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BRIEF COMMUNICATION

Time-Dependent Generalization of Morphine Stimulus Properties to Meperidine: Antagonism by Naloxone

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BARTOLETTI, M., M. GAIARDI, C. GUBELLINI, A. BACCHI AND M. BABBINI. *Time-dependent generalization of morphine stimulus properties to meperidine: Antagonism by naloxone.* PHARMACOL BIOCHEM BEHAV **34**(2) 429–431, 1989.—The time course of the stimulus generalization to morphine by meperidine (20 mg/kg) was determined in rats trained to discriminate morphine (10 mg/kg) from saline in a standard two-lever procedure with food reinforcement. It was found that morphine lever selection following meperidine was a strictly time-dependent phenomenon. Naloxone (0.3 mg/kg) antagonized the stimulus properties of both morphine and meperidine; however, the antagonism was significantly more pronounced against morphine. The results suggest that there may be certain differences in the neuropharmacology of the stimulus properties of morphine and meperidine.

Drug discrimination Morphine Meperidine Rat

MEPERIDINE produces morphine-like subjective effects in humans and it has been shown to possess morphine-like discriminative properties in rats and squirrel monkeys (4,10). However, meperidine is an opiate somewhat different from morphine. High doses of meperidine, but not of morphine, can produce psychotomimetic effects; furthermore, meperidine does not substitute well for morphine in organisms dependent on the alkaloid. Meperidine differs from morphine also with regard to its interaction with opioid antagonists; in fact high doses of naloxone are ineffective in antagonizing the rate decreasing effects of meperidine on schedule-controlled behavior of rats and pigeons (8).

In view of the previously mentioned dissimilarities between morphine and meperidine, the present study has been performed to further analyse their cueing effects. To this end both the time course of the stimulus effects of morphine and meperidine and its sensitivity to naloxone antagonism were determined in rats trained to discriminate morphine from saline.

METHOD

Seven drug-naive male SD rats served as subjects. They were housed in standard laboratory cages located in an animal quarter where a regular twelve-hour day-night cycle was imposed by electric lighting. Water was always available ad lib. Food was available during a 90-min period, beginning 1 hr after each daily session.

Animals were trained to discriminate morphine from saline in a two-lever food reinforced operant task (tandem VI60 FR10). Treatments (10 mg/kg morphine or 2 cc/kg saline) were administered according to the following two sequences, which were presented alternatively: M, S, S, M, M and S, M, M, S, S. The subjects were allowed to respond for 30 min. Two types of data were recorded following each session: 1) the number of responses the animal made on either lever before obtaining the first reinforcement (FRF); 2) the total number of responses (TR) made on both levers during the entire session. Stimulus generalization tests began when a subject reached the training criterion consisting of FRF <12 on at least 8 out of 9 consecutive daily training sessions. On test days, rats were injected IP with morphine (10 mg/kg) or meperidine (20 mg/kg) 15 or 30 or 60 min before the trial. This dose of meperidine was chosen because in a preliminary experiment rats failed to get any reinforcement after an higher dose (30 mg/kg) (data not reported). On generalization tests it was noted on which lever the rat totalized 10 responses first (selected lever); then the rat was given its first food pellet and was reinforced throughout the trial upon pressing (tandem VI60 FR10) the selected lever. The FRF and TR were measured and TR was expressed as percent of the TR found in the most recently preceding saline session. This proportional value will be subsequently referred to as the "response rate." Naloxone tests were performed as described above except that rats were treated with naloxone (0.3 mg/kg) five min before morphine or meperidine.

