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Evidence for Opioids as Partial Antagonists for Indole Hallucinogens

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Various observations have supported the hypothesis that endogenous opioid peptides are involved in psychoses either therapeutically or pathogenically (Rimón et al. 1980; Pickar et al. 1981). Prior to the advent of neuroleptics, opioids such as morphine were used historically to treat mental disease. Hence, the role of opioids in psychoses is obscure and complex. It was decided to use an animal model of drug-induced psychotic behavior to investigate this interaction further (Ruffing et al. 1979; Ruffing & Domino 1981). Several opioid agonists, antagonists, and synthetic enkephalin analogues were studied on N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD-25) induced disruption of food-rewarded FR_4 bar-pressing behavior in the rat. The striking interactions observed are reported herein.

Method

Adult male Holtzman rats were maintained at 70 percent of their expected free-feeding weight. Stable food-rewarded fixed ratio 4 (FR_4) bar pressing behavior was established, followed by daily 60-minute bar pressing sessions for a minimum of days prior to injections. Animals were then randomly assigned to groups (N = 5-12), scheduling each rat to serve as its own control to compare hallucinogen-induced effects with and without assigned pretreatment drugs. Control groups were pretreated with 0.9 percent NaCl intraperitoneally (i.p.) prior to DMT (3.2-10.0 mg/kg) and LSD (0.1 mg/kg) injections. A minimum 7-day drug-free interval was observed between scheduled injections. Predetermined behaviorally noneffective pretreatment drug doses given 10-20 minutes prior to DMT or LSD were as follows: morphine sulfate and methadone hydrochloride (0.32-3.2 mg/kg), (+)-MR 2267 (5.6-10.0 mg/kg), (−)-MR 2266 (3.2 mg/kg), (+)-naloxone hydrochloride (3.2 mg/kg), (−)-naloxone hydrochloride (1.0-3.2 mg/kg), naltrexone (1.16-3.7 mg/kg), (+)- and (−)-WIN 44,441-2/3 enantiomers (1.47-3.52 mg/kg), Lilly 127623 (0.0032-0.32 mg/kg), and FK 33-824(0.0001-0.01 mg/kg). All drug dosages refer to free base and were administered i.p. Two-tailed Student's t-test paired comparison determinations, calculated according to Snedecor (1956), were used to analyze pretreatment and/or hallucinogen drug effect interactions (i.e., antagonism, potentiation, or no effect). Due to the limited quantity of (+)-naloxone HCl and (−)-MR 2266, incomplete dose-effect relations are reported.

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Results

DMT (3.2-10.0 mg/kg) and LSD (0.1 mg/kg) induced a reproducible disruption of food-rewarded bar pressing. Characteristic DMT and LSD-induced gross behavioral effects (evident within 2-5 minutes following i.p. injections) consisted of: lying quietly with the eyes open in an excessively flattened position for prolonged intervals, periodic Straub tail, muscular twitching and/or body movements, circling in a flattened position or reverse crawling, splayed and/or extension of the hind limbs, periodic stereotypic repetitious body movements, sustained periods of arching, and disinterest in food and/or bar pressing. The DMT and LSD-induced gross behavioral effects described above or with pretreatment drugs were consistent in all groups tested excepting morphine, methadone, and (-)-MR 2266 pretreated groups. In the morphine pretreated animals fewer and less intense gross behavioral effects were observed with periodic interest in food and/or bar pressing. Paradoxically, intensified gross behavioral effects were observed in the methadone and (-)-MR 2266 pretreated groups (i.e., increased and excessive flattening with frequent sustained repetitious head/body movements and markedly increased Straub tail). At the cessation of drug effects the rats would appear normal and abruptly start and continue bar pressing at pre-injection response rates.

