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Further Characterization of the Three-Choice Morphine, Cyclazocine and Saline Discrimination Paradigm: Opioids with Agonist and Antagonist Properties[1]

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ABSTRACT

Rats were trained in a three-choice morphine (3.0 mg/kg), cyclazocine (0.3 mg/kg) and saline discrimination using a discrete-trials avoidance procedure. Behavior was considered to be under stimulus control when an animal reliably completed at least 18 trials of a 20-trial session on the correct lever after s.c. administration of either morphine, cyclazocine or saline. In tests of stimulus generalization, levorphanol produced a dose-related increase in trials completed on the morphine choice lever, whereas its optical enantiomer, dextrorphan, produced predominantly cyclazocine-appropriate responding, indicating that stimulus control of behavior was stereoselective. Ethylketocyclazocine, ketocyclazocine, levallorphan and SKF 10,047 engendered stimulus control of behavior that was unambiguously cyclazocine-like. In contrast, three other opioids with mixed agonist and antagonist properties occasioned responding on both the morphine- and cyclazocine-appropriate choice levers consistent with the mixture of morphine- and cyclazocine-like activity exhibited by these drugs in other procedures in animals and man. The stimulus effects of phencyclidine, a nonopioid compound, were not clearly interpretable within the present experimental context. This three-choice discimination paradigm provides an approach for studying concurrently the morphine- and cyclazocine-like discriminative stimulus effects of opioids with multiple components of action and may lead to a more precise characterization of the stimulus properties of mixed-acting opioids than has been possible with conventional two-choice discrimination paradigms alone.

Morphine and cyclazocine have been considered prototypes of the pure opiate agonists and the nonmorphine-like mixed agonist-antagonists, respectively. Studies of the discriminative stimulus properties of morphine and cyclazocine have demonstrated the distinctiveness of these opioids as well as the existence of commonalities between the two. In an earlier study (White and Holtzman, 1981), we demonstrated that rats could be trained to respond differentially to administration of morphine, cyclazocine and saline in a three-choice discimination task. The training doses of morphine and cyclazocine were chosen so as to maximize the overlap in the discriminative stimulus effects of the two drugs and thereby to minimize the possibility of a discrimination based on quantitative rather than on qualitative differences in drug effects. The lack of cross-generalization between morphine and cyclazocine in generalization tests suggests that stimulus control of behavior was indeed based on the qualitative differences in the stimulus effects of the two drugs.

In one of the generalization tests carried out as part of that study, pentazocine, an opioid with mixed agonist and antagonist properties, produced both morphine- and cyclazocine-appropriate responding, often at the same dose. Pentazocine has been previously shown to have both morphine (Shannon and Holtzman, 1976)- and cyclazocine-like (Teal and Holtzman, 1980a) stimulus effects in two-choice procedures in the rat. Thus, not only were the discriminative stimulus effects of morphine and cyclazocine made mutually exclusive in the three-choice discrimination paradigm, but a drug with morphine- and cyclazocine-like properties was shown to produce both morphine- and cyclazocine-appropriate responding in a situation in which both types of activity could be manifested concurrently.

We also showed that two nonopioids, *d*-amphetamine and secobarbital, produced neither morphine- nor cyclazocine-like stimulus effects, indicating pharmacologic specificity and that the discriminative stimulus effects of both morphine and cyclazocine could be blocked completely by appropriate doses of the narcotic antagonist naltrexone (White and Holtzman, 1981). Thus, the results of this study showed good agreement with those obtained in two-choice procedures, but also suggested that the three-choice paradigm would afford a greater degree of precision in characterizing the discriminative stimulus effects of opioids, especially those with mixed agonist and antagonist-properties. In the present study, the application of the three-choice procedure was extended to include a much wider variety

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of drugs. Among these were a range of opioids with mixed agonist and narcotic antagonist properties.

