Psychopharmacology 72, 265–267 (1981)

Psychopharmacology

Discriminative Stimulus Effects of Etorphine in Rhesus Monkeys

Seymore Herling and James H. Woods

Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor, Michigan 48109, USA

Abstract. Two rhesus monkeys were trained to discriminate the IM injection of etorphine (0.001 mg/kg) from saline in a task in which 20 consecutive responses on one of two levers resulted in food delivery. In both monkeys, etorphine (0.0001–0.0018), meperidine (0.1–1.0 mg/kg), morphine (0.1–3.2 mg/kg), and codeine (0.3–3.2) produced dose-related increases in the percentage of total session responses that occurred on the etorphine-appropriate lever. In contrast, ethylketazocine, SKF-10047, and pentazocine, at doses up to and including those that suppressed response rates, produced responses primarily on the saline-appropriate lever. Thus, etorphine-like narcotics, including morphine, have discriminative stimulus effects in rhesus monkeys which can be distinguished from those produced by narcotics with nonmorphine-like actions such as ethylketazocine, SKF-10047, and pentazocine.

Key words: Etorphine – Drug discrimination – Rhesus monkeys

Although numerous studies have demonstrated that narcotics can function as discriminative stimuli in several species of animals (Shannon and Holtzman 1976; Schaefer and Holtzman 1977; Colpaert 1978; Teal and Holtzman 1980; Herling et al. 1980), there are no reports of the discriminative effects of morphine-like narcotics in the rhesus monkey. This is somewhat surprising considering the rather extensive literature that has developed on the reinforcing stimulus characteristics of opiates in this species (Johanson and Balster 1978; Hoffmeister 1979).

In the present experiment, two rhesus monkeys were trained to discriminate the effects of an intramuscular injection of etorphine (tetrahydro-7α-[1-hydroxy-1-methylbutyl]-6,14-endoethenooripavine), a narcotic analgesic that is 200–10000 times more potent than morphine, depending on the assay (Blane et al. 1967; Kosterlitz et al. 1974). The ability of a number of prototypic narcotics to produce an etorphine-like discriminative effect was then investigated.

Offprint requests to: S. Herling

Materials and Methods

The subjects were two adult male rhesus monkeys (*Macaca mulatta*) maintained at approximately 90% (8.0–9.0 kg) of their free-feeding weights. Each monkey was fed sufficient Purina Monkey Chow after each session to maintain these reduced weights. Both monkeys had participated in various behavioral experiments prior to this study and had received a variety of drugs, including narcotics. Neither monkey, however, had participated in an experiment or received any drugs for at least six months before the start of this study.

Prior to each experimental session, the monkeys were removed from their individual home cages and placed in primate restraining chairs. Monkey and chair were then placed in wooden experimental chambers that were fitted with two levers mounted on either side of a food cup. Other essential details of the chamber and other apparatus used in this study have been provided elsewhere (Hein et al. in press).

Initially, each monkey was required to depress one of two levers in order to obtain a 300 mg banana-flavored food pellet. The appropriate lever to obtain reinforcement was determined by the injection the monkey received prior to the session, i.e., either etorphine hydrochloride (right lever) or saline (left lever). The number of responses required for food delivery was gradually increased to 20 (fixed-ratio 20), with the added requirement that the responses occur in succession. Responses on the inappropriate lever reset the fixed-ratio requirement on the appropriate lever. Sessions ended after 75 deliveries of food or 90 min, whichever occurred first.

Training sessions were usually conducted six days a week. Each monkey was injected IM 20 min prior to each session with either 0.001 mg/kg etorphine or saline (0.1 ml/kg). Etorphine and saline injections alternated from one session to the next. Training continued until each monkey met the criteria of emitting fewer than 40 lever presses before the first food delivery of the session and of distributing at least 90% of the total session responses on the appropriate lever. Each monkey was required to meet these criteria for five consecutive sessions during which saline and etorphine injections alternated, and then for four consecutive sessions during which saline and etorphine were administered in a double alternation sequence (e.g., etorphine, etorphine, saline, saline).

