Psychopharmacology (1984) 84: 356–361

Psychopharmacology

Antagonism of the discriminative effects of ethylketazocine, cyclazocine, and nalorphine in macaques

Alice M. Young* and Kenneth R. Stephens**

Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI 48109, USA

Abstract. *dl*-Ethylketazocine (EKC, 0.01 mg/kg) and saline were established as discriminative stimuli for food-maintained responding in macaque monkeys. Thirty consecutive presses on a right or left lever were reinforced with food, contingent on whether EKC or saline were administered before the session. For tests of antagonism, naltrexone, or UM 979 [(*l*)-5,9-alpha-dimethyl-2-(3-furylmethyl)-2′-hydroxy-6,7-benzomorphan] was administered concomitantly with EKC, *dl*-cyclazocine, or nalorphine. Both antagonists blocked completely the EKC discriminative stimulus. The antagonism of the stimulus and rate-altering effects of EKC was surmountable, with considerable intersubject variability in the magnitude of the EKC dose increase required to overcome the blockade. Cyclazocine and nalophine, mixed agonist-antagonist opioids that share stimulus properties with EKC, were also susceptible to antagonism. Naltrexone antagonized completely the EKC stimulus effects of nalorphine; naltrexone and UM 979 antagonized completely the EKC stimulus effects of cyclazocine. Naltrexone antagonism of the cyclazocine stimulus was not surmountable, due to a lack of antagonism of the rate-decreasing effects of high cyclazocine doses.

Key words: Drug discrimination – κ opioids – Ethylketazocine – Cyclazocine – Nalorphine – Naltrexone – Macaque monkeys

Drug discrimination studies have demonstrated considerable overlap among the stimulus properties of putative κ opioids (Herling and Woods 1981; Holtzman 1982; Tang and Code 1983; Young et al. 1984). The reference stimuli *dl*-ethylketazocine (EKC) and nalorphine generally display symmetrical discriminative effects in macaques and rats, sharing stimulus properties with each other and a range of other κ opioids, including *dl*-cyclazocine (Hein et al. 1981; Hirschhorn 1977; Shearman and Herz 1982; Tang and Code 1983; Young et al. 1984). The reference stimulus *dl*-cyclazocine, explored primarily in rats and squirrel monkeys, also shares stimulus properties with many putative κ opioids, as well as an additional group of phencyclidine-like drugs (Herling and Woods 1981; Holtzman 1982 for reviews).

One dimension along which these stimuli may differ is their susceptibility to opioid antagonists. An EKC training stimulus is antagonized completely by naltrexone, naloxone, and the benzomorphan antagonist MR 2266 in macaques and rats (Hein et al. 1981; Herling and Shannon 1982; Shearman and Herz 1982); a nalorphine training stimulus is blocked by naloxone in macaques (Tang and Code 1983). A cyclazocine training stimulus, in contrast, is antagonized completely by naltrexone or naloxone in squirrel monkeys (Schaefer and Holtzman 1978; Teal and Holtzman 1980b, c), but is not readily antagonized in rats (Teal and Holtzman 1980a). Additionally, the cyclazocine-like stimuli produced by certain other mixed agonist-antagonist opioids are not sensitive to naloxone or naltrexone antagonism (Schaefer and Holtzman 1978; Teal and Holtzman 1980b).

The present experiment further compared the ability of opioid antagonists to block the discriminative effects of EKC, nalorphine, and cyclazocine in macaques trained to discriminate a single agent (EKC). Experiments assessed both the ability of naltrexone to block discriminably similar doses of each drug, and also the ability of EKC and cyclazocine to surmount such antagonism. Additionally, since previous workers have suggested that benzomorphan derivatives may be selective antagonists of κ opioids (Roemer et al. 1980; Shearman and Herz 1982), the ability of the representative benzomorphan UM 979 to antagonize the stimulus effects of EKC and cyclazocine was assessed.

Materials and methods

One male rhesus macaque (*Macaca mulatta,* 975) and two male pigtail macaques (*Macaca nemestrina;* 1204, 1205) served as subjects. Each monkey had a history of lever-press responding maintained by food or IV drug injections and had received opioids and various other behaviorally active drugs in previous studies. Monkey 975 had participated in a previous study of the EKC stimulus (Hein et al. 1981). All monkeys were maintained at approximately 85% of their free-feeding weights (7.5–9.0 kg) by Purina Monkey Chow delivered after each session and at midday on weekends. Dietary supplements included vitamins every day and fresh fruit when available. Each monkey was given 40 mg isoniazid on a sugar cube

* *Present address:* Department of Psychology, Wayne State University, 71 West Warren Avenue, Detroit, MI 48202, USA

** *Present address:* Mantech/CADCOM, Suite 1111 Century Mall Building, 2341 Jefferson Davis Highway, Arlington, VA 22202, USA

Offprint requests to: A. Young

each day and was tested for tuberculosis every 6 months. The monkeys were housed in individual primate cages with water freely available.

