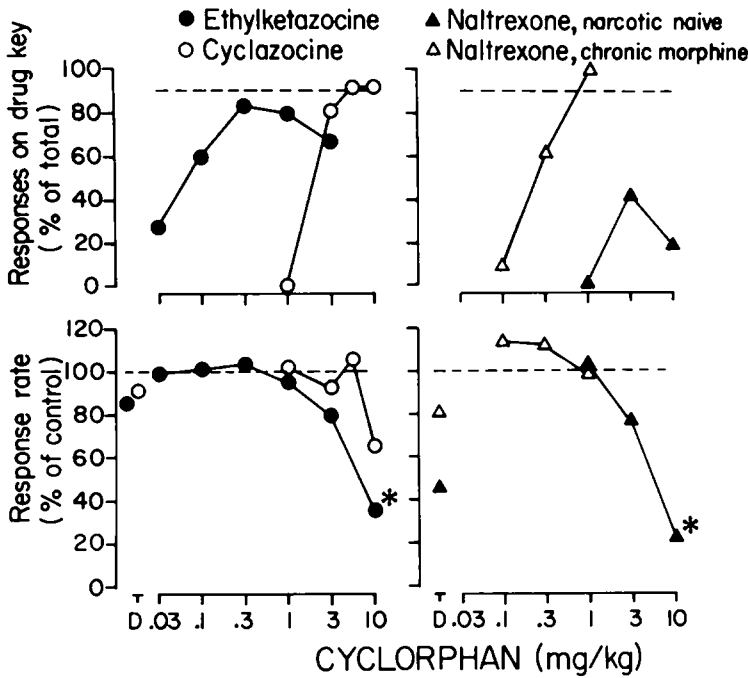


FIG. 1

Discriminative stimulus and rate-decreasing effects of cyclorphan. Upper panel ordinates: average number of responses emitted on the drug-appropriate key, expressed as a percentage of the total session responses. Lower panel ordinates: average rate of responding following drug injection, expressed as a percentage of the rate of responding on saline training sessions. Response rates following saline injections ranged in individual pigeons from 1.32 to 3.89 responses/sec. Abscissae: cyclorphan dose, mg/kg. Each point is the average of 4 (ethylketazocine-trained), 2 (cyclazocine-trained), 3 (naltrexone-trained, narcotic-naive), or 3 (naltrexone-trained, morphine-treated) pigeons, except as noted below. Training conditions are indicated by different symbols in the key to the figure. Points at D in the lower panels indicate the rate of responding following the administration of the training drugs. Refer to the text for additional information on the training conditions. \*Only 3 ethylketazocine-trained pigeons received 10 mg/kg cyclorphan. Following this dose of cyclorphan, only 1 of these pigeons responded during the one hr session, and this pigeon responded exclusively on the saline-appropriate key. One naltrexone-trained, narcotic-naive pigeon did not respond during the session following 10 mg/kg cyclorphan. The dashed lines at 90% in the upper panels indicate the minimum level of drug-appropriate responding that the training drugs were required to produce before test sessions were conducted with cyclorphan.

trained to discriminate ethylketazocine from saline, 36 for pigeons trained to discriminate cyclazocine from saline, 49 for narcotic-naive pigeons trained to discriminate 32 mg/kg naltrexone from saline, and 33 for morphine-treated pigeons trained to discriminate 0.1 mg/kg naltrexone from saline.

Cyclorphan produced varying degrees of drug-appropriate responding that depended both on the training conditions and on the dose of cyclorphan administered (Fig. 1, upper panels). In pigeons trained to discriminate ethylketazocine from saline, cyclorphan produced a dose-related increase in the number of responses that were made on the ethylketazocine-appropriate key, the maximum effect (83%) occurring at 0.3 mg/kg cyclorphan. This dose of cyclorphan produced at least 90% ethylketazocine-appropriate responding in 3 out of 4 pigeons and only 35% in the fourth. Higher cyclorphan doses did not increase the average percentage of drug-appropriate responses. In the one pigeon that responded only 35% on the drug-appropriate key after the administration of 0.3 mg/kg cyclorphan, as the dose of cyclorphan increased beyond 1 mg/kg, drug-appropriate responding decreased.