Once these criteria were met, test sessions were conducted with a range of doses of etorphine, morphine sulfate, codeine phosphate,

0033-3158/81/0072/0265/$01.00

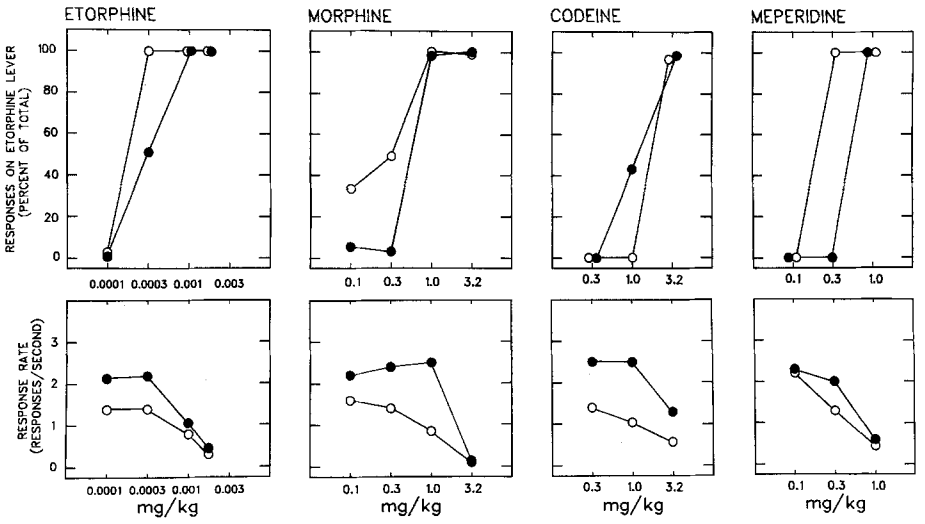

Fig. 1
Discriminative stimulus and rate decreasing effects of four narcotic agonists in two rhesus monkeys trained to discriminate etorphine (0.001 mg/kg) from saline. Upper panel ordinates: number of responses on the etorphine-appropriate lever, expressed as a percentage of the total session responses. Lower panel ordinates: rate of lever pressing, responses per second. Average rates of responding ± 1 SEM during saline training sessions were 1.49 ± 0.06 (monkey 911; $N = 7$) and 2.26 ± 0.06 (monkey 756; $N = 7$). Abscissae: drug dose, mg/kg. Each point represents a single determination. Open circles: monkey 911. Closed circles: monkey 756

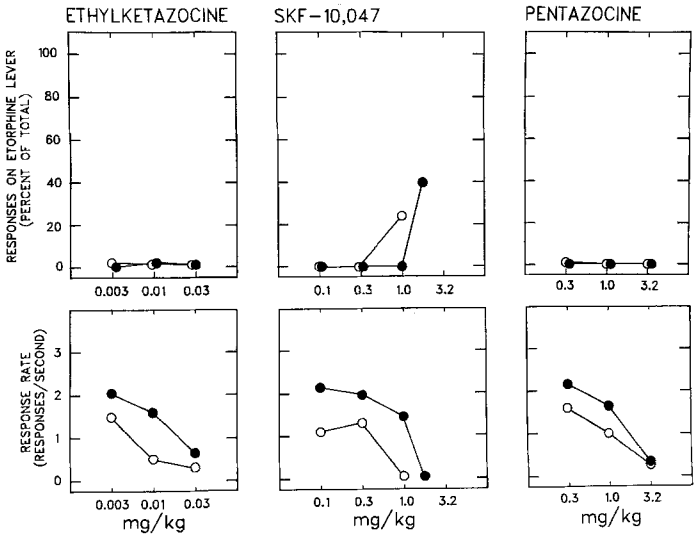

Fig. 2
Discriminative stimulus and rate-decreasing effects of ethylketazocine, SKF-10047, and pentazocine in two rhesus monkeys trained to discriminate etorphine (0.001 mg/kg) from saline. Ordinates, abscissae, and symbols, as in Fig. 1. Average response rates ± 1 SEM following saline injections were 1.31 ± 0.14 (monkey 911; $N = 5$) and 2.30 ± 0.05 (monkey 756; $N = 5$).