Validation of a new procedure requires the testing of compounds in which the outcome may be predicted on the basis of results obtained using established assays of pharmacologic activity. Therefore, several compounds with prominent cyclazocine-like stimulus effects in two-choice procedures were tested, including ketocyclazocine and ethylketocyclazocine (Schaefer and Holtzman, 1978; Teal and Holtzman, 1980a,b). Two other compounds which share stimulus effects with cyclazocine PCP and SKF 10,047 (Teal and Holtzman, 1980a,b), were also tested. The high degree of stereospecificity in the effects of opioids is evidenced by the fact that only the levorotatory isomers of the pure agonists have morphine-like stimulus properties (Winter, 1975; Colpaert, 1978). However, in the squirrel monkey (Teal and Holtzman, 1980c) and in the pigeon (Herling *et al.*, 1981), dextrorotatory isomers have stimulus effects in common with cyclazocine. The stereoselectivity of stimulus control in the three-choice procedure was examined by testing the enantiomers, levorphanol and dextrorphan.

Methods

Subjects. The subjects were six male CFE rats (Charles River Breeding Laboratories, Inc., Wilmington, MA) weighing from 210 to 430 g at the start of discrimination training. Five of the animals had already been trained and used in our previous study on three-choice, morphine, cyclazocine and saline discrimination (White and Holtzman, 1981); the sixth (B31) was trained before beginning the present investigation. Between experimental sessions the rats were housed in groups of two or three in a large colony room. Food and water were continuously available in the home cage and a 12-h light-dark cycle was maintained.

Apparatus. Two identical modular test chambers (model E10-10, Coulbourn Instruments, Inc., Lehigh Valley, PA) were employed. In each, one wall was divided into three vertical sections into which different modules could be fitted. A 3-cm wide rat lever, protruding 2 cm from the chamber wall, was placed 7 cm above the grid floor in each section. Sets of three colored stimulus lights were positioned 3 cm above the levers. The sections were separated by two clear Plexiglas panels mounted perpendicular to the wall, extending from 1 cm above the grid floor to the ceiling and protruding 6 cm into the chamber. A 5-cm speaker, through which white noise could be carried, was positioned at the top of the middle section. In the center of the opposite wall, 6.5 cm above the grid floor, was an omnidirectional lever. This was covered with a 5.5 cm length of 1 cm outside diameter plastic tubing. A houselight was placed in the center of the ceiling. Electric shock could be delivered to the grid floor by a solid state shocker/distributor (model E13-16, Coulbourn Instruments).

Discrimination training. The rats were trained in a discrete-trial avoidance procedure modified from that described by Shannon and Holtzman (1976). Each trial began with the onset of white noise and the illumination of the houselight and one of the stimulus lights in each of the three sets: the left of the three stimulus lights above the left lever, the center of the three above the center lever and the right of the three above the right lever. The white noise was terminated by the first response on the omnidirectional (observing) lever after trial onset, whereas the lights remained on until the trial ended. Beginning 5.0 sec after trial onset, a 1.0 mA shock of 0.5 sec duration was regularly presented until the end of the trial. The intershock interval was 1.0 sec.

Termination of each trial required the completion of a two-response chain that consisted of an observing lever response followed by a response on the correct choice lever. A trial could be terminated at any point, either before or after the start of shock delivery. During training sessions, one of the three choice levers was designated correct according to the substance injected into the animal before the session. Depression of an incorrect choice lever after operation of the observing lever did not affect shock presentation but started a timer. Trials could not be terminated by a press on the correct lever when this timer was operating. Each subsequent incorrect choice response reset the timer. The timer period was gradually increased during training to a final length of 10 sec (*i.e.*, 10 sec error-delay). This contingency ensured that, after operation of the observing lever, a correct response was functional only if an incorrect one had not occurred in the previous 10 sec. Multiple responses on the observing lever had no programmed consequences. In test sessions, a trial could be terminated by the first response on any of the three choice levers after a response had been emitted on the observing lever.