In pigeons trained to discriminate cyclazocine from saline, a dose of cyclorphan (1 mg/kg) that produced 80% ethylketazocine-appropriate responding, produced only saline-appropriate responding (Fig. 1). As the dose of cyclorphan increased, cyclazocine-appropriate responding increased to above 90% at 5.6-10.0 mg/kg cyclorphan.

Cyclorphan produced the least amount of drug-appropriate responding in narcotic-naive pigeons trained to discriminate 32 mg/kg naltrexone from saline, resulting in an average maximum effect of less than 50% drug-appropriate responding at 3.2 mg/kg cyclorphan (Fig. 1). In contrast, in pigeons that were chronically administered 100 mg/kg/day morphine and trained to discriminate 0.1 mg/kg naltrexone, cyclorphan produced a dose-related increase in the percentage of total responses that were emitted on the naltrexone-appropriate key, with 1.0 mg/kg cyclorphan producing 100% drug-appropriate responding in each pigeon. These effects of cyclorphan occurred across a range of doses that also produced ethylketazocine-appropriate responding.

When tested at sufficiently high doses, cyclorphan produced similar dose-related effects on the rate of responding in each group of pigeons (Fig. 1, lower panels). A dose of 10 mg/kg cyclorphan generally suppressed responding in each pigeon tested, and marked ataxia and loss of postural reflexes were noted. Two ethylketazocine-trained pigeons and 1 naltrexone-trained pigeon did not respond at all following the administration of this dose of cyclorphan.

Cyclorphan effects on schedule-controlled responding. The effects of cyclorphan, administered alone or in combination with 10 mg/kg morphine or 1 mg/kg naloxone, on performances maintained under the multiple schedule of food delivery are shown in Fig. 2. When administered alone (open circles), 1-3.2 mg/kg cyclorphan had little or no effect on FR or FI response rates or on FI quarter-life values. However, the highest dose of cyclorphan (10 mg/kg) decreased responding in both components of the schedule and decreased the FI quarter-life value to approximately 60% of control. The co-administration of 1 mg/kg naloxone (open triangles), a dose of naloxone sufficient to reverse completely the effects of 10 mg/kg morphine on schedule-controlled responding in pigeons (26,27), did not block the effects of 10 mg/kg cyclorphan either on FR or FI rates of responding or on FI quarter-life.

Morphine (10 mg/kg), when administered alone (Fig. 2, closed circles at "M"), suppressed responding in both components of the schedule to less than 10% of the control rate and decreased the FI quarter-life by 20%. When administered with morphine, increasing doses of cyclorphan (closed circles) resulted in a

