The effects of morphine on conditioned suppression in rhesus monkeys¹

STEPHEN G. HOLTZMAN² and JULIAN E. VILLARREAL, *The University of Michigan, Ann Arbor, Mich. 48104*

Suppression of operant responding maintained by a variable-interval schedule of food reinforcement was established in two rhesus monkeys by the presentation of a preshock stimulus under conditions that resulted in long-term baseline stability. Reports in the literature that morphine restores operant behavior suppressed by preshock stimuli were not confirmed. Morphine produced only dose-related decreases in responding.

Morphine has been reported to restore operant responding in rats suppressed by CSs that precede the delivery of an electric shock (Hill et al, 1954; Maxwell et al, 1961). Hill et al (1954, 1966) have suggested that this effect of morphine is due to a reduction in anxiety associated with the anticipation of pain, and that reduction of pain-anticipatory anxiety may be an important factor in the analgesic efficacy of morphine. Lauener (1963), however, failed to confirm this effect of morphine in the rat using the same procedure but with different parameter values. The present study was designed to examine further the generality of the effects of morphine on behavior suppressed by preshock stimuli.

SUBJECTS

The Ss were two experimentally naive rhesus monkeys (*Macaca mulatta*), one male and one female. They were housed in a group cage, measuring 4 x 5 x 7 ft, where they had free access to water. The monkeys were maintained at 3-3.5 kg, about 75% of their free-feeding weight. The food obtained during experimental sessions was supplemented with Purina Monkey Chow, with isoniazid added as prophylaxis for tuberculosis.

APPARATUS

During the experimental sessions, the monkeys were restrained in a Plexiglas primate chair. Two adjustable Plexiglas horizontal plates locked the monkey at the level of the waist. A lever operandum

(Lehigh Valley Electronics Model 1380) was mounted on one side of the chair at the level of the waist. A Foringer pellet dispenser released 0.7 g Dietrich and Gambrill monkey pellets into a tray situated adjacent to the response lever.

All experimental sessions were conducted with the monkeys in a lightproof, sound-attenuated, and ventilated chamber. The chamber was provided with a constant level of white noise and was illuminated by a 15-W fluorescent bulb mounted on the ceiling. Illumination of two 60-W red lightbulbs, mounted on the door of the chamber directly in front of the monkey, served as the preshock stimulus. Electric shocks were delivered to the monkey through a clip-on electrode fastened to the tail. A one-way glass in the door of the chamber allowed observation of the monkeys during the experimental sessions. Current intensity of the shock was monitored with an oscilloscope.

PROCEDURE

The monkeys were trained to press the lever for food pellets, which were delivered on a variable-interval schedule of reinforcement, with mean intervals of 1 min and with limited holds of 10 sec (VI 1-min, LH 10-sec). The length of each session was 70 min. Daily sessions were conducted at least five times a week.

When the rate of lever responding on the above schedule had become stable from

day to day, the conditioned-suppression procedure of Estes & Skinner (1941) was superimposed on the VI baseline. At regular intervals during each session, a visual stimulus was presented and was terminated simultaneously with the delivery of an unavoidable electric shock to the tail of the monkey.

To obtain an intermediate level of suppression during the preshock stimulus that had long-term stability, the effects of variations in the following parameters were determined: (1) Current intensity of the shock was varied between 5 and 30 mA, (2) shock duration was varied from 0.2 to 10 sec, (3) length of the preshock stimulus was varied between 2 and 5 min, and (4) the preshock stimulus was presented two, four, or five times in each session.

DRUG ADMINISTRATIONS

Drugs were administered subcutaneously 1½ h prior to the start of the session. Drug trials were conducted not less than 1 week apart, and at least four control sessions were interposed between successive drug sessions. The drugs used were morphine sulfate in aqueous solution, and diazepam³ base dissolved in 40% propylene glycol and 10% alcohol. The order of drug administrations was randomized.