Experiments were conducted in enclosed ventilated chambers, as described by Hein et al. (1981). Each chamber was equipped with two response levers, an externally mounted pellet dispenser, and a receptacle for 300 mg banana-flavored food pellets (Noyes, Formula G, Lancaster, NH). Lights of various colors were mounted at the top of the front wall of the chambers. Experiments were controlled and data collected by a Texas Instruments 960A computer located in an adjacent room.

EKC (0.01 mg/kg IM) and saline were established as discriminative stimuli for food-maintained responding by the method described by Hein et al. (1981). Before each training session, the subject was placed in a primate chair, injected with EKC or saline, and placed in the experimental chamber. After a 10-min pretreatment interval, a light was illuminated to signal the start of the session. The light remained on until the end of the session, except for the brief time of each pellet delivery. Following EKC administration, responses on only one of the two levers produced food delivery; following saline administration, responses on the other lever produced food delivery. The response requirement was gradually increased over successive sessions until 20 consecutive responses on the correct lever were required for food delivery. Responses on the incorrect lever reset the response requirement on the correct lever. Sessions ended after 75 pellet deliveries or 1 h, whichever occurred first.

EKC and saline administration alternated daily during training. Training continued until two criteria were met for nine consecutive sessions: The total number of responses emitted before the first pellet delivery was less than 40, and at least 90% of the total session responses were emitted on the appropriate lever. Training sessions were conducted 6 days/week.

Once the above criteria were met, saline, and various doses of EKC, nalorphine, cyclazocine, naltrexone, and UM 979, alone and in combination, were examined for their capacity to cause drug-appropriate responses. Test sessions were identical to training sessions, except that the pretreatment time was extended to 20 min, and 20 consecutive responses on either lever were reinforced. Test days alternated with training days to ensure that the discrimination remained intact. If a subject failed to meet the performance criteria on a training day, further testing was deferred until 2 consecutive days of acceptable performance had occurred.

Initially, dose-effect curves were generated for EKC, cyclazocine, and nalorphine. The doses tested covered a range from a dose that evoked saline-appropriate responses to doses that evoked predominantly drug-appropriate responses or markedly reduced response rates. Naltrexone and UM 979 were then tested alone at doses of 0.01–1.0 mg/kg. For antagonism tests, a dose of EKC (0.01 mg/kg), cyclazocine (0.03 mg/kg), or nalorphine (0.32 mg/kg) that produced complete EKC-appropriate responding was administered concomitantly with selected doses of naltrexone or UM 979. For tests of surmountable antagonism, effective doses of naltrexone were given concomitantly with a range of EKC and cyclazocine doses, and effective doses of UM 979 were given concomitantly with a range of EKC doses.

Data are presented as two functions of dose. First, the number of responses emitted on the lever appropriate to the EKC training dose is expressed as a percentage of the total number of responses emitted during the session. Second, the overall rate of responding on the two levers is presented as a percentage of the average rate for the saline training sessions conducted during the period of each antagonism study. The distribution of responses on the two levers was not evaluated if fewer than 100 responses were emitted during the session.

The following compounds were used: *dl*-cyclazocine base and *dl*-ethylketazocine methane sulfonate (gifts of Dr. W. Michne, Sterling-Winthrop Research Institute, Rensselaer, NY), nalorphine hydrochloride (obtained from Eli Lilly and Company, Indianapolis, IN), naltrexone hydrochloride (gift of Endo Laboratories, Garden City, NY), and UM 979 [MR 1452; (*l*)-5,9-alpha-dimethyl-2-(3-furylmethyl)-2′-hydroxy-6,7-benzomorphan methane sulfonate;

