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Opioid-Hallucinogen Interactions[1]

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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 (FR_4) 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 FR_4 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 antagonist (−)-naloxone enhanced the effects of DMT and LS (−)-Naloxone enhanced the effects of DMT and LSD Potentiation of DMT-induced behavioral disruption was attributed 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

DMT LSD Opioid-hallucinogen interactions

IN recent years, the role of endogenous opioids in human psychoses has been extensively studied At best, one can conclude that their interaction is complex and far from clear For the past 10 years my colleagues and I have used animal models of psychotic states induced by DMT, LSD and other hallucinogens Our working hypothesis is that drugs which enhance or reduce the effects of DMT, LSD or PCP may shed light on the actions of these hallucinogens and possibly have relevance to human psychoses, or at least to human hallucinogen abuse Antagonists of various hallucinogens should have therapeutic utility in the management of "bad trips " The present paper summarizes our own studies on DMT and LSD-opioid interactions which have been published in detail previously [1, 5, 6, 7]

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 (FR_4), 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 FR_4 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 Kovacic 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

[1]Supported in part by the Psychopharmacology Research Fund (Domino)

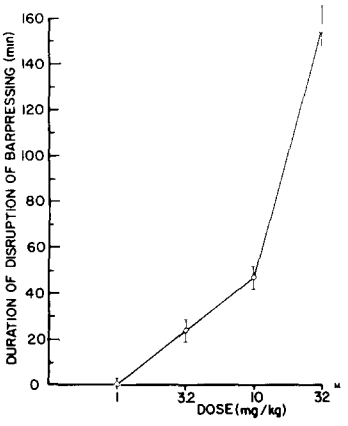

FIG 1 Dose-effect relations of DMT in producing disruption of rat bar pressing behavior The mean ±S E duration in min of groups of 6–8 rats per dose given IP is shown

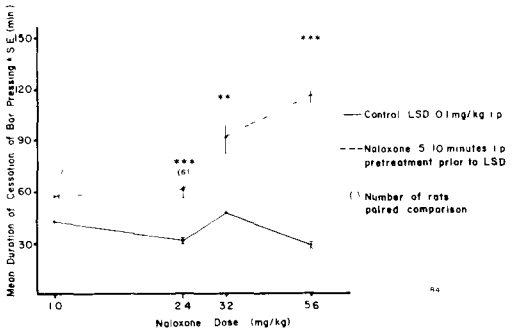

FIG 3 Dose-effect relations of naloxone enhancement of LSD suppression of FR_4 behavior in the rat The experimental design was similar to that described in the legend of Fig 2, except that LSD was used instead of DMT

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

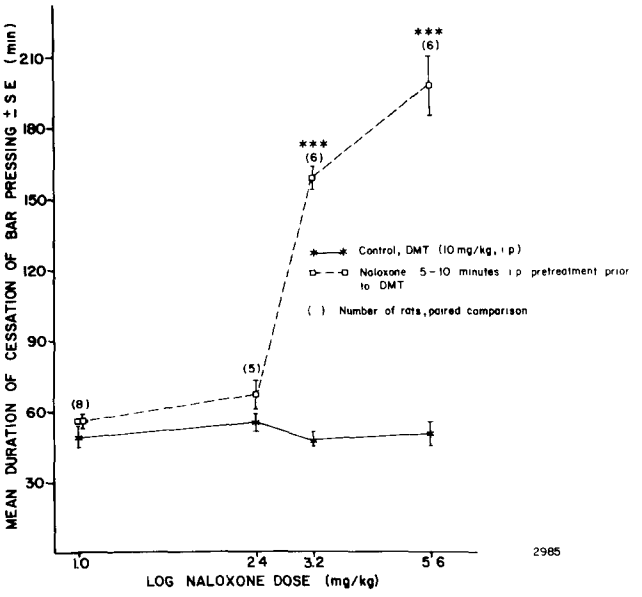

FIG 2 Dose-effect relations of naloxone enhancement of DMT suppression of FR_4 behavior in the rat Increasing doses of naloxone were given to each group of 5–8 animals per point 5–10 min prior to DMT Control animals received DMT alone A fixed dose of 10 mg/kg of DMT was used for both groups of animals Each animal given naloxone plus DMT was also given at a different time the hallucinogen alone Although the different groups show some variability to DMT, naloxone significantly enhanced the suppressant effects In this and subsequent figures $*p<0.5$, $**p<0.01$, and $***p<0.001$ All injections were IP

