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# Generalization of Morphine and Lysergic Acid Diethylamide (LSD) Stimulus Properties to Narcotic Analgesics

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*Abstract.* The present investigation sought to determine whether the stimulus properties of morphine and lysergic acid diethylamide (LSD) would generalize to several narcotic analgesics which vary in their subjective effects. Morphine and saline served as discriminative stimuli for one group of rats in a 2-lever discrimination task. LSD and saline were discriminative stimuli for a second group. Depression of one lever in an operant chamber resulted in reinforcement following the administration of morphine or LSD and the opposite lever was reinforced after saline. After discriminated responding was stable, stimulus generalization tests with narcotic analgesics and antagonists showed that the stimulus properties of morphine generalized to methadone and meperidine, and partially to pentazocine, all of which produce morphine-like subjective effects in humans. Morphine stimulus properties did not generalize to nalorphine or cyclazocine, which produce dissimilar subjective effects. The stimulus properties of LSD generalized partially to cyclazocine, but not to nalorphine. In humans cyclazocine and nalorphine produce a high incidence of psychotomimetic effects, but the subjective effects of cyclazocine are differentiable from those of LSD.

*Key words:* Narcotic analgesic – Narcotic antagonist – Psychotomimetic – Discriminative stimulus.

Drugs presently available for the relief of severe pain all have serious side effects. Narcotic analgesics all produce some degree of physical dependence and, sometimes, psychological dependence (Jaffe, 1970). Physical dependence is not always associated with drug craving and a high abuse liability. Some narcotic-antagonist analgesics, such as cyclazocine and nalorphine, produce physical dependence with chronic administration, but withdrawal does not result in drug seeking behavior (Martin et al., 1965; Martin and Gorodetzky, 1965). However, both cyclazocine and nalorphine have subjective side effects characterized by dysphoria and hallucinations (Haertzen, 1970) which render them unsuitable for therapeutic use. Pentazocine, a less potent antagonist of morphine than cyclazocine and nalorphine, more closely resembles morphine in its pharmacological effects and has a somewhat greater incidence of non-medical use than antagonists of the nalorphine type (Paddock et al., 1969).

In the continuing search for analgesics with less serious side effects, methods for detecting and quantifying analgesia, physical dependence, abuse liability, and subjective side effects in animals are of great value. A number of animal tests have been developed which have proved useful for predicting analgesic activity in man (e.g., Eddy and Leimbach, 1953; Harris and Pierson, 1964) and physical dependence can be measured in animals (e.g., Way et al., 1969). However, an animal model for subjective effects in humans has not been available. There are techniques which can determine whether animals will voluntarily self-administer drugs intravenously (Deneau et al., 1969) and drug self-administration is presumably related to certain subjective effects such as euphoria. Animal models are needed for the other subjective effects produced by these drugs.

The observation that certain drugs can serve as discriminative stimuli for laboratory animals (Barry, 1974; Overton, 1968) demonstrates that animals can distinguish the effects of these drugs from the non-drug condition and suggests a possible method by which subjective drug effects can be studied in animals. Both

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morphine (Hill et al., 1971; Hirschhorn and Rosecrans, 1973) and lysergic acid diethylamide (LSD) (Hirschhorn and Winter, 1971; Cameron and Appel, 1973) can serve as discriminative stimuli for the rat. The present investigation sought to determine whether the stimulus properties of morphine and LSD would generalize to several narcotic analgesics which vary in their subjective effects.

## METHODS

*Subjects.* Male Sprague-Dawley rats (Flow Research Animals, Dublin, Va.), without previous drug or behavioral experience, were approximately 10 weeks of age at the beginning of the investigation. They were housed in individual home cages where water was freely available, and exposed to a 12-h light-dark cycle. They were maintained at 70–80% of their free feeding weights with adjusted feedings of a commercial rat chow (experimental weights, 400–440 g).

*Behavioral Methods.* The training and testing procedures were similar to those previously described (Hirschhorn and Winter, 1971). The experimental space was a standard operant test chamber (Lehigh Valley Electronics model 1417) with 2 levers always present. Reinforcement was sweetened condensed milk diluted 1:2 with tap water and delivered by a 0.1 ml dipper. Rats were trained to press both levers and then discrimination training began. Each daily session was preceded by one of two treatments. Following the injection of drug (7.5 mg/kg of morphine for one group of 9 animals, 0.1 mg/kg of LSD for another group of 5 animals), depression of one of the two levers resulted in reinforcement. When saline was given, responses on the opposite lever were reinforced. For one-half of the subjects in each group, the right lever was reinforced after drug and the left lever was correct following saline; these conditions were reversed for the other half of the animals. Experimental sessions were 15 min in duration. In the first 4 sessions, drug and saline administration were alternated daily and each correct bar press resulted in reinforcement. Subsequent sessions were composed of an initial 2.5 min segment during which no responses were reinforced followed by a 12.5 min period during which every fourth response on the appropriate lever resulted in delivery of reinforcement (FR-4). During these sessions, 2 days of drug treatment were followed by 2 days of saline treatment (double alternation).