The opioid agonist pretreatment groups (Figure 1) showed selective biphasic effects, i.e., morphine (0.32-1.0 mg/kg) and methadone (0.32 mg/kg) antagonized the effects of DMT and LSD-induced bar pressing disruption, whereas larger doses of morphine (3.2 mg/kg) and methadone

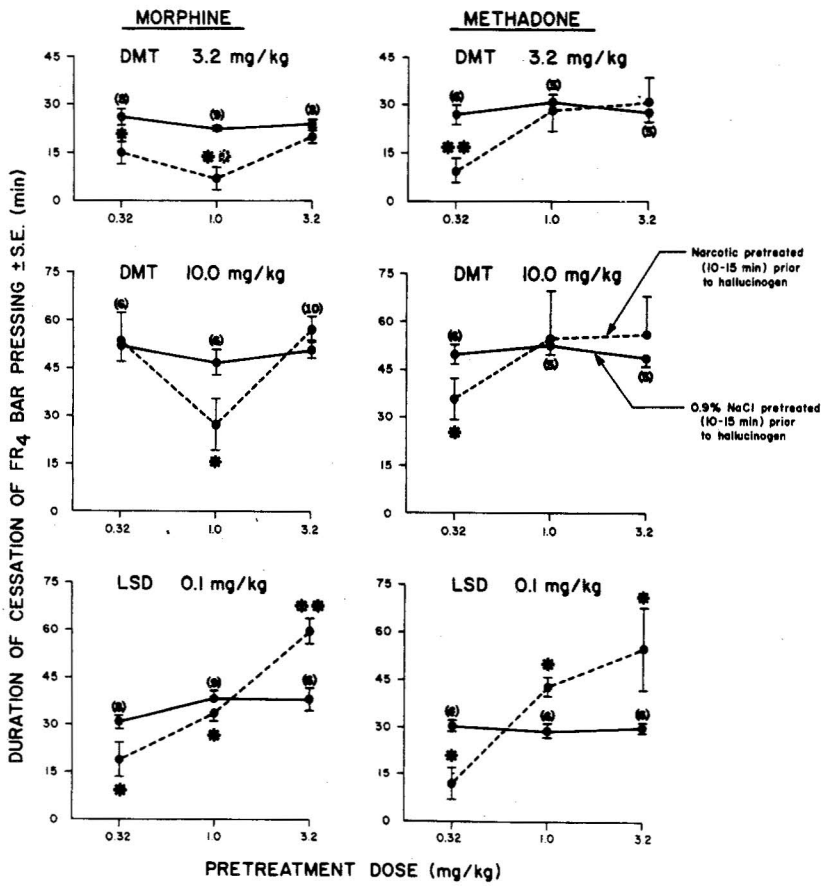

FIGURE 1. Effects of morphine and methadone pretreatment on DMT and LSD-induced disruption of FR_4 bar pressing behavior in the rat.

(1.0-3.2 mg/kg) selectively potentiated only LSD-induced effects with no differences noted in the DMT groups. The data indicate morphine as the more effective antagonist for DMT (3.2 mg/kg) and LSD-induced activity.

Conversely, the opioid antagonists, naloxone and naltrexone in pretreatment doses of 1.0-3.2 and 1.16-3.7 mg/kg, respectively, potentiated the behavioral DMT and LSD-induced effects as shown in Figure 2. Potentiation of DMT-induced effects was attributed to a stereospecific opioid antagonist effect of (−)-naloxone in that the (+)-naloxone enantiomer failed to interact or potentiate DMT (Ruffing & Domino 1981).

Pretreatment with stereo-isomers of two selected synthetic opioid antagonists, (+)-WIN 44,441-2, (−)-WIN 44,441-3, (+)-MR 2267, and (−)-MR 2266, unexpectedly demonstrated no interaction with DMT (3.2 mg/kg) induced disruption of FR_4 behavior, whereas both (+)- and (−)-WIN 44,441 enantiomers selectively potentiated the behavioral induced LSD effects, while only the (−)-MR 2266 stereo-isomer selectively antagonized behaviorally induced LSD effects (Figure 3).