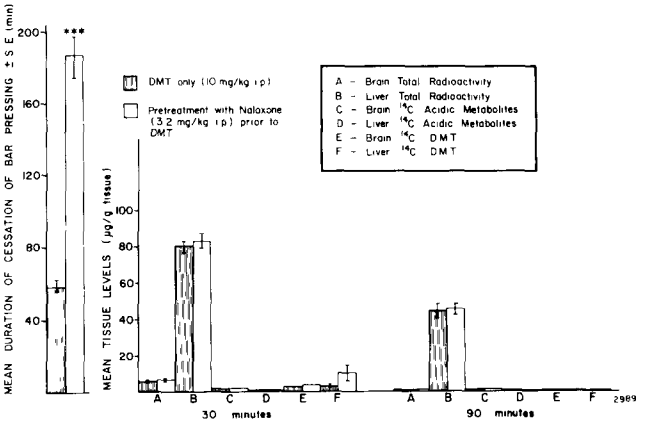

FIG 4 Effect of naloxone on DMT suppression of FR_4 behavior and ^{14}C-DMT brain and liver content The two vertical bars on the left indicate the potentiating effects of naloxone on DMT in a group of trained rats The remaining bars toward the right show the comparison of radioactivity levels in the brain and liver of ^{14}C-DMT (10 0 mg/kg) control groups and naloxone pretreated groups (3 2 mg/kg 5 min prior to ^{14}C-DMT) Untrained rats (8 per group) were given either naloxone plus DMT or DMT alone with an identical schedule as trained animals The animals were killed 30 and 90 minutes after ^{14}C-DMT Their brains and livers were removed and assayed for ^{14}C-DMT, total ^{14}C, and ^{14}C-acidic content No differences were noted

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-

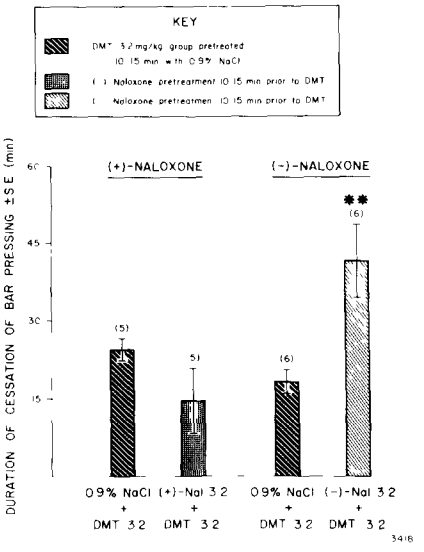

FIG 5 Effects of (+)- and (−)-naloxone pretreatment on DMT-induced disruption of FR_1 bar pressing behavior in the rat Note that only (−)-naloxone enhanced the effects of DMT

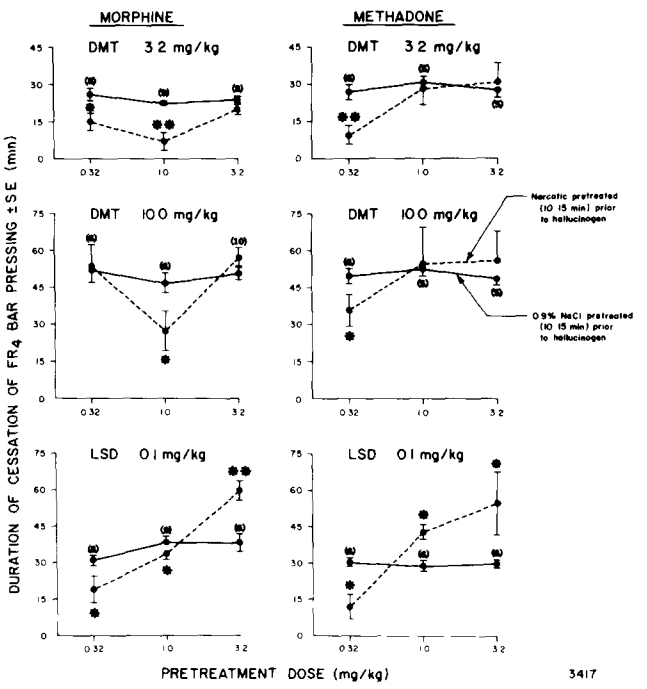

FIG 6 Biphasic effects of morphine and methadone pretreatment on DMT and LSD-induced disruption of FR_4 bar pressing behavior in the rat Groups of 5–10 rats received fixed doses of 3 2 or 10 0 mg/kg of DMT or 0 1 mg-kg LSD for control and pretreatment injections with each rat serving as its own control The control treatment was 0 9% NaCl 5–10 minutes prior to DMT or LSD Predetermined behaviorally noneffective 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 FR_4 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

tained from the Sigma Chemical Company LSD (Delysid) was obtained from the National Institute on Drug Abuse Morphine sulfate was obtained from Pierce (Rockford, IL 61105) and methadone HCl from Eli Lilly (Indianapolis, IN 46285) and were administered in 0 9% NaCl (−)-Naloxone HCl (naloxone) was generously supplied through the courtesy of the Endo Laboratories (Garden City, NY 11530) (+)-Naloxone HCl (NIH 9548), supplied through the courtesy of Dr Arthur E Jacobson of the National Institute of Health, was prepared by dissolving the compound in a solution of 0 9% NaCl and 0 1 N HCl, and adding 0 1 N NaOH to adjust the acidity of the final volume, rendering a pH of 4 3 LY 127623 (Metkephamid) and FK 33-824 log doses were administered in 0 9% NaCl, and supplied through the courtesy of Dr R Frederickson (Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN) and Drs Graffenried and del Pozo (Department of Experimental Therapeutics, Biological and Medical Research Division, Sandoz Limited, Basel, Switzerland), respectively