Stimulus generalization tests with narcotic analgesics were performed after discriminated responding was established and stable. The same animals continued to receive drug and saline treatments according to the same schedule. However, test session of 2.5 min duration in which no responses were reinforced were interposed among discrimination training sessions. The various doses of the narcotic analgesics were administered in a mixed sequence. An odd number of training sessions, generally 3, separated any 2 test sessions.

*Drugs.* The drugs used in this study were: lysergic acid diethamide tartrate, morphine sulfate, methadone HCL, meperidine HCL, nalorphine HCL, and pentazocine and cyclazocine as free bases. Drug doses are expressed in terms of these salts and bases with the exception of LSD which is calculated as the free base. All drugs were dissolved in 0.9% saline. Pentazocine and cyclazocine were first dissolved in a small amount of 8.5% lactic acid resulting in final solutions with a pH of 4–5. Drugs were injected intraperitoneally in a volume of 1 ml/kg. Morphine, LSD and meperidine were injected 45, 5, and 15 min, respectively, before the experimental session. The remaining drugs were each injected 30 min before the session.

## RESULTS

The animals were given 40 sessions under both conditions before the stimulus generalization tests. During these sessions, the 5 LSD-saline animals made 77% of their total responses (in the initial unreinforced 2.5 min) on the LSD-correct lever when they received LSD, and 28% of their total responses on the same lever when given saline. This difference is statistically significant ($P < 0.05$, one tail) by the binomial sign test ($N = 5$). The animals in the morphine-saline group ($N = 9$) made 68% of their total responses on the morphine-correct lever following morphine and 20% of their responses on this lever after saline ($P < 0.01$, one tail, $N = 9$).

The results of stimulus generalization tests for the animals which were trained to discriminate morphine from saline are shown in Figures 1 and 2. During the regular non-test sessions at the time of the stimulus generalization testing, discrimination remained stable at 90% morphine-correct responses following morphine and 9% morphine-correct responses following saline. When various doses of morphine were given, a typical dose-response relationship was obtained, i.e., the percentage of total responses on the morphine-correct lever varies directly with the dose of morphine (Fig. 1). Stimulus generalization to methadone and meperidine is apparent. Both drugs, in appropriate doses, produced a high percentage of morphine-correct responses. Methadone is seen to be approximately equipotent with morphine in terms of its ability to produce morphine-appropriate responding. Higher doses of meperidine were required to produce an equivalent response. Of the three narcotic-antagonist analgesics tested, only pentazocine produced responding appropriate for morphine treatment. Pentazocine is less potent than morphine in eliciting morphine-appropriate responding and the highest dose tested (20 mg/kg), failed to produce as high a percentage of morphine-correct responses (73%) as the training dose of morphine (90%). Since a dose of only 10 mg/kg of pentazocine is a strong discriminative stimulus (unpublished observation), 20 mg/kg should be adequate to produce stimulus generalization, so we did not test a higher dose. Because nalorphine, in doses of 1–20 mg/kg, produced an approximately equal number of responses on each lever, one might anticipate that higher doses of this drug would increase the percentage of morphine-correct responses. However, 40 mg/kg appeared to produce a decrease in

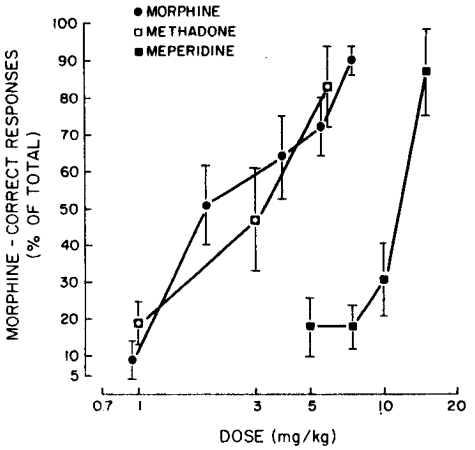


Fig. 1. Generalization of discriminated responding to narcotic agonists in rats previously trained to discriminate morphine from saline. Rats were trained to respond differentially to morphine (7.5 mg/kg) and saline. Then, test sessions of 2.5 min duration, during which no responses were reinforced, were interposed among the regular training sessions. The rats received various doses of narcotic agonists in test sessions. Ordinate: number of responses on the morphine-correct lever expressed as a percentage of total responses. Abscissa: dose of test drug plotted on a log scale. Each point is the mean of one determination in each of 9 animals. Vertical lines indicate ± S.E.M.