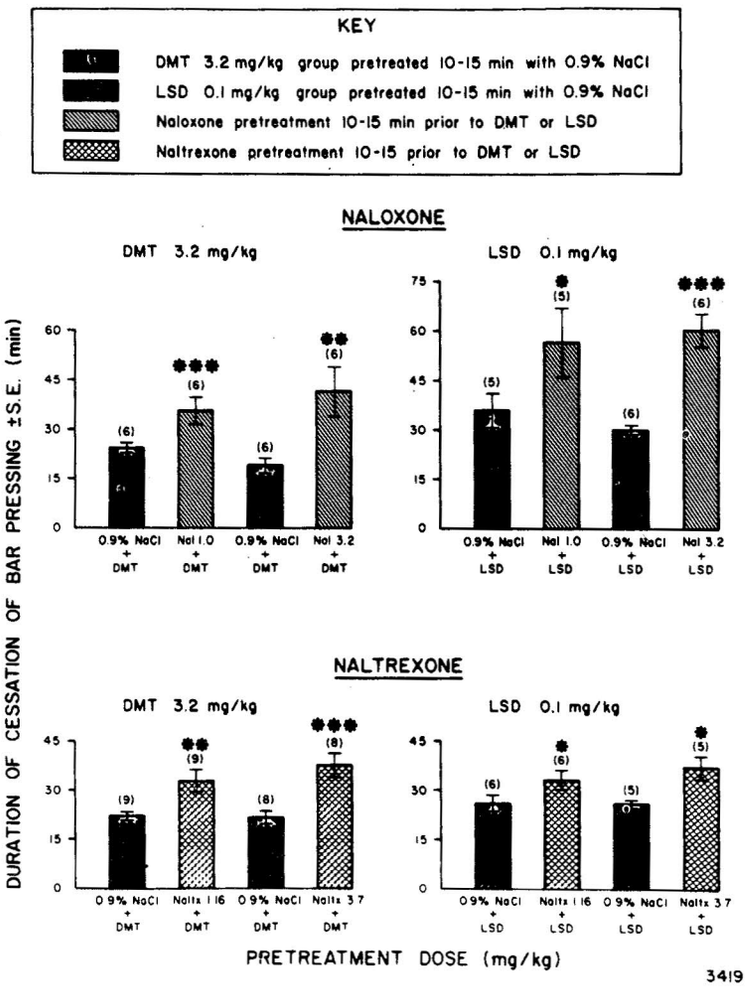

FIGURE 2. Potentiation of DMT and LSD-induced disruption of FR_4 bar pressing behavior in rats pretreated with naloxone and naltrexone.

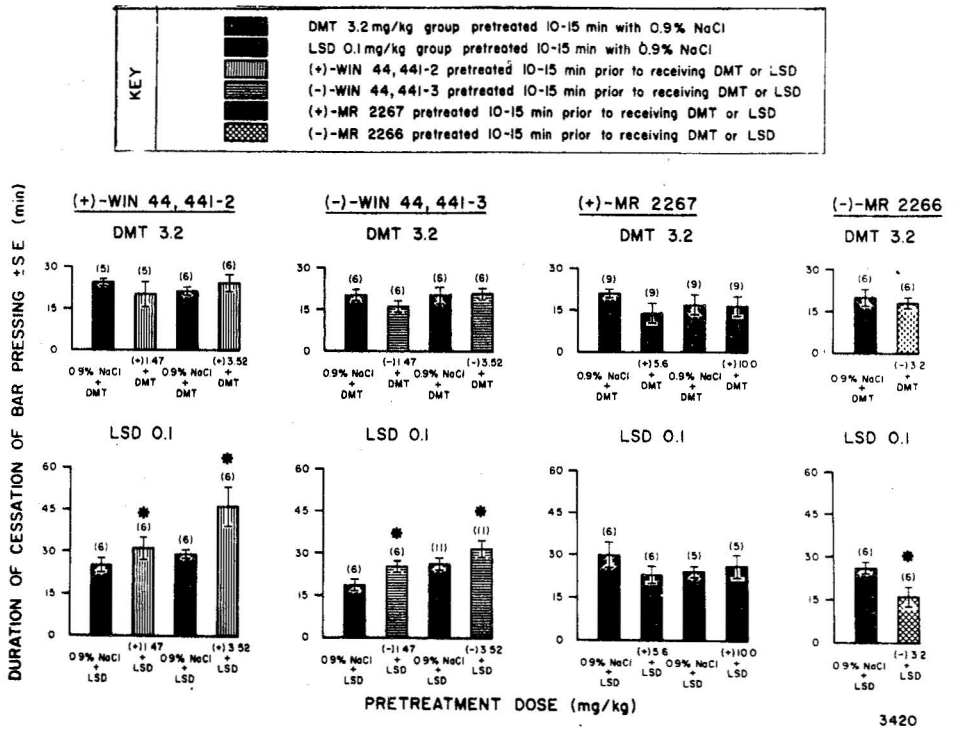

FIGURE 3. Effects of pretreatment with WIN 44,441-2, WIN 44,441-3, MR 2266, and MR 2267 on DMT and LSD-induced disruption of FR_4 bar pressing behavior in the rat.