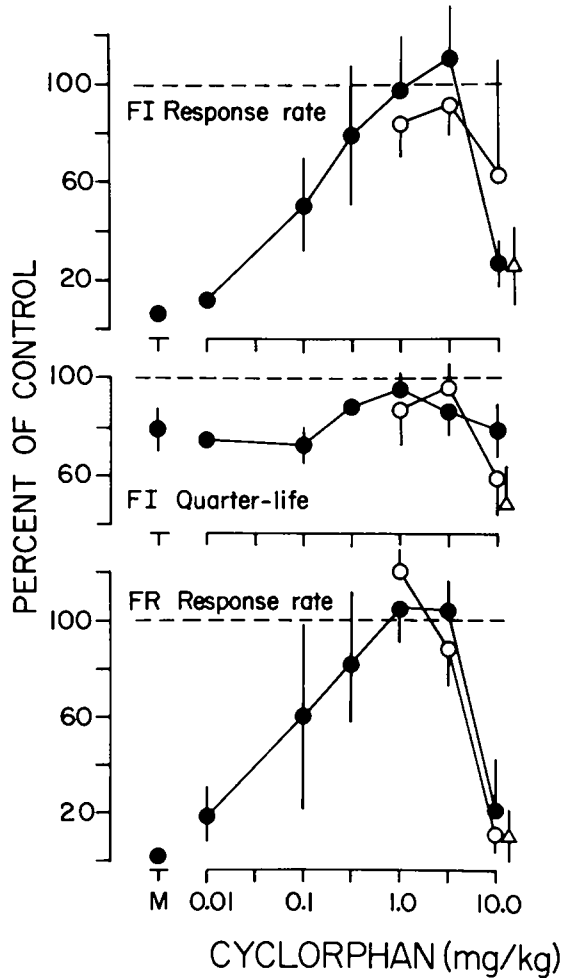


FIG. 2

Effects of cyclorphan, administered alone (open circles) or in combination with 10 mg/kg morphine (closed circles) or 1.0 mg/kg naloxone (open triangles), on responding maintained under a multiple FI, FR schedule of food presentation. Ordinates: percent of control. Control values were calculated from sessions in which saline was administered. Average response rates following saline injections were 0.91 and 2.87 responses/sec during the FI and FR components, respectively. The FI quarter-life value for these sessions was 174 sec (58% of the 5-min interval). Abscissae: cyclorphan dose, mg/kg. Each point represents the mean of a single observation in each of 4 pigeons. Lines through the points indicate  $\pm 1$  S.E.M. Points at M represent the effects of 10 mg/kg morphine administered alone.

dose-related reversal of the effects of morphine on all measures of schedule-controlled behavior. The highest dose of cyclorphan (10 mg/kg) was considerably less effective as an antagonist of morphine on all aspects of performance than were appropriate lower doses of cyclorphan.

### Discussion

Cyclorphan produced discriminative effects that varied as a function of dose and training condition. In pigeons trained to discriminate ethylketazocine from saline, cyclorphan produced greater than 90% drug-appropriate responding in 3 out of 4 pigeons and a maximum average response of 83% at 0.3 mg/kg, indicating considerable ethylketazocine-like activity. Although ethylketazocine has usually been shown to have discriminative effects that differ from those of morphine in many species (8,11,28), the discriminative effects of morphine and ethylketazocine are virtually indistinguishable in the pigeon (18,24). Moreover, in pigeons trained to discriminate morphine from saline, cyclorphan produces effects (unpublished observations) almost identical to those observed in the present study in pigeons trained to discriminate ethylketazocine from saline (Fig. 1). Thus, appropriate doses of cyclorphan appear to produce discriminative effects similar to those of ethylketazocine or morphine in the pigeon.

The inability of cyclorphan to produce greater than 90% ethylketazocine-appropriate responding in all pigeons tested suggests that cyclorphan may have effects, particularly at higher doses, that differ from those of ethylketazocine. In pigeons trained to discriminate cyclazocine from saline, cyclorphan produced greater than 90% cyclazocine-appropriate responding at 5.6-10 mg/kg, doses of the drug 20-30 times higher than the lowest doses needed to produce ethylketazocine-appropriate responding. While ethylketazocine has discriminative effects in pigeons that are similar to those of morphine, the discriminative effects of cyclazocine differ considerably from those of either morphine or ethylketazocine (18,24), but are similar to those of the non-narcotics phencyclidine and ketamine (13). In addition, the discriminative effects of cyclazocine and cyclazocine-like compounds, including phencyclidine and ketamine, are not well antagonized, if at all, by naloxone or naltrexone in rats (12,14) or pigeons (unpublished observations), indicating that certain of the effects of these drugs are mediated through non-narcotic mechanisms. Thus, at relatively high doses, cyclorphan appears to have non-narcotic, cyclazocine-like discriminative effects. The non-narcotic discriminative effects of cyclorphan, cyclazocine and phencyclidine may reflect interactions with the proposed "phencyclidine" receptor (29,30), since the relative potencies of these compounds in producing these discriminative effects are in close agreement with their relative potencies in displacing [<sup>3</sup>H] PCP binding to rat brain homogenates (cf. Fig. 1; 13,31). That the high dose effects of cyclorphan are non-narcotic in nature is also supported by the finding that the effects of 10 mg/kg cyclorphan on schedule-controlled responding were not reversed by naloxone (Fig. 2).