meperidine hydrochloride, ethylketazocine methane sulfonate, SKF-10047 hydrochloride (N-allyl-normetazocine), or pentazocine (base). Throughout a test session, 20 consecutive responses on either the etorphine-appropriate or saline-appropriate lever resulted in food delivery; in all other respects, test sessions were identical to training sessions. Etorphine and morphine were injected 40 min prior to test sessions; all other drugs were injected 20 min before the sessions. Test sessions alternated with training sessions. If during a training session an animal failed to meet the training criteria, further testing was postponed until the animal met the criteria on at least two consecutive training sessions.

Pentazocine and ethylketazocine were dissolved in sterile water to which a small amount of lactic acid was added; if needed, sodium hydroxide was used to adjust the pH of the solutions to above 4. All other drugs were dissolved in 0.9% sterile saline. Drug doses refer to the forms described above. Injections of all drugs and saline were made into the thigh muscle in a volume of 0.1 ml/kg.

Data Analysis. The data for test sessions are presented as the average number of responses throughout the session that were emitted on the etorphine-appropriate lever, expressed as a percentage of the total responses. A test drug was considered to produce discriminative effects similar to the training dose of etorphine if 90% of the total session responses were emitted on the etorphine-appropriate lever. The overall rate of responding on the two levers was also recorded during each session. The distribution of responses on the two levers was not evaluated if less than 100 responses were made during the session.

Results

The etorphine-saline discrimination was established in 29 (monkey 756) and 44 (monkey 911) sessions. In both monkeys, morphine, codeine, and meperidine produced effects similar to those produced by etorphine. That is, at the lowest doses of these drugs, responding occurred primarily on the saline-appropriate lever (Fig. 1, upper panels). However, as the dose of the drugs increased, each drug produced responding on the etorphine-appropriate lever that reached a maximum above 90% of the total session responses. In addition, each of the drugs produced a dose-related decrease in the rate of responding (Fig. 1, lower panels). These

drugs were approximately 1000 (meperidine) to 10000 (codeine) times less potent than etorphine in producing both discriminative stimulus effects (Fig. 1, upper panels) and rate-decreasing effects (Fig. 1, lower panels).

In contrast to these effects, ethylketazocine, SKF-10047, and pentazocine resulted in predominantly saline-appropriate responding at doses up to and including those that markedly decreased the rate of responding (Fig. 2).

Discussion

Although a discriminative stimulus effect for etorphine has not previously been reported, it appears to be similar to that produced by morphine. In rats, the discriminative effect produced by morphine is shared by codeine and meperidine (Lal et al. 1977), and in the squirrel monkey, morphine and meperidine have similar discriminative stimulus effects (Schaefer and Holtzman 1977). In the present experiment, the discriminative stimulus produced by etorphine in rhesus monkeys was also produced by morphine, codeine, and meperidine.

In contrast, ethylketazocine, SKF-10047, and pentazocine did not produce discriminative stimulus effects similar to those of etorphine. This result is consistent with other nonmorphine-like behavioral actions of these narcotics in rhesus monkeys (Downs and Woods 1976; Woods et al. 1979; Young et al. in press). Furthermore, the inability of ethylketazocine, SKF-10047, and pentazocine to produce an etorphine-like discriminative effect was not due to the lack of discriminable effects of these drugs, since each of these compounds has been shown to produce stimulus control of responding under a variety of circumstances in several species of animals (Teal and Holtzman 1980; Herling et al. 1980; Hein et al. in press). In rhesus monkeys, for example, SKF-10047 appears to share discriminative stimulus effects with ethylketazocine, while etorphine, morphine, codeine, meperidine, and pentazocine do not (Hein et al. in press). Thus, the discriminative stimulus effects of pentazocine in the rhesus monkey appear to be unlike those of either morphine-like or ethylketazocine-like narcotics.