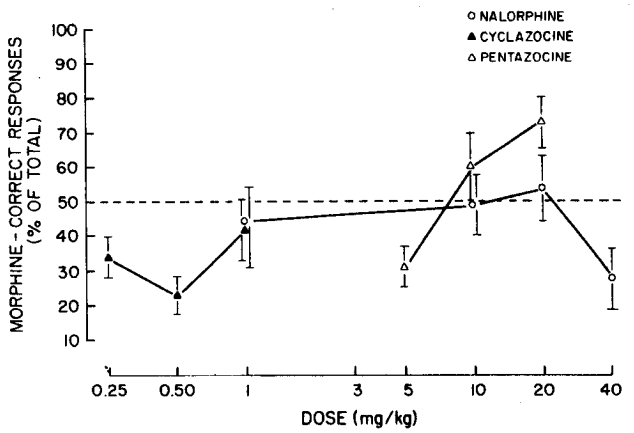


Fig. 2. Generalization of discriminated responding to narcotic antagonists in rats previously trained to discriminate morphine from saline. All details are as in Figure 1, except that narcotic antagonists were given in test sessions

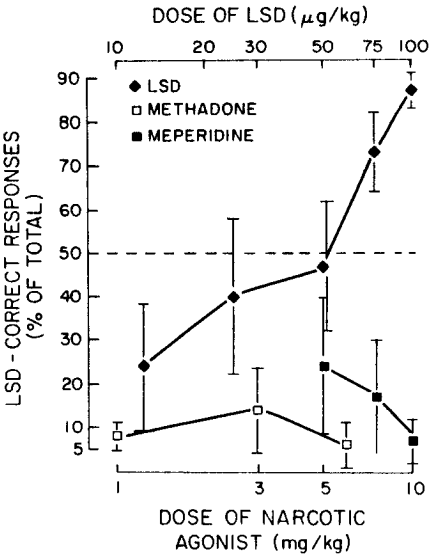


Fig. 3. Generalization of discriminated responding to narcotic agonists in rats previously trained to discriminate LSD from saline. Rats were trained to respond differentially to LSD (0.1 mg/kg) and saline. Then, as in Figure 1, various doses on narcotic agonists were administered in test sessions. Ordinate: number of responses on the LSD-correct lever expressed as a percentage of total responses. Each point is the mean of one determination in each of 5 animals. Other details are as in Figure 1

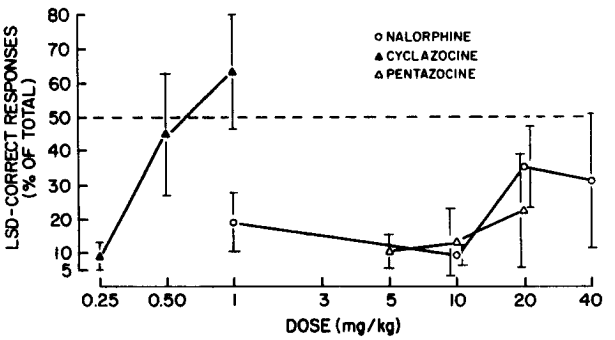


Fig. 4. Generalization of discriminated responding to narcotic antagonists in rats previously trained to discriminate LSD from saline. All details are as in Figure 3, except that narcotic antagonists were given in test sessions

morphine-correct responses. No stimulus generalization was observed with cyclazocine. A higher dose of cyclazocine (2 mg/kg) completely depressed the response rate.

Figures 3 and 4 show the results of stimulus generalization tests for the animals which were trained to discriminate LSD from saline. During the non-test sessions at this phase of the experiment, 87% of the responses were on the LSD-correct lever when LSD was given and 24% of the responses were on the same lever after saline. A characteristic dose-response relationship was obtained for LSD. Of the 5 drugs tested for stimulus generalization, only cyclazocine produced a regular, dose-related increase in the percentage of LSD-correct responses. Complete generalization was not obtained, however, since the highest dose of cyclazocine which did not abolish responding (1 mg/kg) produced only 63% LSD-correct responses compared with 87% LSD-correct responses obtained with 0.1 mg/kg of LSD.