Termination of a trial resulted in darkening of the chamber for 30 sec before onset of the next trial. Sessions were terminated after 21 trials or 30 min, which ever came first. Data were taken from the last 20 trials and consisted of the first choice response emitted after operation of the observing lever on each trial.

The rats were first trained to make the observing lever-center lever chain with the other two choice levers made unavailable by covering the left and right sections of the choice panel. In subsequent sessions they were injected s.c. with either saline, morphine (3.0 mg/kg) or cyclazocine (0.3 mg/kg) 30 min before the start of the session and were trained to select the appropriate choice lever. For all rats the center lever was correct when saline had been injected. For rats B11, B12 and B25 the left lever was correct when morphine had been injected and the right lever was correct when cyclazocine had been injected, whereas for B13, B24 and B31 the right lever was correct after morphine and the left lever was correct after cyclazocine.

Training sessions were conducted twice a day, 5 days a week. Each day began with a saline session followed by a morphine or cyclazocine session 2 to 3 hr later. The scheduling of morphine and cyclazocine days was irregular, but with equal frequencies of each over 2-week periods. Training continued until the rat could complete at least 18 of 20 trials on the appropriate choice lever in four consecutive training sessions over 2 days (a saline session followed by a morphine session on 1 day and a saline session followed by a cyclazocine session on the other day). Four more sessions were then conducted, identically scheduled, but with all three choice levers effective in terminating trials. If the rat could complete 18 of the 20 trials on the appropriate choice lever in these four sessions, drug substitution testing was begun, otherwise training was recommenced, continuing until the criteria were met.

Training sessions, in which a trial could be terminated only by a response on the appropriate (*i.e.*, correct) choice lever, were conducted 4 days a week (Monday, Tuesday, Thursday and Friday) during the period of drug substitution testing in order to maintain stable discriminative performance. Test sessions, in which a trial could be terminated by a response on any of the three choice levers, were scheduled for Wednesday and Saturday of each week provided the subject met the criterion of 18 of 20 trials completed on the appropriate choice lever in all of the four training sessions held on the preceding 2 days (*i.e.*, two saline sessions, one morphine and one cyclazocine session). The order of the various drug series was different for each animal and doses within each drug series were tested in random sequence. Control values that appear in figures 1 to 4, were obtained from test sessions, two saline, one morphine (3.0 mg/kg) and one cyclazocine (0.3 mg/kg), conducted on the 2 days that followed each pair of drug series. In all other instances, only a single test session was conducted on a test day. All drugs were administered s.c. 30 min before the start of a session.

Data analysis. Data are presented as the mean number of trials completed on the morphine- or cyclazocine-appropriate choice levers in a 20-trial session. The remaining trials were always completed on the saline-appropriate choice lever. A test drug was considered to produce discriminative stimulus effects that substituted for those of morphine or cyclazocine (*i.e.*, to produce a comparable degree of stimulus control of behavior) if the group completed an average of at least 18 trials on a drug-appropriate choice lever.

Drugs. The following drugs were used in this study: morphine sulfate (Penick Corp., Newark, NJ), cyclazocine base, ketocyclazocine base and ethylketocyclazocine base (Sterling-Winthrop Research Institute, Rensselaer, NY), levallorphan tartrate, levorphanol tartrate and

dextrorphan tartrate (Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, NJ), nalmexone hydrochloride and nalbuphine hydrochloride (Endo Laboratories, Garden City, NY), butorphanol tartrate (Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, NY), PCP hydrochloride and naltrexone hydrochloride (National Institute on Drug Abuse, Rockville, MD) and SKF 10,047 (N-allylnormetazocine base; Smith Kline and French Laboratories, Philadelphia, PA). The vehicle for cyclazocine base, ketocyclazocine base, ethylketocyclazocine base and SKF 10,047 was 8.5% lactic acid and 1.0 N sodium hydroxide in a 3:2 ratio; for nalbuphine hydrochloride the vehicle was distilled water; all other drugs were dissolved in 0.9% saline. Drug solutions and saline were administered s.c. in a volume of 1.0 ml/kg b.wt. All drug doses are expressed in terms of the free base.