RESULTS

Figure 1 top panels summarize the time-effect curves for

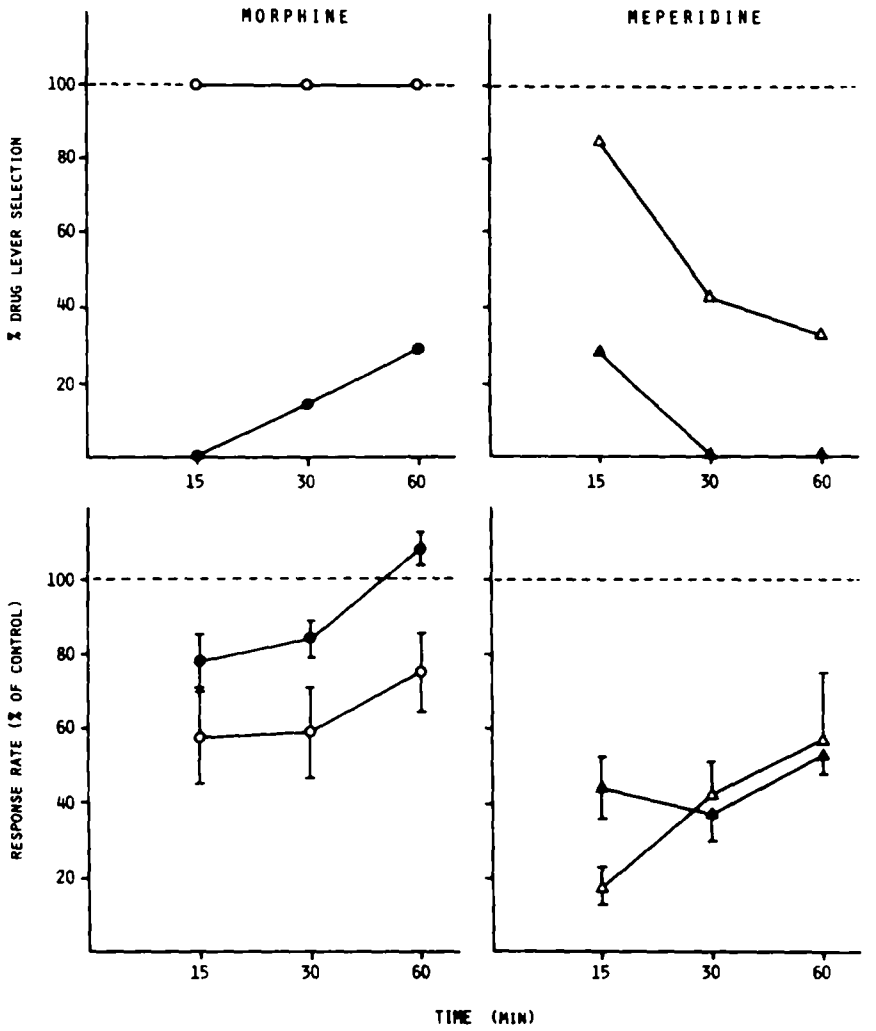

FIG. 1. Time-effect curves of morphine (10 mg/kg) and meperidine (20 mg/kg) in rats trained to discriminate 10 mg/kg morphine from saline. Open symbols represent the effects of drug alone; filled symbols represent the effects of drug in the presence of a 0.3 mg/kg dose of naloxone. Top panels: percentage of subjects selecting the morphine lever. Bottom panels: mean response rate ± SEM.

morphine-appropriate responding after the administration of morphine or meperidine (alone or in the presence of a 0.3 mg/kg dose of naloxone).

The data show that a constant 100% drug lever selection was obtained up to 1 hr after morphine administration. On the contrary, drug lever selection was a strictly time-dependent phenomenon following a meperidine injection; in fact the generalization to morphine was maximal 15 min after the treatment, then the effect rapidly decreased (33% drug lever selection after 60 min). As regards the effectiveness of naloxone pretreatment, the partition of a chi-square (11), performed on the total number of rats selecting the morphine lever at any time, revealed that naloxone antagonism was significantly more pronounced against morphine than against meperidine (drug × naloxone interaction: $\chi^2 = 3.52$, $p = 0.06$).

The TR data (Fig. 1, bottom panels) indicate that both morphine and meperidine decreased the response rate. An ANOVA performed according to a 3-factor design (drug, naloxone, time) showed that the "drug × naloxone" interaction approached statistical significance, $F(1,46) = 2.79$, $p = 0.1$, naloxone antagonism being effective in morphine-treated animals, $F(1,46) = 9.31$, $p < 0.01$, but not in rats injected with meperidine ($F < 1$).

DISCUSSION

Data from the present experiment confirm that meperidine possesses morphine-like discriminative stimulus properties in rats (4,10). However, the results indicate that the time-effect characteristics of these properties are dissimilar from those of morphine. In fact, meperidine produced a substantial drug lever selection (6 out of 7 rats) 15 min after its administration but not later on; moreover, the only unresponsive rat selected the morphine lever when session started 5 min after the injection of the morphine-like drug (data not reported). It is, therefore, evident that the generalization between meperidine and morphine is restricted to a very short period. It is well known that meperidine is shorter acting than morphine (its analgesic effect in man lasts about two-thirds of the morphine effect and the same ratio has been observed for motility effects in rats) (1). However, the difference between the time course of meperidine and morphine stimulus properties is possibly greater than that observed for the above mentioned actions. Even

if it is difficult to make comparisons between the two drugs (since only one dose of each has been used), the present results are in line with other drug discrimination works; in fact a 15 mg/kg dose of meperidine has been reported to produce a response equivalent to a 7.5 mg/kg training dose of morphine in rats when tests were conducted 15 min after the treatment (7). On the other hand, the percent drug lever selection we observed 30 min after meperidine administration is roughly similar to that attainable in the same experimental conditions after a 6 mg/kg dose of morphine (5) and meperidine has been found one-third to one-tenth as potent as morphine in producing morphine-like discriminative stimulus when administered 30 min prior to the session to rats trained to discriminate between saline and morphine (10).

The stimulus effects of morphine were antagonized by naloxone to a greater extent than that of meperidine. In this regard it is worth noting that naloxone could not cancel a meperidine effect slightly smaller than that of morphine. Thus, although only one dose of the antagonist was used, the data do suggest that the morphine-like subjective effects of meperidine are not only short lasting but also somewhat different in nature.

The time courses of morphine and meperidine's actions on response rate were similar; however, the depressant effect of meperidine was more evident and, as already reported by others (8), apparently insensitive to naloxone antagonism. This confirms that the discriminative stimulus properties of narcotics do not covary with their response rate-modifying effect (3), since naloxone antagonized, at least partly, the cueing effect of meperidine.

In summary, the data of the present work provide suggestive evidence that, although meperidine substitutes for morphine in discriminative stimulus experiments in rats, the neuropharmacology of their stimulus properties may differ to some extent. As regards the possible basis of these differences, it can be noted that binding studies demonstrated a relatively greater kappa activity for meperidine (9). Consistently, meperidine, as morphine, codeine and pentazocine, did not produce discriminative effects equivalent to ethylketazocine (EKC) in rhesus monkeys trained to discriminate EKC from saline; nevertheless, the highest percentage of EKC appropriate responding was observed after meperidine (6). The finding that naloxone reversed morphine's effects to a greater extent than those of meperidine supports the conclusion that the stimulus effect of this drug is at least partly mediated by a different subpopulation of opiate receptors. Thus, since naloxone exhibits preferential effects for the μ type of opioid receptors (2), the results obtained might reflect the greater κ activity of meperidine.

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