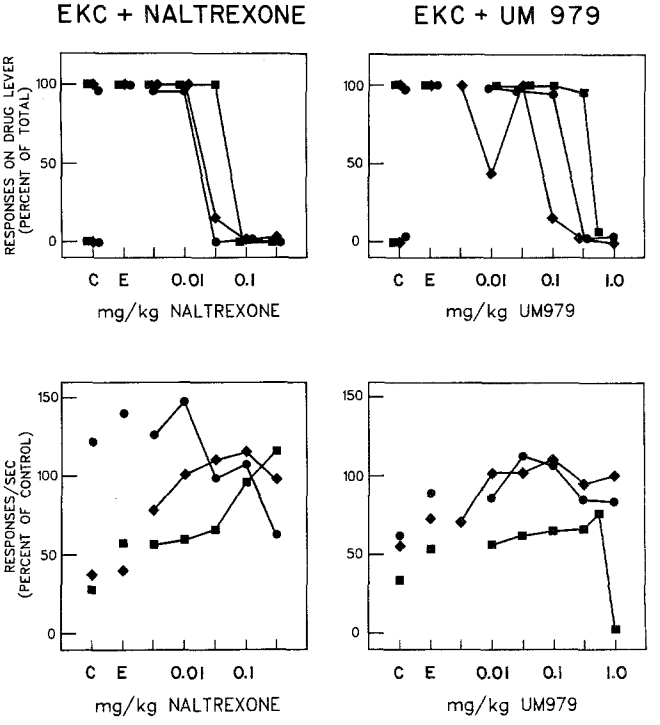

Fig. 1. Effects of graded doses of naltrexone or UM 979 in combination with 0.01 mg/kg ethylketazocine (EKC) in individual macaque monkeys for which 0.01 mg/kg EKC and saline served as discriminative stimuli for food-reinforced responses. *Upper panel ordinates:* number of responses emitted on the EKC-appropriate lever, expressed as a percentage of the total session responses. *Lower panel ordinates:* rate of responding during the session, expressed as a percentage of the mean response rates during saline training sessions. *Abscissae,* mg/kg doses of naltrexone *(left panels)* or UM 979 *(right panels)* administered concomitantly with 0.01 mg/kg EKC. Each drug combination data point represents a single determination in each subject. Points at *E* represent tests 20 min after concomitant administration of 0.01 mg/kg EKC and saline. Points at *C* in the *upper panels* represent the average percentage of responses emitted on the EKC-appropriate lever during training sessions that preceded test sessions. Points at *C* in the *lower panels* present the effects of 0.01 mg/kg EKC on rate of responding during training sessions. The symbol and average response rates (responses/s) during saline training sessions for each monkey are as follows: 975 ●, 1.86; 1205 ■, 1.92; 1204 ◆, 2.22

gift of Dr. H. Merz, Boehringer Ingelheim, Federal Republic of Germany).

EKC and cyclazocine were dissolved in sterile water to which a small amount of lactic acid was added. Sodium hydroxide was used to adjust the pH of the solutions to above pH 4. Nalorphine, naltrexone, and UM 979 were dissolved in 0.9% saline. Doses of all drugs are expressed as the forms given above. Solutions were prepared to deliver each mg/kg injection dose in 0.1–1.5 ml. Injections were made into the thigh muscle; when drug combinations were studied, each injection was made into a different leg.

Results

Discriminative control by 0.01 mg/kg EKC and saline was achieved in 86 or 109 sessions in the two new monkeys 1205 and 1204. During test sessions, an EKC dose of 0.001 mg/kg evoked only saline-appropriate responses; higher doses (0.003 or 0.01–0.03 mg/kg) evoked primarily drug-appropriate responses. Naltrexone or UM 979 doses of 0.01–1.0 mg/kg produced only saline-appropriate responses and generally did not alter the response rates usually emitted in the presence of saline (data not shown). In monkey 1205, however, 1.0 mg/kg UM 979 completely abolished responding throughout the 1-h experimental session. Lower doses of UM 979 did not decrease response rates in this subject.

Naltrexone and UM 979 blocked the EKC stimulus in a dose-dependent fashion (Fig. 1, upper panels). Complete antagonism of the EKC stimulus was achieved with naltrexone doses of 0.03 or 0.1 mg/kg and with UM 979 doses of 0.1, 0.32, or 0.56 mg/kg. The antagonists also blocked the rate-altering effects of EKC (Fig. 1, lower panels). During the period of EKC-naltrexone combinations, EKC decreased response rates in monkeys 1204 and 1205 and increased rates in monkey 975. Naltrexone blocked both effects, generally at doses that also blocked the EKC stimulus. During the period of EKC-UM 979 combinations, EKC decreased response rates in all monkeys. For monkeys 975 and 1204, UM 979 blocked these rate decreases at doses of 0.01 mg/kg and above. For monkey 1205, no UM 979 dose completely blocked the rate-decreasing effects of EKC, and the combination of 1.0 mg/kg UM 979 and 0.01 mg/kg EKC eliminated responding throughout the 1-h session.