The drug treatments had variable effects on the rate of responding. For both groups of rats, the response rate per min on both levers combined during the first 2.5 min (unreinforced) was similar after drug and saline treatments and averaged 7.1. Responding was almost abolished (mean rate less than 0.2 per min) by the highest dose of cyclazocine (2.00 mg/kg) in both the LSD-saline group and the morphine-saline group and by 15 mg/kg of meperidine in the LSD-saline group. Other decreases in the rate of responding were found with 15 mg/kg of meperidine in the morphine-saline group (mean of 2.2 per min) and with 6 mg/kg of methadone in the LSD-saline group (mean of 3.5 per min). Some of the doses, generally the lower ones, of each of the test drugs produced increases in response rate compared to the training drug and saline conditions. The following treatments produced mean rates of between 15 and 22 per min: in the LSD-saline group, LSD (0.050 and 0.075 mg/kg), meperidine (5.0 mg/kg), nalorphine (1 and 20 mg/kg) and cyclazocine (0.50 mg/kg), and in the morphine-saline group, morphine (0.94 mg/kg), methadone (1 mg/kg), meperidine (5.0 mg/kg), nalorphine (10 mg/kg) and pentazocine (10 and 20 mg/kg). There was no apparent correlation between the rate of responding and stimulus generalization.

## DISCUSSION

The five narcotic analgesics tested for stimulus generalization from morphine and LSD can be divided into three categories (Jaffe, 1970): (1) Methadone and meperidine are morphine-like analgesics. They are synthetic compounds with chemical structures considerably different from morphine, but they produce physical and subjective effects qualitatively similar to those of morphine. (2) Nalorphine and cyclazocine have both morphine antagonist and morphine-like (agonist) pharmacological properties, including analgesic efficacy. The subjective effects of these drugs differ from these of morphine. In contrast to the euphoria which is so pronounced with morphine, nalorphine and cyclazocine produce dysphoria and a high incidence of psychotomimetic effects. (3) Pentazocine also has both antagonist and agonist activity, but it is too strong an agonist and too weak an antagonist to be classified with nalorphine and cyclazocine. The subjective effects of pentazocine given intravenously are essentially morphine-like (Jasinski et al., 1970).

The results of the present study indicate a good correlation between the degree of similarity of the subjective effects of these drugs in man and the stimulus properties in rats. Stimulus generalization occurred from morphine to the two morphine-like narcotic analgesics and to pentazocine, although only partial generalization was obtained with the latter drug, in the doses tested. Furthermore, the relative potency of these drugs in producing morphine-appropriate responding is similar to the relative potency for analgesia and subjective effects in humans. Methadone, approximately equipotent to morphine in terms of analgesia and subjective effects (Denton and Beecher, 1949; Isbell et al., 1948), was found to be also equipotent in stimulus properties. The lower potency of meperidine and pentazocine in the present study is also congruent with the clinical data. Meperidine is one-sixth to one-tenth as potent as morphine in producing analgesia and morphine-like subjective effects (Lasagna and Beecher, 1954; Houde and Wallenstein, 1958) and pentazocine is approximately one-half to one-fourth as potent (Beaver et al., 1966; Keats et al., 1964). Nalorphine and cyclazocine, which have subjective effects in man dissimilar to those of morphine, did not produce stimulus generalization from morphine.

Of the 5 drugs tested, only cyclazocine produced evidence for stimulus generalization in rats trained to discriminate LSD from saline. If the stimulus properties of cyclazocine are indistinguishable from those of LSD, then an appropriate dose of cyclazocine should produce as high a percentage of LSD-correct responses as the training dose of LSD. The result obtained, that the highest dose of cyclazocine that could be tested produced mostly LSD-correct responses, but a lower percentage than was obtained with LSD is more difficult to interpret. One possible interpretation is that the stimulus properties of the two drugs are similar, but have some differences. This would be analogous to the situation in man were both cyclazocine and LSD produce similar psychotomimetic phenomena, but the overall pattern of subjective effects are clearly different (Haertzen, 1970).

Since nalorphine and cyclazocine produce highly similar subjective effects in humans, one might anticipate that the stimulus properties of these two drugs in rats are also highly similar. The different results obtained with nalorphine and cyclazocine in the LSD generalizations suggest differentiable stimulus properties. However, the present experiments do not directly compare the stimulus properties of these two drugs, and only such direct comparisons can determine whether the stimulus properties of nalorphine and cyclazocine are indeed differentiable.

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