Pharmacology Biochemistry & Behavior, Vol. 13, pp. 601–603. Printed in the U.S.A.

Naloxone Potentiates the Disruptive Effects of Mescaline on Operant Responding in the Rat

R. L. COMMISSARIS,[1] K. E. MOORE AND R. H. RECH

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824

Received 3 July 1980

COMMISSARIS, R. L., K. E. MOORE AND R. H. RECH. *Naloxone potentiates the disruptive effects of mescaline on operant responding in the rat.* PHARMAC. BIOCHEM. BEHAV. 13(4) 601–603, 1980.—Food-deprived male rats were trained to press a lever on a fixed ratio-40 (FR-40) operant schedule for food reinforcement. Administration of mescaline (4.0–10.0 mg/kg) immediately before the start of the operant session resulted in a cessation of responding for some portion of the 40-min period ("hallucinatory pause"). The duration of this pause was found to be dose-dependent. Although administration of naloxone alone (1.0–8.0 mg/kg, five minutes prior to the start of the session) had no effect on FR-40 responding *per se*, pretreatment with this agent significantly potentiated the disruptive effects of mescaline. This potentiation by naloxone was further shown to be dose-dependent. These data suggest that the effects of the phenethylamine hallucinogen mescaline are potentiated by pretreatment with the narcotic antagonist naloxone.

Hallucinogens Mescaline Naloxone

A NUMBER of investigators have reported interactions between narcotic analgesics or antagonists and *d*-lysergic acid diethylamide (LSD) [4, 6, 7, 12]. Fertziger and Fischer [4] reported that pretreatment with the narcotic antagonist naloxone enhanced the cataleptic effects produced by a high dose of LSD. Recently, Ruffing *et al.* [12] reported that pretreatment with naloxone markedly enhanced the capacity of the indolealkylamine hallucinogens LSD and N,N-dimethyltryptamine to produce periods of suppressed responding in rats performing on a fixed ratio (FR) operant schedule. The present study was designed to determine if this interaction between naloxone and the indolealkylamine hallucinogens could be extended to mescaline, a member of the phenethylamine class of hallucinogens.

METHOD

Subjects

The subjects were four male Sprague Dawley rats (Spartan Farms, Haslett, MI) weighing 350–400 g at the start of the experiment. All subjects were maintained at 70–80% of their free-feeding weights and housed individually in a room with 12-hr light-dark cycle (lights on 0700–1900 hr).

Apparatus

Testing was conducted between 1100 and 1200 hr in one of four standard operant chambers (LVE no. 143-20-215) equipped with food pellet dispensers; these chambers were located in sound attenuating boxes. Each chamber contained a single lever which required a force of 10–15 g to activate. All experimental events were controlled by electromechanical programming circuits and responses were recorded on electromagnetic counters and cumulative recorders. Two parameters of operant responding were monitored; (1) the number of reinforcements obtained (a reflection of the average response rate) and (2) the period of non-responding, or "pausing". To quantify the period of non-responding a pause interval counter [2] was incorporated into the program. This device operated in the following manner. Each response by the subject reset a 10-sec timer. If the subject responded before the 10 sec elapsed, the timer reset and the program continued. If the subject failed to respond during this 10-sec interval, the timer automatically reset but the programming recorded the event as a pause interval. Therefore, the number of times the pause interval timer reset itself without an intervening response assessed the duration of the period of non-responding.

Behavioral Procedure

Prior to the start of the experiment the subjects were trained to bar press on a FR-40 operant schedule for food reinforcement (every 40th response elicited a 45 mg Noyes food pellet). Daily sessions were 40 min in duration. Each animal was run at the same time of day and in the same cage seven days a week. After FR-40 responding had become stable (2–3 weeks) the animals were exposed to low doses of various hallucinogens and *d*-amphetamine, the results of which will be presented elsewhere. Following a two-week

[1]To whom all correspondence should be addressed.