As shown in the Table, the peptide synthetic enkephalinanalog pretreatment doses of Lilly 127623 (0.01-0.32 mg/kg) and FK 33-824 (0.001-0.01 mg/kg) significantly antagonized the effects of DMT (3.2 mg/kg), while pretreatment doses of Lilly 127623 (0.10-0.32 mg/kg) and FK 33-824 (0.00032-0.01 mg/kg) significantly antagonized the effects of DMT (3.2 mg/kg), while pretreatment doses of Lilly 127623 (0.10-0.32 mg/kg) and FK 33-824 (0.00032-0.01 mg/kg significantly antagonized LSD-induced effects. Additionally, Lilly 127623 (0.032 mg/kg) pretreatment also significantly antagonized the behaviorally induced disruptive bar pressing effects of DMT 10.0 mg/kg.

Discussion

The results of the present study extend previous observations that naloxone potentiated DMT and LSD-induced disruption of food-rewarded bar pressing in the rat (Ruffing et al. 1979). It is generally known that the biologically active narcotic antagonist is the (-)-naloxone isomer. Thus, it is of special interest that (+)-naloxone was inactive in potentiating the effects of DMT, confirming stereospecificity.

There is evidence that DMT and LSD, while sharing similar hallucinogenic effects, also show differences in the extent of dopaminergic and serotonergic agonist effects. For example, LSD has been shown to produce potent dopaminergic activity not produced by DMT (Nichols 1981). It is also abundantly clear that there are multiple neurotransmitter and opioid receptors, so that many of these agents differ in their molecular mechanism of action (Snyder & Goodman 1980). The present study indicates that the various opioid agonists and antagonists have very complex interactions with DMT and LSD. Although no simple theory explains all of the data obtained in this investigation, the present study indicates that there are very important interactions between these hallucinogens and opioids in the rat. The dramatic antagonistic effects of the opioid peptides, Lilly 127623 and FK 33-824, are especially prominent and deserve additional investigation with various behavioral paradigms in different species of animals including man.

Table

Mean Duration of DMT and LSD-Induced Disruption of Food-Rewarded FR_4 Bar Pressing in Control 0.9% NaCl Pretreated and Corresponding Lilly 127623 or FK 33-824 Pretreated Rats

	Mean duration of FR_4 bar pressing disruption (± S.E.)							
	DMT 3.2 mg/kg (i.p.)				LSD 0.1 mg/kg (i.p.)			
Pretreatment Drug/Dose mg/kg (i.p.)	(N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p^a	(N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p^a
Lilly 127623 (0.0032)	(6)	26 ± 2	27 ± 3	N.S.	—	—	—	—
Lilly 127623 (0.01)	(10)	27 ± 2	12 ± 3	***	—	—	—	—
Lilly 127623 (0.032)	(10)	28 ± 2	10 ± 4	***	(6)	31 ± 2	27 ± 3	N.S.
Lilly 127623 (0.10)	(12)	26 ± 1	14 ± 3	*	(8)	29 ± 1	10 ± 3	***
Lilly 127623(0.32)	(10)	27 ± 3	14 ± 4	*	(8)	28 ± 3	18 ± 2	*
FK 33-824 (0.0001)	-	-	-	-	(6)	30 ± 1	32 ± 3	N.S.
FK 33-824 (0.00032)	(6)	28 ± 2	25 ± 1	N.S.	(9)	29 ± 1	11 ± 4	***
FK 33-824 (0.001)	(8)	26 ± 2	7 ± 3	***	(8)	31 ± 1	13 ± 3	***
FK 33-824 (0.0032)	(6)	25 ± 3	14 ± 3	*	(8)	27 ± 3	10 ± 4	*
FK 33-824 (0.01)	(6)	30 ± 4	24 ± 5	*	(6)	29 ± 2	19 ± 2	**

	DMT 10.0 mg/kg (i.p.)			
Pretreatment Drug/Dose mg/kg (i.p.)	(N)	Control 0.9% NaCl Pretreated	Drug Pretreated	p^a
Lilly 127623 (0.032)	(6)	51 ± 3	21 ± 7	**

All pretreatment injections were given 15-20 min prior to DMT or LSD.
p_a values represent paired comparison t-tests.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; N.S. - not significant

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