Both naltrexone and UM 979 exerted a surmountable antagonism of the stimulus and rate-decreasing effects of EKC (Figs. 2 and 3). There was considerable intersubject variability in the magnitude of the EKC dose increase required to overcome naltrexone or UM 979 antagonism. The dose of EKC required for discriminative control was increased 3–56-fold in the presence of 0.1 mg/kg naltrexone, and was increased 18–560-fold in the presence of 1.0 mg/kg naltrexone. The dose of EKC required for discriminative control was increased 3–10-fold in the presence of 0.32 or 1.0 mg/kg UM 979. In general, smaller increases in EKC dose were required to surmount antagonism of its rate-decreasing effects. Comparison of the two antagonists showed that the lowest effective dose of each produced equivalent antagonism of the EKC stimulus in the two monkeys tested with both combinations. Equivalent increases in EKC dose were required to overcome the effects of 0.10 mg/kg naltrexone and 0.32 mg/kg UM 979 in monkeys 975 and 1204.

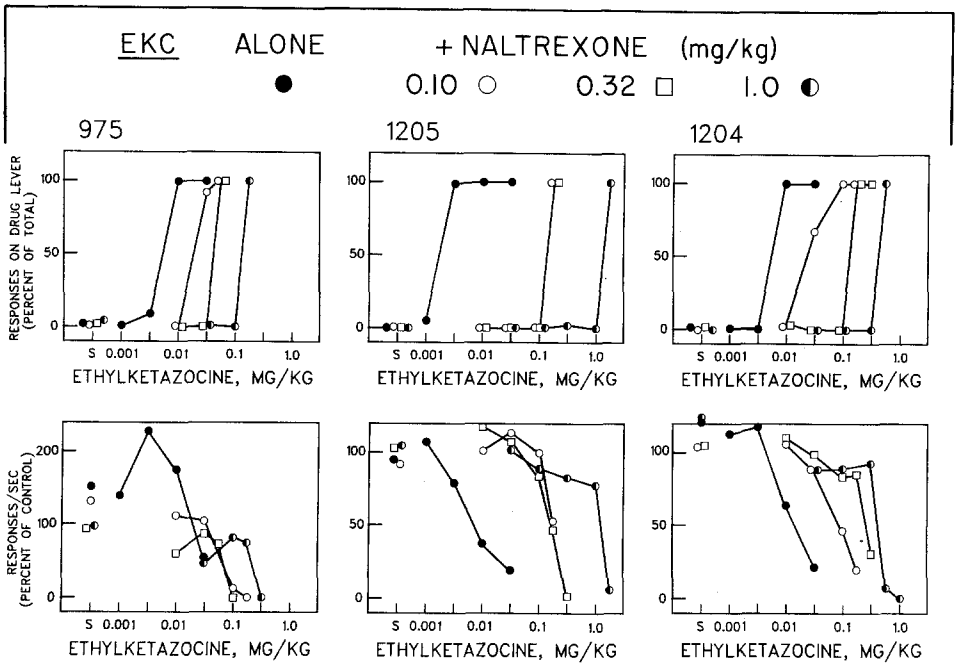

Fig. 2. Ethylketazocine (EKC) dose-response curves determined alone (●) or in combination with graded doses of naltrexone (○ 0.10 mg/kg; □ 0.32 mg/kg; ◐ 1.0 mg/kg) in three macaques for which 0.01 mg/kg EKC and saline served as discriminative stimuli for food-reinforced responses. *Upper panel ordinates:* number of responses emitted on the EKC-appropriate lever, expressed as a percentage of the total session responses. *Lower panel ordinates:* rate of responding during the session, expressed as a percentage of the mean response rate during saline training sessions. *Abscissae:* mg/kg dose of EKC. Each point represents a single determination in each subject. Points at *S* represent tests after saline administered alone or in combination with each dose of the antagonist. Average response rates (responses/s) for individual monkeys during saline training sessions were: 975, 1.71; 1205, 1.92; 1204, 2.20

