Opioid-Hallucinogen Interactions

EDWARD F DOMINO

Department of Pharmacology, M6414 Medical Science Bldg. 1, Box 035
University of Michigan, Ann Arbor, MI 48109-0010

DOMINO, E F Opioid-hallucinogen interactions. PHARMACOL BIOCHEM BEHAV 24(2):401-405, 1986 — Before the advent of neuroleptics, opioids such as morphine were used occasionally in the treatment of schizophrenia and other mental disorders. Recent interest in the possible therapeutic role of endogenous opioid peptides in various mental states has prompted a new look at the opioids. The present paper summarizes the research to date in the author's laboratory on opioid-hallucinogen interactions. A model behavioral state was induced in rats with N,N-dimethyltryptamine (DMT) or lysergic acid diethylamide-25 (LSD). Several mu opioid agonists, antagonists, and synthetic enkephalin analogs interacted with DMT and LSD. Adult male Holtzman rats trained on a positive reinforcement fixed ratio four (FR4) behavioral schedule (i.e., a reward of 0.01 ml sugar-sweetened milk was earned on every fourth bar press) were used in these studies. DMT (3.2 and 10.0 mg/kg) given with a 0.9% NaCl pretreatment IP, disrupted established food rewarded FR4 bar pressing behavior in a dose-related fashion. Pre-determined behaviorally ineffective doses of mu opioid agonists showed selective biphasic effects against DMT and LSD. Low doses antagonized the effects of both hallucinogens, whereas larger doses enhanced their effects. In contrast to the antagonistic effects of low doses of mu opioid agonists, the mu-kappa opioid antagonists (−)-naloxone enhanced the effects of DMT and LSD. (−)-Naloxone enhanced the effects of DMT and LSD. Potentiation of DMT-induced behavioral disruption was ascribed to a stereospecific opioid antagonist effect of (−)-naloxone in that the (+)-naloxone enantiomer failed to potentiate the effects of DMT. Further studies are indicated to determine hallucinogen-opioid interactions in various species, including man. The present findings reinforce a possible antagonist role of opioid substances in mental processes involving hallucinations.

METHOD

Subjects

Male Holtzman rats at least 90 days old were maintained at approximately 70% of their expected free feeding weight and housed individually in a rodent facility where constant temperature and humidity were maintained.

Procedure

Rats were trained to press a bar for one hour daily using 0.01 ml of sugar sweetened, water diluted evaporated milk as a positive reinforcement. The milk was prepared by combining 400 ml of evaporated milk with 400 ml of tap water and 60 g of granulated sugar. Daily experiments were conducted in a darkened, isolated room using Lehigh Valley Electronics rodent operant test cages model 143-21. The daily bar-pressing schedule was fixed ratio four (FR4), i.e., every fourth bar press earned a milk reward. Cumulative recorders automatically recorded bar presses, reinforcements, and any disruption of normal bar pressing. Upon stabilization of the FR4 behavior, each rat was subjected to a daily schedule of one hour of bar pressing for a minimum of 5 days prior to any injections. The training and testing procedures were similar to those previously described by Kovacec and Domino [2]. Animals used in this study were usually drug free for a minimum of 7 days prior to the experiment and had no past history of being given long-acting compounds. Rats served as their own controls to compare the effect of a hallucinogen with and without naloxone pretreatment. All rats were scheduled in randomly assigned groups. Drug-free intervals of 1 week were observed for all pretreatment groups. Because of the short duration of action of DMT, less than a full week was accepted as a drug-free interval for the DMT control groups. Doses of DMT (1.0, 3.2, and 10.0 mg/kg) or LSD (0.1 mg/kg) were administered IP to disrupt food-rewarded fixed ratio bar pressing in a dose-related fashion. Log doses of naloxone (1.0, 2.4, 3.2, and 5.6 mg/kg), which had no effect on normal bar pressing behavior for periods up to 60
minutes, were used as pretreatment doses. No 0.9% NaCl pretreatments were used for the control hallucinogen studies since it had previously been demonstrated that 0.9% NaCl pretreatment does not alter reactions to DMT or LSD [2, 3].