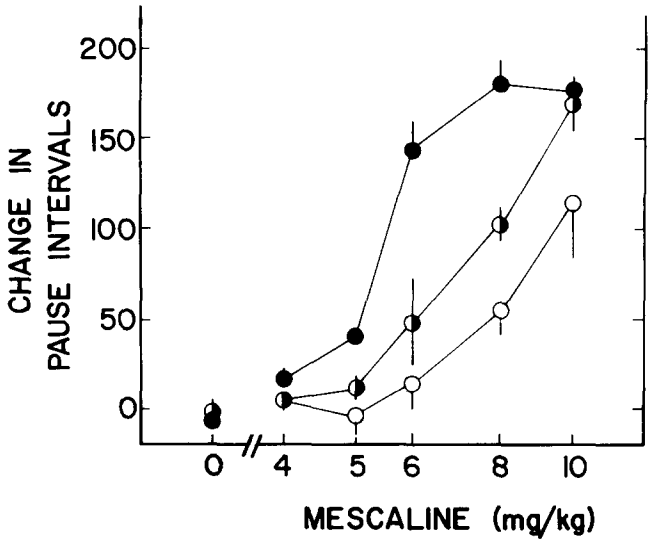

FIG. 1. Effects of mescaline on FR-40 operant responding with and without naloxone pretreatment. The effects of various doses of mescaline alone (open circles) or in combination with 1.0 (half-filled circles) or 4.0 (filled-circles) mg/kg naloxone were determined on the change in pause intervals produced in FR-40 operant sessions. Each symbol and vertical bar represent the mean±SEM obtained from four subjects. Naloxone was administered five minutes and mescaline was administered immediately prior to the start of the forty-minute operant session. Control responses (average of all baseline values) were 117±24 (mean±SEM; n=4) reinforcements and 56±15 pause intervals per session. Naloxone pretreatment significantly potentiated the effects of mescaline as determined by factorial analysis of variance, $p<0.05$. The administration of 1.0 and 4.0 mg/kg naloxone alone (0.0 mescaline) had no significant effect on pause intervals.

drug-free period, the experimental protocol discussed here was begun. In the first phase of the experiment, the effects of various doses of mescaline HCl (4, 5, 6, 8 and 10 mg/kg; obtained from NIDA) alone or in combination with 1 and 4 mg/kg naloxone HCl (obtained from Endo Labs, Garden City, NY) on FR-40 responding were assessed. Both drugs were dissolved in saline and doses refer to the salts. In the second phase of the experiment, the effects of various doses of naloxone (1, 2, 4, and 8 mg/kg) on FR-40 responding were determined. In the third phase, 6.0 mg/kg mescaline was combined with the same doses of naloxone as in phase 2. In all three phases of the experiment, the order of doses administered was completely randomized for each subject. Each drug administration day was preceded by at least three non-drug sessions to avoid the possibility of tolerance development. Both drugs were given by the intraperitoneal route; mescaline was administered immediately prior to the start of the FR-40 session and naloxone was administered five minutes prior to the start of the session.

Statistical Analyses

Drug effects were assessed by comparing the data from test days to the average of the three days prior to the test day (base-line). Student's *t*-test for paired data was used to evaluate the effects of individual doses of drugs. Dose-response relationships were compared by analysis of variance in a block design. In all statistical evaluations $p<0.05$ was used as the criterion for statistical significance.

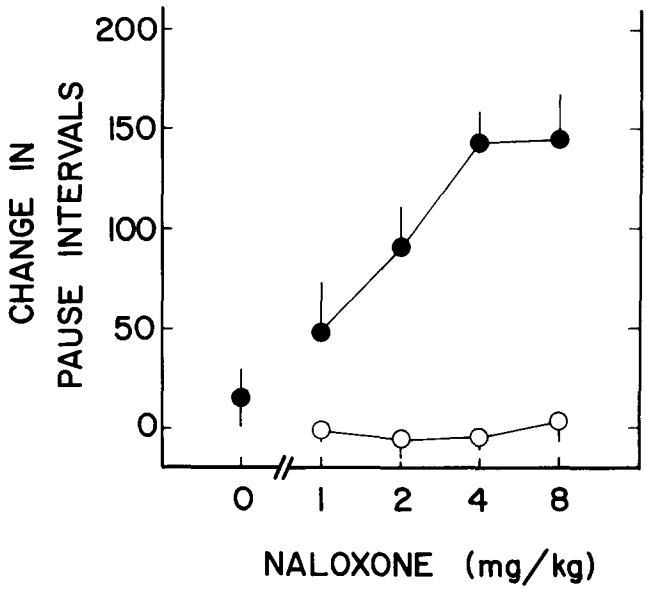

FIG. 2. Effects of naloxone on FR-40 operant responding with and without mescaline. The effects of various doses of naloxone alone (open circles) or in combination with 6.0 mg/kg mescaline (filled symbols) were determined on the change in pause intervals produced in FR-40 operant sessions. Naloxone produced a significant ($p<0.05$) and dose-dependent potentiation of the effects of mescaline. At the dose employed mescaline alone (0.0 naloxone) did not significantly change the number of pause intervals. See Fig. 1 legend for further information.