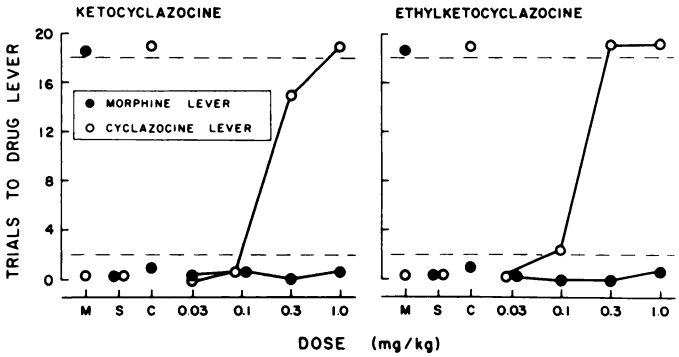

Fig. 1. Cyclazocine-like discriminative stimulus effects of ketocyclazocine and ethylketocyclazocine in rats trained to discriminate among 3.0 mg/kg of morphine and saline and 0.3 mg/kg of cyclazocine. Each point is the mean number of trials completed on the morphine-appropriate (solid points) or the cyclazocine-appropriate (open points) choice lever in a 20-trial session; the remaining trials of the session were completed on the saline-appropriate choice lever. Each mean is based upon one observation in each of three rats. The isolated points above M, S and C indicate the number of trials completed on the morphine-, saline- and cyclazocine-appropriate levers in test sessions with 3.0 mg/kg of morphine and saline and 0.3 mg/kg of cyclazocine, respectively. The upper horizontal dashed line denotes the minimum level of morphine- and cyclazocine-appropriate responding maintained during training sessions with each of those drugs. The lower dashed line denotes the maximum level of morphine- and cyclazocine-appropriate responding maintained during training sessions with saline.

Results

Ketocyclazocine and ethylketocyclazocine. Each of the two benzomorphans, ketocyclazocine and ethylketocyclazocine, produced a dose-related increase in trials completed on the cyclazocine-appropriate choice lever. Stimulus control of behavior comparable to that produced by the training dose of cyclazocine was engendered by 1.0 mg/kg of ketocyclazocine (fig. 1, left), and by 0.3 and 1.0 mg/kg of ethylketocyclazocine (fig. 1, right). No animal completed more than two trials on the morphine-appropriate choice lever at any dose of the two drugs.

Mixed agonist-antagonists. Four opioids with mixed agonist and antagonist properties, butorphanol, nalmexone, nalbuphine and levallorphan, produced differing patterns of choice responding (fig. 2). Butorphanol, in the dose range of 0.3 to 3.0 mg/kg, engendered 95 to 100% responding on the morphine-appropriate lever in two rats and on the cyclazocine-appropriate lever in a third. A fourth rat completed 70 and 80% of the trials on the cyclazocine-appropriate lever at 0.3 and 1.0 mg/kg of butorphanol and 90% of the trials on the morphine-appropriate