In the control procedure, rats were placed in an operant chamber for 15 minutes of bar pressing, injected IP with the hallucinogen, and returned immediately to the operant chamber until the rat recovered and bar pressed at a rate of 90% of control for a 60 minute period. Animals were observed and their behavior was noted for the duration of the drug effect.

For the pretreatment procedure, rats were pretreated with the opioid (IP) and immediately placed in the operant chamber to bar press for 5–10 minutes, injected with the hallucinogen (IP), and returned immediately to the operant chamber until the rat recovered and bar pressed steadily for 60 minutes or more.

**Drugs**

(−)-Naloxone hydrochloride was administered in 0.9% NaCl. Concentrations refer to free base. DMT doses refer to free base, solutions were prepared by dissolving the free base in 1 N HCl, adding to 0.9% NaCl, and adjusting the pH with 0.1 N NaOH, rendering the final volume at a pH of 4.5–6.0. Doses of LSD refer to LSD-25. DMT was ob-
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FIG 5 Effects of (+)- and (-)-naloxone pretreatment on DMT-induced disruption of FR4 bar pressing behavior in the rat. Note that only (-)-naloxone enhanced the effects of DMT.

FIG 6 Biphasic effects of morphine and methadone pretreatment on DMT and LSD-induced disruption of FR4 bar pressing behavior in the rat. Groups of 5-10 rats received fixed doses of 3.2 or 10.0 mg/kg of DMT or 0.1 mg/kg LSD for control and pretreatment injections with each rat serving as its own control. The control treatment was 0.9% NaCl 5-10 minutes prior to DMT or LSD. Pretreatment doses were administered 5-10 minutes prior to DMT or LSD. Morphine (0.32-1.0 mg/kg) and methadone (0.32 mg/kg) pretreatment doses antagonized the effects of DMT- and LSD-induced disruption of FR4 behavior; whereas larger doses of morphine (3.2 mg/kg) and methadone (1.0-3.2 mg/kg) potentiated LSD-induced but not DMT effects.

Data Analysis

The duration of the drug effect was measured by the horizontal line generated by the cumulative recorder during the cessation of normal bar pressing. Since both onset and recovery of DMT and LSD effects are sudden and complete, the duration of the drug effect could easily be calculated from the length of the horizontal segment. To statistically analyze these data, two-tailed Student t-tests were calculated using the value of p < 0.05 as significant.

RESULTS

Acute DMT Effects

Increasing doses of DMT given IP caused progressively longer disruption of bar pressing (Fig 1). The mean ± S.E. suppression of bar pressing for groups of 6-8 rats was determined for each dose. As can be seen, a dose of 1 mg/kg of DMT caused little or no disruption of bar pressing. A dose of 3.2 mg/kg of DMT caused the rats to stop bar pressing for about 25 minutes, while 10 mg/kg abolished bar pressing for about 50 minutes. A very large dose of 32 mg/kg of DMT disrupted bar pressing for about 150 minutes. However, the rats had marked motor symptoms including convulsions.

Chemical Methods

Unfasted male Holtzman rats weighing approximately 500 g were used for the chemical analysis. Pretreated rats were injected with naloxone 3.2 mg/kg IP 5 minutes prior to 14C-DMT 10 mg/3 μCi/kg, IP. Control rats received only 14C-DMT 10 mg/3 μCi/kg IP. The rats were sacrificed by guillotine 30 and 90 minutes after 14C-DMT injection. The entire brain and approximately 2 g of liver from each rat were immediately removed and homogenized in ice-cold 1 N HCl. The homogenates were assayed for total radioactivity, total acidic metabolites, and DMT [4].