RESULTS

Mescaline caused a dose-dependent increase in the duration of pausing in animals responding on an FR-40 operant schedule (Fig. 1). This mescaline-induced disruption of responding was enhanced if animals were pretreated with naloxone. That is, pretreatment with 1 or 4 mg/kg naloxone caused the dose-response curve to mescaline to be shifted to the left as determined by analysis of variance. This effect was due to an enhancement of the mescaline response since these doses of naloxone *per se* did not alter operant responding. The lack of effect of naloxone is further demonstrated in Fig. 2 in which doses of 1–8 mg/kg, when administered alone, did not alter the number of pause intervals. On the other hand, when these same doses of naloxone were administered together with a dose of mescaline that has no effect *per se* (6 mg/kg) there was a dose-related increase in the number of pauses. That is, although 6 mg/kg mescaline was without effect when administered alone, it disrupted responding when administered along with 1 mg/kg naloxone; a maximal effect was observed after 4 mg/kg naloxone.

DISCUSSION

Mescaline alone produced a dose-dependent increase in pause intervals and a decrease in reinforcements obtained. Examination of the cumulative records of these animals indicated that this disruptive effect was characterized by periods of non-responding or "pausing" as has been reported previously for hallucinogens of both the indolealkylamine and phenethylamine classes [1–3, 10, 11].

Ruffing *et al.* [12] previously reported that pretreatment with naloxone potentiates the disruptive effects of the indolealkylamine hallucinogens LSD and N,N-dimethyltryp-

tamine. This study extends these findings to mescaline, a member of the phenethylamine hallucinogen class. This study also demonstrates this potentiation at a lower dose of naloxone; that this effect is not simply additive to the dose-dependent "pausing" produced by mescaline is apparent from the absence of any effect of 1–8 mg/kg naloxone alone.

Although the mechanism for the naloxone potentiation of the behavioral effects of hallucinogens has not been elucidated, a number of hypotheses could be advanced. Interactions with 5-HT neurons could be responsible for these observed results. Considerable evidence has suggested that brain 5-HT systems are important in the behavioral effects of hallucinogens, as the effects of members of both the phenethylamine and indolealkylamine classes have been shown to be enhanced by reductions in 5-HT neuronal activity produced by 5,7-dihydroxytryptamine [1,3] or *p*-chlorophenylalanine administration (PCPA; [1]). PCPA has also been reported to antagonize the analgesic effect of morphine in Sprague Dawley rats [13], an effect which is similarly blocked by naloxone [8]. These data suggest that the naloxone potentiation of mescaline effects observed could be due to naloxone interactions with 5-HT neurons.

Naloxone appears to interact with cyclazocine and other hallucinogenic opioid agents at sigma receptors [5], the activity of which may account for the psychotomimetic actions of cyclazocine [14]. If naloxone acts at sigma receptors as a weak partial agonist, it may not exert appreciable hallucinogenic activity in its own right. However, the drug may thus alter the influence of other hallucinogenic agents that act at these sites or on closely related systems. This proposal should be explored by examining interactions between mescaline and various types of opioids, both agonists and antagonists.

It is also possible that naloxone alters the disposition of mescaline to allow for greater concentrations of the hallucinogen at the site of action. However, Ruffing *et al.* [12] have shown that the naloxone potentiation of the disruptive effects of the hallucinogen N,N-dimethyltryptamine is not associated with changes in the disposition of this agent. Therefore, it seems unlikely that the interaction described here is dispositional in nature, although a definitive answer to this question will have to await results of kinetic studies.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the excellent technical assistance of Barbara Z. Stetler and David R. Semeyn. This study was supported by Grant No. DA-01836 from the National Institute on Drug Abuse. R. Commissaris is a predoctoral student supported by USPHS Training Grant GM 07392.

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