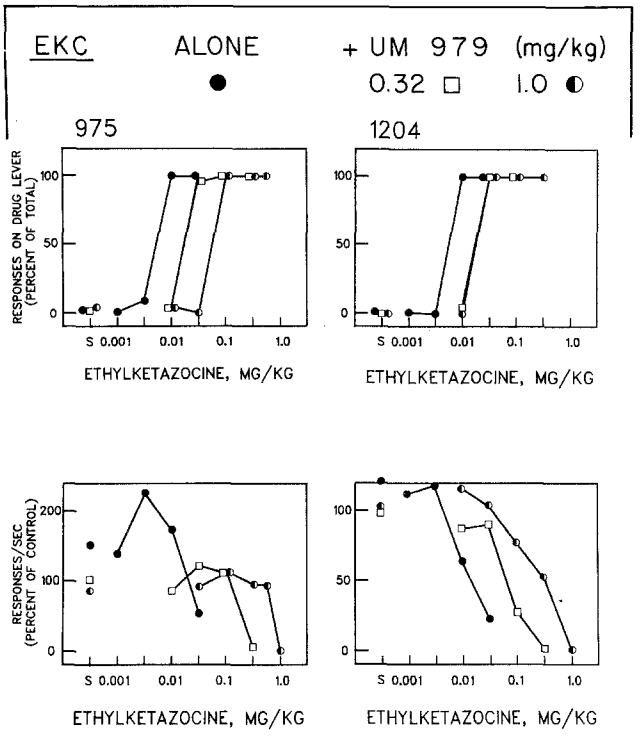

Fig. 3. Ethylketazocine (EKC) dose-response curves determined alone (●) or in combination with graded doses of UM 979 (□ 0.32 mg/kg; ◐ 1.0 mg/kg) in two macaques for which 0.01 mg/kg EKC and saline served as discriminative stimuli for food-reinforced responses. Average response rates (responses/s) for individual monkeys during saline training sessions were: 975, 1.71; 1204, 2.08. Other details as in Fig. 2

The mixed agonist-antagonists cyclazocine and nalorphine exerted EKC-like stimulus effects that were also susceptible to antagonism by naltrexone or UM 979 (Fig. 4). Naltrexone and UM 979 were tested in combination with the lowest dose of cyclazocine (0.03 mg/kg) required to evoke complete EKC-appropriate responses in all monkeys. A naltrexone dose of 0.32 mg/kg blocked the cyclazocine stimulus in all three monkeys; certain naltrexone doses blocked the rate decreases produced by cyclazocine in two monkeys. UM 979 (0.32 or 0.56 mg/kg) also blocked the cyclazocine stimulus in all monkeys. UM 979-cyclazocine combinations had extremely variable effects on response rate. In general, UM 979 doses of 0.03–0.32 mg/kg blocked cyclazocine's rate-decreasing effects in individual monkeys. The combination of cyclazocine and higher UM 979 doses abolished responding in two monkeys.

Only naltrexone was tested in combination with the lowest dose of nalorphine (0.32 mg/kg) required to evoke EKC-appropriate responses (Fig. 4, right panels). A dose of 0.003, 0.03, or 0.32 mg/kg naltrexone was required to block the nalorphine stimulus in monkeys 1205, 1204, and 975, respectively. During tests of nalorphine-naltrexone combinations, 0.32 mg/kg nalorphine continued to evoke EKC-appropriate responses when tested alone or in combination with saline. However, when nalorphine was again tested after an interval of several months, it did not evoke EKC-appropriate responses at any dose. Therefore, tests of nalorphine-UM 979 combinations were not conducted.

Naltrexone antagonism of the cyclazocine stimulus was not surmountable (Fig. 5). A naltrexone dose of 0.32 mg/kg