N,N-Dimethyltryptamine side chain-14C-hydrogen oxalate was purchased from New England Nuclear, Boston, MA. The 14C-DMT 10 mg/3 μCi/ml solution was prepared by mixing nonradioactive DMT with radioactive DMT.
Naloxone Enhancement of DMT and LSD Suppression of FR₄ Behavior

Pretreatment with behaviorally ineffective doses of naloxone (1–5 mg/kg, IP) dramatically enhanced the effects of DMT as well as LSD, as shown in Figs 2 and 3. A dose of 10 mg/kg of DMT was chosen to study more extensively. Such a dose of DMT in control rats would suppress mean bar pressing for about 50 minutes (Figs 1 and 2). Increasing doses of naloxone, especially 3, 2, and 5.6 mg/kg, IP, markedly potentiated the effects of DMT. A dose of 3.2 mg/kg of naloxone plus 10 mg/kg of DMT was as effective as 32 mg/kg of DMT alone (compare Figs 1 and 2).

A dose of 0.1 mg/kg of LSD IP suppressed bar pressing for 30–50 minutes in control groups of rats (Fig 3). This dose caused comparable suppression of FR₄ behavior to about 10 mg/kg of DMT. Naloxone pretreatment (1 to 5 mg/kg) caused a similar potentiation of LSD disruptive effects.

Failure of Naloxone Pretreatment to Alter ¹⁴C-DMT Brain and Liver Levels

Rat brain and liver levels of ¹⁴C-DMT were assayed to determine whether naloxone pretreatment was interfering with DMT biotransformation. In this experiment, a dose of 10 mg/kg, IP of non-radioactive DMT caused about 60 minutes of suppression of bar pressing which was prolonged 3 fold to about 180 minutes (p<0.001) by 3.2 mg/kg of naloxone, as shown in the left hand portion of Fig 4. Control untrained groups of rats were given 10 mg/kg of DMT containing 3 μCl of ¹⁴C-DMT and their brains and livers removed 30 and 90 minutes later. The mean level of radioactivity of these groups was compared to rats receiving 3.2 mg/kg of naloxone pretreatment plus the same of non-radioactive and ¹⁴C-DMT. When analyzed by group comparison Student t-tests, no significant differences were found in brain or liver ¹⁴C-DMT, total radioactivity, or ¹⁴C-acidic metabolites.

Stereospecific Effects of Naloxone Enantiomers

The differential effects of (+) and (−)-naloxone pretreatment on DMT-induced disruption of FR₄ behavior in individual rats. Pretreatment with FK 33-824 antagonized these effects. The antagonism of LSD was greater than that of DMT.

DISCUSSION

The evidence that the opiate antagonist (−)-naloxone enhances the behavioral effects of DMT and LSD is impressive. This effect is not due to increased brain or liver levels of DMT. Furthermore, small doses of mu opioid agonists antagonize DMT and LSD behavioral effects. Thus, the data obtained substantiate important interactions of the indole hallucinogens with opioids in the rat and strengthen the evidence for involvement of endogenous opioids in the pathogenesis of chemically induced psychoses. The dramatic hallucinogenic antagonistic effects of LY 127623 and FK 33-824 are especially interesting and parallel the findings of morphine and methadone in antagonizing the behavioral disruptive effects of DMT and LSD. These results suggest that DMT and LSD effects are modulated by a specific and selective opioid agonist action. It would be of interest to extend these findings using kappa opioid agonists as well.

To date, all of our studies involve the use of opioid agonists as pretreatments. Opioid agonists also should be given after DMT or LSD to determine if opioid post-treatment will reduce the duration of hallucinogen action. If effective under these latter conditions, human trials involving hallucinogen induced “bad trips” treated with small doses of opioids would be logical to conduct.
ACKNOWLEDGEMENTS

The author would like to acknowledge the efforts of his former colleagues Dr Beverly Kovacic, Ms Diane Ruffing and Ms Sandy Demetriou at the Lafayette Clinic, Detroit, MI 48207. Much of this research has been published with them in different formats elsewhere as given in the list of references.

REFERENCES


