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BRIEF COMMUNICATION

Restricted Feeding Does Not Modify Discriminative Stimulus Effects of Morphine in the Rat

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UKAI, M. AND S. G. HOLTZMAN. *Restricted feeding does not modify discriminative stimulus effects of morphine in the rat.* PHARMACOL BIOCHEM BEHAV **29**(1) 201–203, 1988.—An experiment was performed to determine if the discriminative stimulus effects of morphine are modified by mild food deprivation, a condition that increases drug-reinforced behavior. Rats were trained to discriminate between SC injections of saline and morphine (3.0 mg/kg) in a discrete-trial shock-avoidance procedure. Stimulus generalization curves for morphine were then determined on three occasions by a cumulative-dosing procedure: before, during and after the body weight of the rats had been reduced to 86–87% of normal by restricted feeding. Food deprivation had little or no effect on the morphine generalization curve. Despite a close relationship between the reinforcing and discriminative stimulus properties of opioid drugs, stimulus control of behavior by morphine was not modified by a condition that enhances opioid-reinforced behavior.

Morphine Discriminative stimulus effects Food deprivation Reduced body weight Rat

RESTRICTED feeding is a condition that is often used in several areas of behavioral pharmacology, such as in studies of the stimulus properties of drugs, in effects of drugs on schedule-controlled behavior, and in self-administration procedures used to establish drugs as reinforcers. In the latter instance, chronic restricted feeding enhances oral and intravenous self-administration of drugs from a variety of pharmacological classes, including opioids [2]. The mechanism by which food deprivation increases drug-reinforced behavior is unclear, but one possibility is that deprivation modifies the reinforcing properties of drugs [8]. There appears to be a close relationship between the reinforcing and discriminative stimulus properties of opioid drugs [8]. Consequently, factors that modify one set of properties might also be expected to modify the other. The present experiment was performed to determine whether or not food deprivation modifies the discriminative stimulus effects of morphine in the rat. The behavior of the subjects was maintained with an avoidance/escape procedure rather than with food reinforcement in order to minimize the possiblity of confounding the principal independent variable, restricted feeding.

METHOD

Subjects

The subjects were male Fischer-derived rats (Sasco Inc., Omaha, NE) weighing 200–250 g at the start of discrimination training. The rats were housed individually in a ventilated colony room where they had continuous access to food and water, except during periods of restricted feeding, as described below. The lights in the room were illuminated between 6:00 a.m. and 6:00 p.m.

Discrimination Training

Rats were trained to discriminate between 3.0 mg/kg of morphine and saline in a two-choice discrete-trial avoidance paradigm [6,7]. The onset of a trial was signaled by the simultaneous illumination of the house light and the presentation of white noise. At this time, the rat was required to press the "observing" lever mounted in one wall of the test chamber and then to press one of the two "choice" levers mounted in the opposite wall. The first observing response of the trial terminated the white noise and the appropriate choice response extinguished the house light and ended the trial. Beginning 5.0 sec after the onset of the trial, 1.0 mA-shock was delivered to the grid floor of the chamber every 3.0 sec in 0.5-sec pulses until the two-response chain was completed. The intertrial interval was 50 sec during which time the chamber was dimly illuminated by a red light. Experimental sessions ended after 21 trials or 30 min, whichever came first. The first trial of each session was considered a "warm

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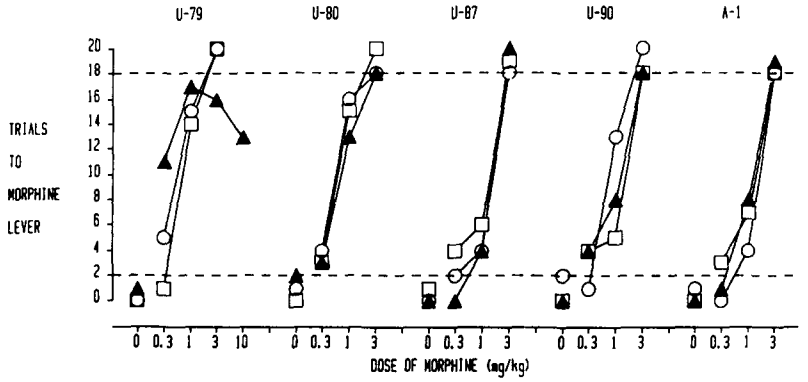

FIG. 1. Cumulative stimulus-generalization curves of morphine in five rats trained to discriminate 3.0 mg/kg of morphine from saline. The stimulus generalization curves for each rat represent the following feeding conditions. ○: normal feeding (prior to restricted feeding), ▲: restricted feeding (86–87% of body weight under normal feeding), □: normal feeding (after restricted feeding). Ordinate: number of trials completed on morphine-appropriate choice lever in 20-trial session; remaining trials of session were completed on lever appropriate for saline. All animals completed all trials of every session. Abscissa: cumulative dose of morphine in milligrams per kilogram (0=saline).

up" and was excluded from the data analysis.

Training sessions were conducted 5 days/week. Either morphine (3.0 mg/kg) or saline was injected SC 30 min before each training session. Training continued until rats could complete reliably at least 18 or 20 trials (i.e., 90% exclusive of the first trial) on the appropriate choice lever under both conditions.