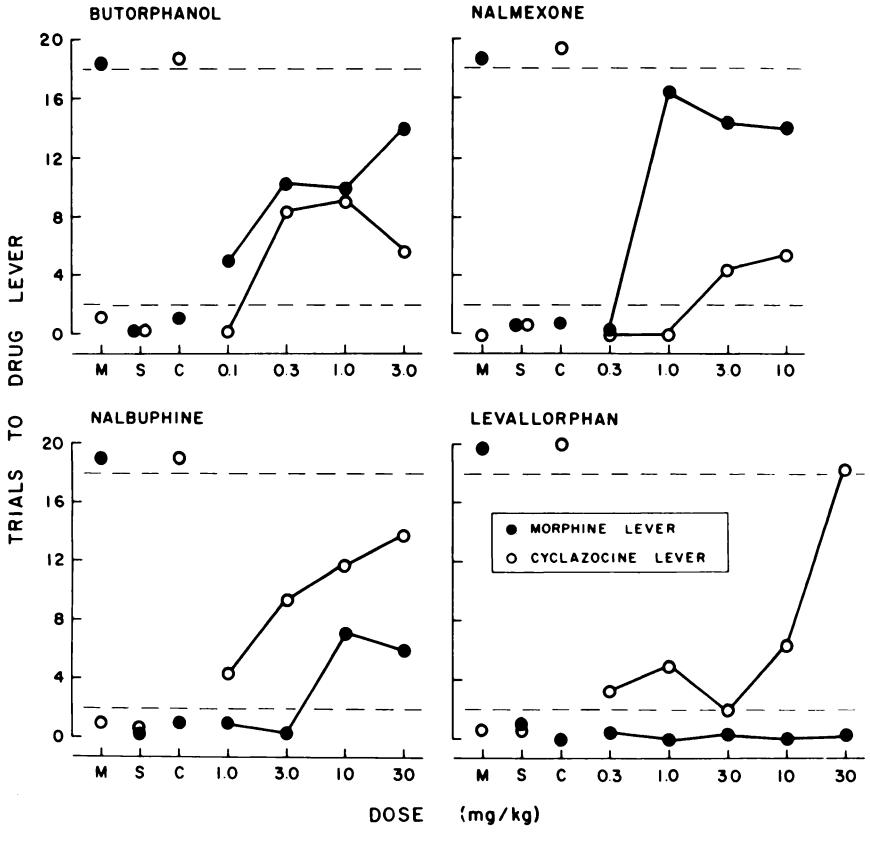

Fig. 2. Stimulus generalization curves for four opioids with mixed agonist and antagonist properties in rats trained to discriminate among 3.0 mg/kg of morphine and saline and 0.3 mg/kg of cyclazocine. Each point is a mean based upon one observation in each of four (butorphanol) or three rats. Other details are the same as in figure 1.

lever at 3.0 mg/kg. Thus, on a group basis, responses were distributed relatively evenly between the two drug levers at 0.3 and 1.0 mg/kg of butorphanol and predominantly on the morphine lever at the highest dose (fig. 2, upper left). Responses on the two drug levers combined accounted for more than 90% of the trials from 0.3 to 3.0 mg/kg.

Nalmexone engendered primarily morphine-appropriate responding from 1.0 to 10 mg/kg, with cyclazocine-appropriate responding emerging at 3.0 and 10 mg/kg (fig. 2, upper right). The opposite was seen with nalbuphine: cyclazocine-appropriate responding predominated from 1.0 to 30 mg/kg, with morphine-appropriate responding becoming apparent at the two highest doses (fig. 2, lower left). At the upper two doses of both nalmexone and nalbuphine, trials completed on the morphine- and cyclazocine-appropriate levers combined exceeded 90%. In contrast to the outcomes with butorphanol, nalmexone and nalbuphine, the stimulus effects of levallorphan (0.3–30 mg/kg) were almost exclusively cyclazocine-like, with 30 mg/kg producing stimulus control comparable to that of the training dose of cyclazocine (fig. 2, lower right).

SKF 10,047 and PCP. The benzomorphan, SKF 10,047, produced a dose-related increase in cyclazocine-appropriate responding that reached 97% of the trials at 3.0 mg/kg (fig. 3, left). Trials completed on the morphine-appropriate lever never exceeded a mean of 5%. PCP produced mixed effects. At 1.0 mg/kg, 46% of the trials were completed on the cyclazocine-appropriate lever, 3% on the morphine lever and 51% on the saline lever, whereas at 3.0 mg/kg, responding was almost evenly divided between the two drug levers in three rats (fig. 3, right) and a fourth was unable to respond.