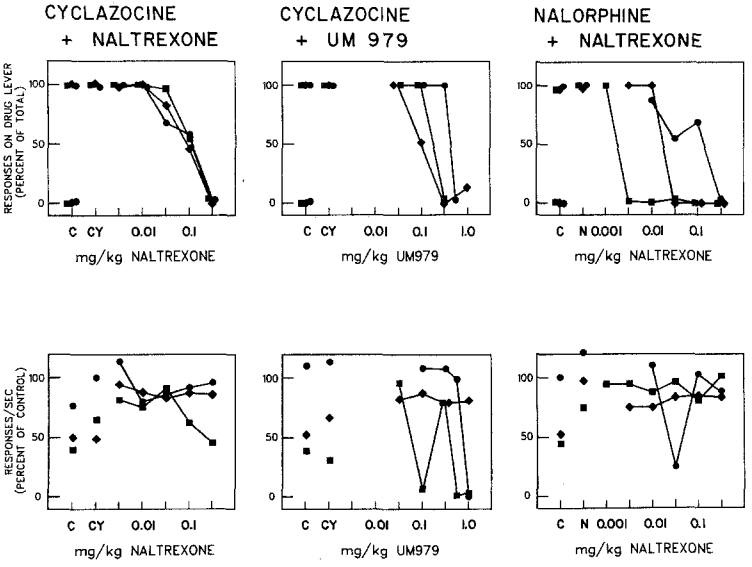

Fig. 4. Effects of graded doses of naltrexone or UM 979 in combination with 0.03 mg/kg cyclazocine *(left, middle panels)* or 0.32 mg/kg nalorphine *(right panels)* in individual macaques for which 0.01 mg/kg ethylketazocine (EKC) and saline served as discriminative stimuli for food-reinforced responses. *Upper panel ordinates:* number of responses emitted on the EKC-appropriate lever, expressed as a percentage of the total session responses. *Lower panel ordinates:* rate of responding during the session, expressed as a percentage of the mean response rate during saline training sessions. *Abscissae:* mg/kg dose of antagonist administered concomitantly with 0.03 mg/kg cyclazocine *(left, middle panels)* or 0.32 mg/kg nalorphine *(right panels)*. Each drug combination data point represents a single determination in each subject. Points at *CY* represent tests after concomitant administration of 0.03 mg/kg cyclazocine and saline; points at *N* represent tests after administration of 0.32 mg/kg nalorphine and saline. Points at *C* in the *upper panels* represent the average percentage of responses emitted on the EKC-appropriate lever during training sessions that preceded test sessions. Points at *C* in the *lower panels* present the effects of 0.01 mg/kg EKC on rate of responding during training sessions. The symbol and average response rate (responses/s) during saline training sessions for each monkey are as follows: 975 ●, 1.83; 1205 ■, 1.60; 1204 ◆, 2.27

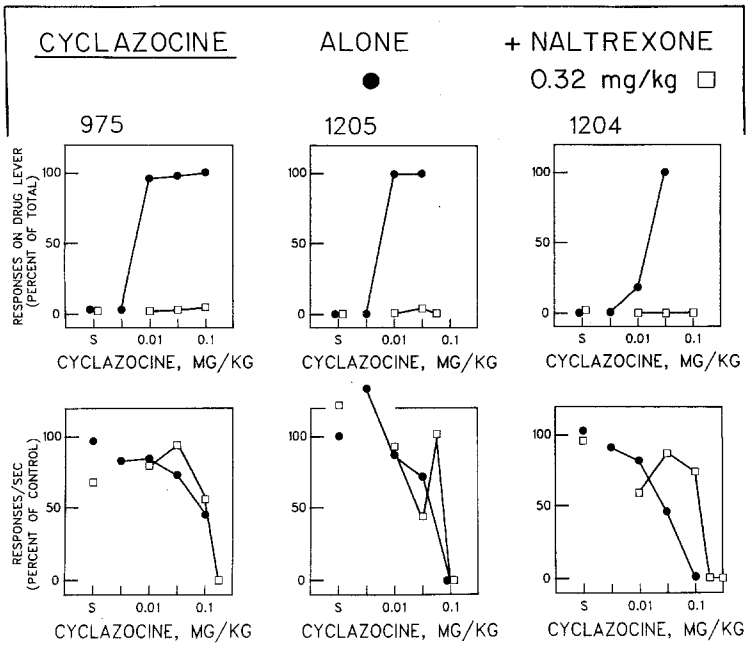

Fig. 5. Cyclazocine dose-response curves determined alone (●) or in combination with 0.32 mg/kg naltrexone (□) in three macaques for which 0.01 mg/kg ethylketazocine and saline served as discriminative stimuli for food-reinforced responses. *Abscissae:* mg/kg dose of cyclazocine. Average response rates (responses/s) for individual monkeys during saline training sessions were: 975, 1.90; 1205, 1.50; 1204, 2.25. Other details as in Fig. 2

blocked the stimulus but not, in general, the rate-decreasing effects of high cyclazocine doses. Thus, the ability of cyclazocine to overcome the stimulus blockade produced by 0.32 mg/kg naltrexone was limited by cyclazocine's insensitivity to naltrexone antagonism of its rate-decreasing effects.

Discussion

In the present experiment, naltrexone exerted a surmountable antagonism of the stimulus and rate-altering effects of EKC. These results extend our previous report that the EKC stimulus in rhesus monkeys is sensitive to naltrexone antagonism (Hein et al. 1981). Similarly, naloxone completely blocks the EKC stimulus in rats (Herling and Shannon 1982; Shearman and Herz 1982). As in the present experiment, naloxone antagonism of the EKC stimulus in rats is surmountable; the EKC dose required for stimulus control is increased threefold by 0.1 mg/kg naloxone and 30-fold by 1.0 mg/kg naloxone (Herling and Shannon 1982). In contrast, naloxone and naltrexone reduce, but do not abolish completely the stimulus control exerted by ketazocine or EKC in squirrel monkeys trained with cyclazocine (Schaefer and Holtzman 1978; Teal and Holtzman 1980b).