Each of the narcotics that produced etorphine-appropriate responding in this experiment – codeine, meperidine, morphine, and etorphine – is also self-injected by rhesus monkeys (Johanson and Balster 1978; Young and Woods 1980). In contrast, ethylketazocine (Woods et al. 1979) and SKF-10047 (Young et al. in press) are not self-administered, and the results of pentazocine self-injection studies are equivocal (Johanson and Balster 1978). Thus, there appears to be a good correlation between narcotics that are self-injected by rhesus monkeys and those that produce etorphine-like discriminative stimulus effects in this species.

Acknowledgements. This research was supported by United States Public Health Service grants DA 00154 and DA 00254. A preliminary report of these data was presented to the 41st Annual Scientific Meeting, The Committee on Problems of Drug Dependence, Inc., Philadelphia, PA, June 1979. The helpful comments and suggestions of Rita J. Valentino and Alice M. Young for improving this report are greatly appreciated. The assistance of Isabel Grumet in preparing the manuscript is gratefully acknowledged.

References

Blane GF, Boura ALA, Fitzgerald AE, Lister RE (1967) Actions of etorphine hydrochloride (M99): A potent morphine-like agent. B J Pharmacol 30:11–22

Colpaert FC (1978) Discriminative stimulus properties of narcotic analgesic drugs. Pharmacol Biochem Behav 9:863–887

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

Hein DW, Young AM, Herling S, Woods JH (in press) Pharmacological analysis of the discriminative stimulus characteristics of ethylketazocine in the rhesus monkey. J Pharmacol Exp Ther

Herling S, Coale EH Jr, Valentino RJ, Hein DW, Woods JH (1980) Narcotic discrimination in pigeons. J Pharmacol Exp Ther 214:139–146

Hoffmeister F (1979) Preclinical evaluation of reinforcing and adversive properties of analgesics. In: Beers RF, Bassett EG (eds) Mechanisms of pain and analgesic compounds. Raven Press, New York, pp 447–466

Johanson CE, Balster RL (1978) A summary of the results of a drug self-administration study using substitution procedures in rhesus monkeys. Bull Narc 30:43–54

Kosterlitz HW, Waterfield AA, Berthoud V (1974) Assessment of agonist and antagonist properties of narcotic analgesic drugs by their actions on the morphine receptor in the guinea pig ileum. In: Braude MC, Harris LS, May EL, Smith JP, Villarreal JE (eds) Narcotic antagonists. Advances in Biochemical Psychopharmacology. Raven Press, New York, Vol 8, pp 319–334

Lal H, Gianutsos G, Miksic S (1977) Discriminable stimuli produced by analgesics. In: Lal H (ed) Discriminative stimulus properties of drugs. Plenum Press, New York, pp 23–45

Schaefer GJ, Holtzman SG (1977) Discriminative effects of morphine in the squirrel monkey. J Pharmacol Exp Ther 201:67–75

Shannon HE, Holtzman SG (1976) Evaluation of the discriminative effects of morphine in the rat. J Pharmacol Exp Ther 198:54–65

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

Woods JH, Smith CB, Medzihradsky F, Swain HH (1979) Preclinical testing of new analgesic drugs. In: Beers RF, Bassett EG (eds) Mechanisms of pain and analgesic compounds. Raven Press, New York, pp 429–445

Young AM, Herling S, Winger GD, Woods JH (1980) Comparison of discriminative and reinforcing effects of ketamine and related compounds in the rhesus monkey. Reported to the 42nd Scientific Meeting of the Committee on Problems of Drug Dependence, Inc. NIDA Research Monograph Series 1980

Young AM, Woods JH (1980) Behavior maintained by intravenous injection of codeine, cocaine, and etorphine in the rhesus macaque and the pigtail macaque. Psychopharmacology 70: 263–271

Received June 2; Final version August 27, 1980