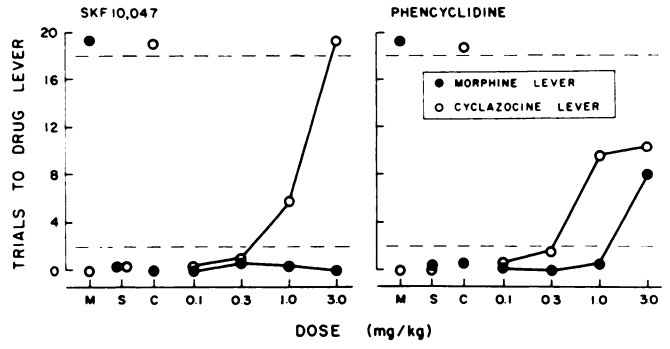

Fig. 3. Stimulus generalization curves for SKF 10,047 and PCP in rats trained to discriminate among 3.0 mg/kg of morphine and saline and 0.3 mg/kg of cyclazocine. Each point is a mean based upon one observation in each of three (SKF 10,047) or four (PCP) rats, except at 3.0 mg/kg of PCP, which is based on observations in three rats. Other details are the same as in figure 1.

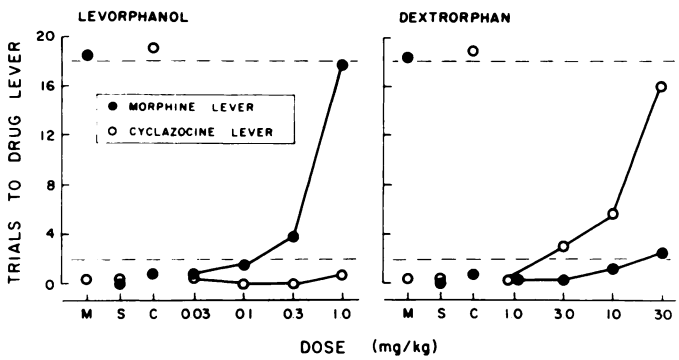

Fig. 4. Stereoselectivity of the stimulus control of behavior in rats trained to discriminate among 3.0 mg/kg of morphine and saline and 0.3 mg/kg of cyclazocine. Each point is a mean based upon one observation in each of four rats. Other details are the same as in figure 1.

Stereospecificity. Levorphanol produced a dose-related increase in morphine-appropriate responding, with a maximum of 89% of the trials being completed on that drug lever at 1.0 mg/kg (fig. 4, left). An average of not more than one trial was completed on the cyclazocine-appropriate lever over the 0.03 to 1.0 mg/kg range of levorphanol doses. In contrast, dextrophan engendered predominantly cyclazocine-appropriate responding over its 1.0 to 30 mg/kg dose range (fig. 4, right). At 30 mg/kg, cyclazocine-appropriate responding averaged 80% and morphine-appropriate responding averaged 13%.

Discussion

One value of the three-choice morphine, cyclazocine and saline discrimination paradigm is the potential that it offers for a precise characterization of the discriminative stimulus properties of opioids, especially those having multiple components of action. For example, rats trained in a two-choice procedure to discriminate saline from 3.0 mg/kg of morphine completed 80% of the trials on the morphine-appropriate lever in generalization tests with 0.3 mg/kg of cyclazocine (Shannon and Holtzman, 1976) and rats trained with saline and 0.3 mg/kg of cyclazocine completed almost 50% of the trials on the cyclazocine lever in tests with 3.0 mg/kg of morphine (Teal and Holtzman, 1980a). In contrast, stimulus effects common to both morphine and cyclazocine were not in evidence in our earlier study using the three-choice procedure (White and Holtzman, 1981). In the present study, two other drugs, ketocyclazocine and levallorphan, that produced intermediate levels (*i.e.*, 70–80%) of morphine-appropriate responding in rats trained to discriminate between saline and morphine (Shannon and Holtzman, 1977) were shown to be exclusively cyclazocine-like in the three-choice situation.