The intermediate level of responding produced by cyclorphan in ethylketazocine-trained pigeons, although limited to 1 out of 4 subjects in the present experiment, is not an uncommon finding in studies of narcotic drug discrimination (see 18,32-35). For example, a number of narcotic analgesics with activity as morphine antagonists (e.g., cyclazocine, nalorphine, levallorphan, nalbuphine) produce average maximum effects less than that produced by the training drug, morphine (34,35). Interpretation of intermediate levels of drug-appropriate responding is difficult, but are often ascribed to being a consequence of the test compound being somewhat similar to the training drug. In man, many narcotic mixed agonist-antagonists, while having morphine-like



subjective effects at low doses, tend to have predominantly non-morphine-like effects including sedation and psychotomimetic effects at higher doses (7). These additional non-morphine-like effects of these compounds may contribute to the intermediate or biphasic nature of dose-effect curves obtained with these drugs in animals trained to discriminate morphine-like compounds. Results of the present experiment suggest that at low doses cyclorphan has morphine-like discriminative effects, and that the drug's non-morphine-like actions can be accounted for by the drug's cyclazocine- or phencyclidine-like activity at higher doses. Indeed, intermediate levels of drug-appropriate responding produced by cyclorphan are completely reversed by naltrexone in pigeons trained to discriminate morphine from saline (unpublished observations) but are enhanced by naltrexone in pigeons trained to discriminate ketamine from saline (36), indicating the existence of at least two components of activity for cyclorphan.

In rats, the discriminative effects of cyclazocine appear to be similarly bimodal. In rats trained to discriminate morphine or fentanyl from vehicle, cyclazocine produces maximum drug-appropriate responding at a dose of approximately 0.3 mg/kg (32,33). Higher doses of the drug produce less morphine- or fentanyl-appropriate responses. These higher doses of cyclazocine in rats have non-morphine-like discriminative effects that are similar to those of phencyclidine (14).

In addition to having both ethylketazocine- and cyclazocine-like discriminative effects, cyclorphan was shown to have discriminative effects similar to those of the narcotic antagonist naltrexone in pigeons chronically administered morphine, but not in morphine-naive pigeons. This effect is similar to that produced by a number of other narcotic antagonists including cyclazocine, nalorphine, and diprenorphine, that result in naltrexone-appropriate responding in morphine-treated pigeons but not in narcotic-naive pigeons (19,20). Compounds that are not antagonists of morphine (e.g., amphetamine, physostigmine, bicuculline) do not produce naltrexone-appropriate responding in chronically morphinized pigeons (37), suggesting that the discriminative effects of cyclorphan in these pigeons are related to the antagonist action of the drug, and it has been proposed that the discriminative effects of narcotic antagonists in morphine-treated animals represent stimuli associated with antagonist-precipitated abstinence (38,39). That the effects of cyclorphan in morphine-treated pigeons are intimately related to the drug's antagonist activity is supported by results of cyclorphan's antagonism of the acute effects of morphine. A dose of cyclorphan (1.0 mg/kg) that produced 100% naltrexone-appropriate responding in pigeons chronically administered morphine (Fig. 1), completely blocked the effects of morphine on schedule-controlled responding (Fig. 2). Interestingly, these antagonist effects of cyclorphan occur within a range of doses of the drug that also produce ethylketazocine-like agonist activity.

Thus, the multiple actions of cyclorphan result in at least 3 distinct classes of discriminative stimuli, the predominant stimulus action being determined by dose and narcotic history. At low doses, cyclorphan produces ethylketazocine-like discriminative effects, and at higher doses, non-narcotic cyclazocine-like activity, the latter effect, perhaps, being analogous to the psychotomimetic effects that are produced by cyclorphan in man. At doses that produce ethylketazocine-appropriate responding, cyclorphan also produces, in pigeons chronically administered morphine, discriminative effects that are naltrexone-like, an effect that is related to the antagonist action of the drug and which may represent stimuli associated with antagonist-precipitated withdrawal.

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