RESULTS

The VI schedule generated a stable baseline of safe component responding; however, the suppressant effect of the preshock stimulus was gradually lost with various parameter values upon repeated exposure to the stimulus and shock pairings. Similar loss of conditioned suppression by a preshock stimulus was reported by Sidman (1960). Suppression levels of the order of 80% to 90%, with

Fig. 1. Effects of morphine and diazepam on response rates during preshock stimulus and safe component. Control values for each component represent the mean response rate for that component ± 2 standard deviations of the mean in 24 nondrug sessions.

Fig. 2. Sample cumulative response records illustrating the effects of morphine and diazepam in one monkey. Each presentation of the preshock stimulus is indicated by an offset of the recorder pen and a horizontal line.

long-term stability, were eventually obtained with the following parameters: a preshock stimulus of 2½ min duration presented four times during each session at regular 12-min intervals, the first coming 12 min after the beginning of the session; a current intensity of 10 mA; and a shock duration of 5 sec. These parameters were in effect during the period of drug testing.

Morphine produced only a dose-related depression of lever responding in both components of the schedule (Fig. 1). Diazepam, a drug reported to increase responding suppressed by a preshock stimulus in rats (Xhenseval, 1964), was tested in the same monkeys. In contrast to morphine, diazepam (4.0 mg/kg) produced a significant increase in responding during the preshock stimulus.

Sample cumulative response records of one monkey are shown in Fig. 2. The increase in lever responding during the preshock stimulus produced by diazepam can be compared with the general depressant action on all responding exerted by morphine.

DISCUSSION

The findings that morphine restored behavior suppressed by preshock stimuli in rats (Hill et al, 1954; Maxwell et al, 1961) prompted Hill et al (1954, 1966) to suggest that morphine is effective in relieving pain-anticipatory anxiety, and that the analgesic action of the drug is partially a reflection of anxiety reduction. However, in the present study, morphine failed to reduce conditioned suppression of behavior

in monkeys and produced only a dose-related depression of operant responding in both components of a VI schedule. A similar depression of behavior by morphine in rats was reported by Lauener (1963). Hill et al (1966, 1967) suggested that the discrepancy between their findings and those of Lauener (1963) was possibly related to differences in such parameter values as the intensity and frequency of presentations of the preshock stimulus.

The findings of the present study, although based on a small number of observations, indicate that the reduction of conditioned suppression by morphine is dependent upon procedural details and perhaps also upon species. Thus, the effect of morphine in reducing conditioned suppression lacks sufficient generality to lend support to the view that the analgesic effect of morphine is related to a reduction in anxiety associated with the anticipation of pain. Furthermore, the restoration of suppressed behavior is not exclusive for drugs with pain-relieving properties, as demonstrated by the fact that conditioned suppression was attenuated by diazepam, a drug devoid of significant analgesic activity (Zbinden & Randall, 1967).

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NOTES

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2. Present address: Department of Pharmacology, Emory University, Atlanta, Ga. 30322.
3. The diazepam used in this study was generously supplied by Mr. Rostom Tandourjian of Hoffman-LaRoche, Inc. Expert technical assistance was provided by Messrs. Fred Adams and Clifton Fly.

Effects of sodium deficiency on sodium saccharin drinking¹

F. SAMUEL BAUER,² University of Illinois, Urbana, Ill. 61801

This experiment attempts to test Warren & Warren's (1966) hypothesis that the persistence of intake of nonnutritive sodium saccharin is due in part to the sodium content of the solution. The intakes of sodium saccharin, sodium chloride, and deionized water by sodium-sufficient and by sodium-deficient rats were compared, using a single-stimulus technique. The results contradict Warren and Warren's findings,

leading to the conclusion that sodium does not play an important role in saccharin preference.

In reply to Warren & Warren (1966), who suggested that the persistence of soluble saccharin intake as compared to that of insoluble saccharin was due in part to the sodium content of the soluble saccharin, Valenstein (1966) showed that the difference in the intakes of these substances was probably due simply to differential taste