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 ^{14}C-DMT 10 mg/3 μCi/kg, IP Control rats received only ^{14}C-DMT 10 mg/3 μCi/kg (IP) The rats were sacrificed by guillotine 30 and 90 minutes after ^{14}C-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-1-^{14}C-hydrogen oxalate was purchased from New England Nuclear, Boston, MA The ^{14}C-DMT 10 mg/3 μCi/ml solution was prepared by mixing nonradioactive DMT with radioactive DMT

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

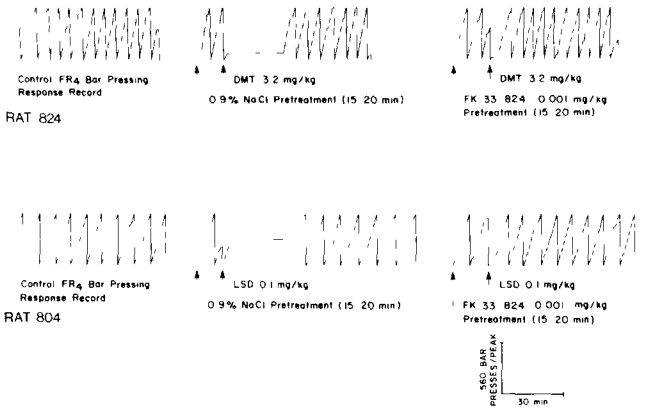

FIG 7 Cumulative bar pressing records of individual rats showing the effects of FK 33-824 in antagonizing the effects of DMT and LSD DMT and LSD both caused an interruption of bar pressing behavior in individual rats Pretreatment with FK 33-824 antagonized these effects The antagonism of LSD was greater than that of DMT

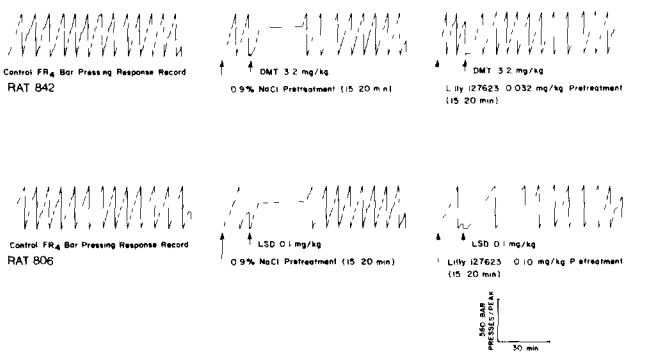

FIG 8 Cumulative bar pressing records of individual rats showing the effects of LY 127623 in antagonizing the effects of DMT and LSD DMT and LSD both caused an interruption in bar pressing behavior in individual rats LY 127623 antagonized this effect The antagonism of DMT was greater than that of LSD

Naloxone Enhancement of DMT and LSD Suppression of FR_4 Behavior

Pretreatment with behaviorally ineffective doses of naloxone (1 0–5 6 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 FR_4 behavior to about 10 mg/kg of DMT Naloxone pretreatment (1 0 to 5 6 mg/kg) caused a similar potentiation of LSD disruptive effects

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

Rat brain and liver levels of ^{14}C-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 μCi of ^{14}C-DMT and their brains and livers removed 30 and 90 minutes later The mean levels of radioactivity of these groups were compared to rats receiving 3 2 mg/kg of naloxone pretreatment plus the same of non-radioactive and ^{14}C-DMT When analyzed by group comparison Student t-tests, no significant differences were found in brain or liver ^{14}C-DMT, total radioactivity, or ^{14}C-acidic metabolites

Stereospecific Effects of Naloxone Enantiomers

The differential effects of (+) and (−)-naloxone pretreatment on DMT-induced disruption of FR_4 bar pressing behavior are shown in Fig 5 Only the (−) enantiomer was effective ($p<0$ 01) in enhancing the effects of DMT in the doses used

Effects of Mu Opioid Agonists

Morphine and methadone in doses of 0 32, 1 0, and 3 2 mg/kg IP prior to DMT (3 2 and 10 mg/kg) or LSD (0 1 mg/kg) showed biphasic dose dependent effects (Fig 6) Significant antagonism of DMT- and LSD-induced behavioral suppression occurred with the smaller doses of morphine and methadone Some differences were observed between the two opioids, as shown in Fig 6

The two synthetic opioid met-enkephalin in peptide analogs, FK 33-824 and LY 127623, were also effective in antagonizing the behavioral disruptive effects of DMT and LSD, as illustrated in Figs 7 and 8

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 hallucinogen antagonistic effects of LY 127623 and FK33-824 are especially interesting and parallel the findings of morphine and methadone with 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

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