The EKC stimulus effects of the mixed agonist-antagonists nalorphine and cyclazocine also were antagonized by naltrexone. Antagonism of the mixed agonist-antagonist stimuli differed from that of the EKC stimulus in at least two respects. First, antagonism of the nalorphine stimulus in individual monkeys required a greater range of naltrexone doses than did antagonism of the EKC stimulus. A similar range of individual sensitivities to naloxone antagonism of a nalorphine stimulus in macaques was reported by Tang and Code (1983). Second, naltrexone antagonism of the cyclazocine stimulus was not surmountable under these conditions. Naltrexone did not alter the rate-decreasing actions of cyclazocine, with the probable result that cyclazocine doses high enough to overcome blockade of its stimulus properties were incompatible with execution of the required responses.

Numerous studies of the ability of naloxone or naltrexone to block the discriminative effects of κ mixed agonist-antagonists have employed cyclazocine as the reference stimulus. Even high doses of the antagonists do not prevent the cyclazocine-like stimulus effects of levallorphan, oxilorphan, or N-allyl-normetazocine in squirrel monkeys (Schaefer and Holtzman 1978; Teal and Holtzman 1980b). The ability of the antagonists to block the cyclazocine stimulus itself varies across experimental conditions. In contrast to the effectiveness of naltrexone and naloxone as antagonists of a cyclazocine stimulus in monkeys (Schaefer and Holtzman 1978; Teal and Holtzman 1980b, c), the antagonists generally do not completely block a cyclazocine stimulus in rats (Hirschhorn 1977; Rosecrans et al. 1978; Teal and Holtzman 1980a). For example, in rats trained to discriminate 0.3 or 1.0 mg/kg cyclazocine and saline, no naltrexone dose, up to 30 mg/kg, completely antagonizes the cyclazocine stimulus (Teal and Holtzman 1980a). However, naltrexone doses of 0.3–3.0 mg/kg do antagonize completely the cyclazocine stimulus in rats trained to discriminate among 0.3 mg/kg cyclazocine, 1.0 mg/kg morphine, and saline (White and Holtzman 1981). The specific factors underlying these disparate results are unclear.

In addition to antagonizing the stimulus effects of κ opioids, naltrexone antagonized the rate-decreasing effects of EKC and, to a lesser extent, of cyclazocine. The naltrexone doses required to block the rate-altering effects of EKC were relatively high, however. Although available data do not allow direct comparisons of naltrexone antagonism of the rate-decreasing effects of EKC and μ agonists in macaques, comparisons with experiments in squirrel monkeys suggest that 10–100-fold higher doses of naltrexone were needed to produce a 10-fold shift in the EKC dose-response curve in the present study than are needed to produce a similar shift in dose-response curves for the prototypic μ agonist morphine (Goldberg et al.

1981). Thus, the present results are consistent with other evidence that the rate-decreasing effects of κ agonists may be less sensitive to antagonism by naloxone or naltrexone than are similar effects of μ agonists (Harris 1980; Leander 1982; Young and Woods 1982).

In the present experiment, naltrexone generally reversed the rate-decreasing effects of a low cyclazocine dose (0.032 mg/kg), but not those of a higher dose. Under other operant behavioral procedures naltrexone and naloxone are also relatively ineffective antagonists of the rate-decreasing effects of cyclazocine and other mixed agonist-antagonists, including nalorphine, pentazocine, and N-allyl-normetazocine (Downs and Woods 1976; Goldberg et al. 1976; Harris 1980; McMillan et al. 1970; Snell and Harris 1982). The inability of opioid antagonists to block the rate-decreasing effects of these mixed agonist-antagonist opioids may suggest that such effects reflect antagonist or even nonopioid actions.

Finally, the present experiments extend a previous report that the EKC stimulus is susceptible to antagonists with benzomorphan structures. UM 979 exerted a surmountable antagonism of the stimulus and rate-altering effects of EKC and blocked the EKC-like stimulus effects of cyclazocine. The diethyl analogue of UM 979, MR 2266, also blocks the EKC stimulus in rats (Shearman and Herz 1982). Previous workers have suggested that MR 2266 is a more selective antagonist of κ opioids than is naloxone (Roemer et al. 1980). For example, in rats, MR 2266 is twice as potent as naloxone as an antagonist of a 0.32-mg/kg EKC stimulus, but is 1.8-fold less potent than naloxone as an antagonist of a 0.04-mg/kg fentanyl stimulus (Shearman and Herz 1982). This apparently selective effect was not exerted, however, by the particular benzomorphan and oxymorphone antagonists used in the present study. UM 979 was slightly less potent than naltrexone in blocking the EKC and cyclazocine stimuli. Additionally, the lowest effective doses of UM 979 and naltrexone required similar increases in EKC dose to surmount their antagonism of the EKC stimulus, while at the highest doses tested, naltrexone required a greater increase in EKC dose to surmount its blockade than did UM 979.