The cyclazocine-like stimulus control of behavior engendered by ethylketocyclazocine and SKF 10,047 is consistent with results from two-choice procedures in which the training drug was either cyclazocine (Teal and Holtzman, 1980a,b) or ethylketocyclazocine (Hein *et al.*, 1981; Shearman and Herz, 1982). Also consistent with two-choice procedures is the stereoselectivity of stimulus control of behavior. Morphine-like stimulus properties are characteristic of pure opiate agonists having a levorotatory conformation, whereas dextrorotatory isomers of opiate agonists can have prominent cyclazocine-like activity (Teal and Holtzman, 1980c; Herling and Woods, 1981). Such steric separation of discriminative stimulus effects was readily apparent in the case of the optical enantiomers, levorphanol and dextrorphan.

One outcome at variance with observations from two-choice discrimination studies was the weak cyclazocine-like effects of PCP. Prominent commonalities in the stimulus effects of PCP and cyclazocine have been demonstrated repeatedly and, in several animal species, regardless of whether the subjects were trained to discriminate cyclazocine from saline (Teal and Holtzman, 1980a; Herling *et al.*, 1981) or PCP from saline (Holtzman, 1980, 1982; Shannon, 1982). On the other hand, PCP and

morphine appear to have no stimulus effects in common in the rat (Shannon, 1981; S.G. Holtzman, unpublished observations). Yet, in the present study, the highest dose of PCP occasioned morphine-appropriate responding on 40% of the trials. These findings could be a consequence of differences in the cuing properties of morphine and cyclazocine in the three-choice procedure as compared with two-choice procedures so that a previously undetectable similarity in the stimulus effects of morphine and PCP became apparent. PCP interacts weakly with morphine binding sites in rat brain homogenates (Vincent *et al.*, 1978; Itzhak *et al.*, 1981). Alternatively, the high dose of PCP may have disrupted stimulus control of behavior, resulting in undifferentiated responding on the choice levers. Additional control drugs will have to be tested before this issue can be resolved.

Between the extremes of opioids that were unambiguously cyclazocine-like (*i.e.*, ethylketocyclazocine, ketocyclazocine, levallorphan and SKF 10,047) or morphine-like (*i.e.*, levorphanol) were three that produced mixed cyclazocine- and morphine-appropriate responding: butorphanol, nalbuphine and nalmexone. It is possible that these outcomes were due not to any specific morphine- and cyclazocine-like stimulus properties of the test drugs. Rather, the animals may have simply discriminated that the drugs were not saline and, therefore, distributed their responses randomly between the two drug levers. However, when *d*-amphetamine, a drug readily discriminable from saline, was tested for generalization over the dose range of 0.03 to 1.0 mg/kg in this same three-choice paradigm, an average of not less than 80% of all trials were completed on the choice lever appropriate for saline (White and Holtzman, 1981).

Although neither butorphanol, nalbuphine nor nalmexone substituted completely for either of the training drugs, the number of trials completed on the morphine- and cyclazocine-appropriate levers combined exceeded 90% at the upper doses of each of those compounds. Such patterns of stimulus generalization are similar to those observed previously with pentazocine (White and Holtzman, 1981) and are consistent with the mixture of morphine- and cyclazocine-like activity exhibited by this group of opioid agonist-antagonists (*i.e.*, butorphanol, nalbuphine, nalmexone and pentazocine) in two-choice discrimination procedures in rats and monkeys (Shannon and Holtzman, 1976, 1977; Schaefer and Holtzman, 1978, 1981; Teal and Holtzman, 1980a) as well as in studies of subjective effects and physical dependence in man (Haertzen, 1974; Jasinski, 1977, 1979). The opportunity to study concurrently the morphine- and cyclazocine-like stimulus effects of opioids with multiple components of action is a potential advantage that the three-choice procedure holds over conventional two-choice discrimination paradigms.

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