Drug Testing

Drug test sessions were conducted provided the rats satisfied the performance criterion in two consecutive training sessions. During test sessions, both choice levers were activated so that a response on either choice lever after the observing response terminated the trial. Test sessions and training sessions were identical in all other aspects. A cumulative dosing procedure [1] was used to test the effects of reduced body weight on discriminative stimulus effects of morphine. On the test day, rats were injected with saline (SC) and placed in the test chamber 15 min later. After the completion of the 30-min test session, rats were removed to their home cage and injected with morphine SC before the start of the next test session 15 min later. Test sessions were conducted in this manner with increasing doses of morphine until the rats completed at least 18 or 20 trials on the morphine-appropriate lever. The cumulative dose-response curves were determined three times for each rat, 7–8 days apart: prior to, during, and after the restricted feeding condition. Body weights were reduced to 86–87% of normal by feeding the rats 5–10 g of laboratory chow (Rat Chow, Ralston Purina Co.) daily for 7–8 days.

Drugs

Morphine sulfate (Penick Corp., Newark, NJ) was dissolved in sterile 0.9% saline for SC injection. Doses of the drug are expressed in terms of the free base. All SC injections were made in a volume of 1.0 ml/kg body weight.

RESULTS

The cumulative doses of morphine engendered morphine-appropriate responding in a dose-dependent manner (Fig. 1). Under the free-feeding condition, all of the rats chose the morphine-appropriate lever when administered 3.0 mg/kg of morphine. The dose-response curves for morphine in food-restricted rats were almost identical to those in food-satiated rats. One of the rats (U-79) in the food-restricted condition failed to choose the morphine lever completely, even at the highest cumulative dose of morphine (10 mg/kg), although lower doses of morphine (0.3 and 1.0 mg/kg) tended to result in more morphine-appropriate responding than the same doses did during unrestricted feeding. The effect of reducing body weight to less than 80% of normal was examined, but most rats were unable to complete successive 30-min test sessions after receiving morphine at that level of food deprivation.

DISCUSSION

The discriminative stimulus effects of morphine were not modified consistently in rats maintained at reduced body weights by restricted feeding. We believe that this is the first study designed specifically to examine the possible influence of food deprivation on the discriminative stimulus effects of a drug in which behavior was not maintained by food reinforcement. Food deprivation also has failed to modify the discriminative stimulus effects of phencyclidine in pigeons responding under a second-order schedule of food reinforcement [5]. However, food deprivation did enhance the potency of morphine as a discriminative stimulus in rats trained to discriminate 10 mg/kg of morphine from saline under a tandem schedule of food reinforcement [4]. In that study, the ED_{50} for selection of the morphine-appropriate lever was lowered significantly, from 7.79 mg/kg in "partially satiated" animals to 6.09 mg/kg in food-deprived subjects. Because the extent of food deprivation was not specified and because there were numerous procedural differences between that study and the present one, the two seemingly discrepant sets of results cannot be reconciled readily.

Food deprivation reliably increases the rate at which animals self-administer many types of drugs. In the present

study it was possible to reduce the body weight of subjects only to 86–87% of their free-feeding weight. Animals could not respond in successive test sessions when body weight was reduced further, possibly because of the stressful nature of the shock-avoidance/escape procedure. Nevertheless, the extent to which body weight was lowered by restricted feeding fell well within the 85–95% range of free-feeding body weight that results in significantly enhanced self-administration [3].

It is possible that morphine administered SC over the range of doses examined in this study, 0.3–3.0 mg/kg, lacks reinforcement efficacy in the rat, or that more prolonged exposure to morphine in the food deprivation condition is necessary for enhancement of discriminative drug effects. Nevertheless, under the conditions of the present experiment, the discriminative stimulus properties of morphine were not altered by food deprivation, a condition that enhances opioid-reinforced behavior. To the extent that the reinforcing and discriminative stimulus properties of opioid drugs are related to one another [8], these results provide no support for the notion that food deprivation modifies reinforcing drug effects *per se*.

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REFERENCES

1. Bertalmio, A. J., S. Herling, R. Y. Hampton, G. Winger and J. H. Woods. A procedure for rapid evaluation of the discriminative stimulus effects of drugs. *J Pharmacol Meth* **7**: 389–399, 1982.
2. Carroll, M. E., C. P. France and R. A. Meisch. Food deprivation increases oral and intravenous drug intake in rats. *Science* **205**: 319–321, 1979.
3. Carroll, M. E. and R. A. Meisch. Increased drug-reinforced behavior due to food deprivation. In: *Advances in Behavioral Pharmacology*, vol 4, edited by T. Thompson, P. B. Dews and J. E. Barrett. Orlando: Academic Press, 1984, pp. 47–88.
4. Gaiardi, M., M. Vartoletti, A. Bacchi, C. Gubellini and M. Babbini. Increased sensitivity to the stimulus properties of morphine in food deprived rats. *Pharmacol Biochem Behav* **26**: 719–723, 1987.
5. Massey, B. W. and D. E. McMillan. Effects of body weight on discriminative-stimulus control by phencyclidine in the pigeon. *J Exp Anal Behav* **47**: 233–239, 1987.
6. Shannon, H. E. and S. G. Holtzman. Evaluation of the discriminative effects of morphine in the rat. *J Pharmacol Exp Ther* **198**: 54–65, 1976.
7. Shannon, H. E. and S. G. Holtzman. Further evaluation of the discriminative effects of morphine in the rat. *J Pharmacol Exp Ther* **201**: 55–66, 1977.
8. Woods, J. H. Classification of narcotics on the basis of their reinforcing, discriminative, and antagonist effects in rhesus monkeys. *Fed Proc* **41**: 221–227, 1982.