Acknowledgements. This research was supported by USPHS grants DA 00154 and DA 00254, (J.H. Woods, Principal Investigator). Preparation of this report was supported, in part, by a Wayne State University Neuroscience Program Small Grant and an NIH Biomedical support grant to A. Young. We thank J.H. Woods for critical comments on the manuscript.

References

Downs DA, Woods JH (1976) Morphine, pentazocine, and naloxone effects on responding under a multiple schedule of reinforcement in rhesus monkeys and pigeons. J Pharmacol Exp Ther 196: 298–306

Goldberg SR, Morse WH, Goldberg DM (1976) Some behavioral effects of morphine, naloxone, and nalorphine in the squirrel monkey and the pigeon. J Pharmacol Exp Ther 196: 625–636

Goldberg SR, Morse WH, Goldberg DM (1981) Acute and chronic effects of naltrexone and naloxone on schedule-controlled behavior of squirrel monkeys and pigeons. J Pharmacol Exp Ther 216: 500–509

Harris RA (1980) Interactions between narcotic agonists, partial agonists and antagonists evaluated by schedule-controlled behavior. J Pharmacol Exp Ther 213: 497–503

Hein DW, Young AM, Herling S, Woods JH (1981) Pharmacological analysis of the discriminative stimulus characteristics of ethylketazocine in the rhesus monkey. J Pharmacol Exp Ther 218: 7–15

Herling S, Shannon HE (1982) Discriminative effects of ethylketazocine in the rat: Stereospecificity and antagonism by naloxone. Life Sci 31: 2371–2374

Herling S, Woods JH (1981) Discriminative stimulus effects of narcotics: Evidence for multiple receptor-mediated actions. Life Sci 28: 1571–1584

Hirschhorn ID (1977) Pentazocine, cyclazocine, and nalorphine as discriminative stimuli. Psychopharmacology 54: 289–294

Holtzman SG (1982) Stimulus properties of opioids with mixed agonist and antagonist activity. Fed Proc 41: 2328–2332

Leander JD (1982) Effects of ketazocine, ethylketazocine and phenazocine on schedule-controlled behavior: Antagonism by naloxone. Neuropharmacology 21: 923–928

McMillan DE, Wolf PS, Carchman RA (1970) Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. J Pharmacol Exp Ther 175: 443–458

Roemer D, Buscher H, Hill RC, Maurer R, Petcher TJ, Welle HBA, Bakel HCCK, Akkerman AM (1980) Bremazocine: A potent, long-acting opiate *kappa*-agonist. Life Sci 27: 971–978

Rosecrans JA, Chance WR, Spencer RM (1978) The discriminative stimulus properties of cyclazocine: Generalization studies involving nalorphine, morphine, and LSD. Res Commun Chem Pathol Pharmacol 20: 221–237

Schaefer GJ, Holtzman SG (1978) Discriminative effects of cyclazocine in the squirrel monkey. J Pharmacol Exp Ther 205: 291–301

Shearman GT, Herz A (1982) Evidence that the discriminative stimulus properties of fentanyl and ethylketazocine are mediated by an interaction with different opiate receptors. J Pharmacol Exp Ther 221: 735–739

Snell D, Harris RA (1982) Interactions between narcotic agonists, partial agonists and antagonists evaluated by punished and unpunished behavior in the rat. Psychopharmacology 76: 177–181

Tang AH, Code RA (1983) Discriminative stimulus properties of nalorphine in the rhesus monkey. J Pharmacol Exp Ther 227: 563–569

Teal JJ, Holtzman SG (1980a) Discriminative stimulus effects of cyclazocine in the rat. J Pharmacol Exp Ther 212: 368–376

Teal JJ, Holtzman SG (1980b) Discriminative stimulus effects of prototypic opiate receptor agonists in monkeys. Eur J Pharmacol 68: 1–10

Teal JJ, Holtzman SG (1980c) Stereoselectivity of the stimulus effects of morphine and cyclazocine in the squirrel monkey. J Pharmacol Exp Ther 215: 369–376

White JM, Holtzman SG (1981) Three-choice drug discrimination in the rat: Morphine, cyclazocine and saline. J Pharmacol Exp Ther 217: 254–262

Young AM, Stephens KR, Hein DW, Woods JH (1984) Reinforcing and discriminative stimulus properties of mixed agonist-antagonist opioids. J Pharmacol Exp Ther 229: 118–126

Young AM, Woods JH (1982) Limitations on the antagonistic actions of opioid antagonists. Fed Proc 41: 2333–2338

Received August 8, 1983; Final version June 13, 1984