

1984

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Mokler, David J.; Rech, Richard H.; Commissaris, Randall L.; and Henck, Judith W., "Behavioral Interactions Of Opioid Agonists And Antagonists With Serotonergic Systems" (1984). *Biomedical Sciences Faculty Publications*. 4.
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Behavioral Interactions of Opioid Agonists and Antagonists With Serotonergic Systems

Richard H. Rech, David J. Mokler,
Randall L. Commissaris, and Judith W. Henck

Morphine interacts with brain serotonergic (5-HT) systems; these systems have been implicated in morphine analgesia and dependence see Cervo et al., 1981). The 5-HT agonist quipazine induces analgesia in rats that is attenuated by naloxone and 5-HT antagonists (Minnema et al., 1980; Samanin et al., 1976). Behavioral disruption by the hallucinogens LSD, DMT and mescaline, mediated primarily through brain 5-HT effects (Rech and Commissaris, 1982), is potentiated by naloxone and naltrexone (Commissaris et al., 1980; Ruffing and Domino, 1981) and is variably antagonized or potentiated by morphine and methadone (Ruffing and Domino, 1981). Cyclazocine causes a disruption of operant behavior similar to that of the hallucinogens which is reversed in part by naloxone and the 5-HT antagonist metergoline, and to a greater extent by the combination of naloxone and metergoline (Henck et al., 1983). These studies indicate that indole and phenethylamine hallucinogens interact to some extent with brain opioid mechanisms as well as brain 5-HT components, whereas opioid drugs influence behavior in part by actions on 5-HT systems.

We have extended these drug studies in an attempt to characterize interactions with 5-HT mechanisms and to identify the various types of opioid receptors involved.

METHODS

Male Sprague-Dawley rats were food deprived to 75-80% of free-feeding weights and trained to a fixed ratio-40 (FR-40) schedule of food reinforcement. The number of reinforcers (Bioserve 45 mg food pellets) and "pause intervals" (a 10 sec period without a response, Commissaris et al., 1980; Rech and Commissaris, 1982) were recorded for daily 40-min sessions. Changes in the patterns of responding were determined after combinations of lysergic acid diethylamide (LSD) or 2,5-dimethoxy-4-methylamphetamine (DOM) with naloxone (NAL), cyclazocine (CYCL) with quipazine (QUIP) or metergoline (MTG), ethylketocyclazocine (EKC) with NAL or MTG, and N-allyl-normetazocine (SKF 10,047; SKF) with NAL or MTG. Dose-response curves were analyzed by a one-way ANOVA using the least significant differences (lsd) test for comparing individual doses to baseline; multiple dose-response curves were compared by a two-

way ANOVA using the lsd test for individual comparisons. The significance level was set at $p < 0.05$.

RESULTS

LSD (12.5-100 $\mu\text{g}/\text{kg}$) or DOM (0.125-1.0 mg/kg) caused a dose-related increase in pause intervals (Fig. 1) that was reciprocally related to a decrease in reinforcers delivered. Pretreatment with 4 mg/kg NAL potentiated the disruptive effects of LSD and DOM, but neither dose-response curve was shifted in a parallel fashion.

CYCL disrupted FR-40 responding as shown in Fig. 2. Like the hallucinogens, CYCL caused a dose-related decrease in reinforcers that was reciprocally related to increases in pausing. This disruption was attenuated over the entire dose range, at least for pauses, by pretreating with a low dose of QUIP (0.5 mg/kg). Additional pretreatment with MTG (1.0 mg/kg) nullified the QUIP antagonism only at the highest dose of CYCL tested. A previous report indicated that the CYCL effects were antagonized over the middle-dose range by both NAL (4 mg/kg) and MTG (1 mg/kg) pretreatment, and combination of these pretreatments showed additive protection (Henck et al., 1983).

FR-40 disruption was also observed with QUIP (Fig. 3) and a dose-related reciprocal increase in pausing was again associated with the decrease in reinforcers. Therefore, the hallucinogens, certain opioids, and 5-HT agonists appear to affect FR-40 responding in this manner. Pretreatment with NAL (4 mg/kg) slightly potentiated the disruptive effects of low doses of QUIP but had no significant effect at higher doses. Likewise, pretreatment with a small dose of CYCL (0.5 mg/kg) slightly potentiated low dose QUIP without influencing the effect of higher doses. However, when the NAL and CYCL pretreatments were combined, the marked disruption observed after 2.0 mg/kg QUIP alone was greatly attenuated. Thus, the disruptive effects of QUIP may involve both 5-HT and opioid mechanisms.

The prototype kappa agonist EKC (Fig. 4) decreased reinforcers in a dose-related manner with a reciprocal increase in pauses, but, unlike the hallucinogens, exhibited a steep dose-response curve. Pretreatment with NAL slightly potentiated the disruptive effects of low doses of EKC but prominently antagonized the effects of higher doses. Pretreatment with MTG also enhanced the effects of low doses of EKC and antagonized EKC disruption only at the 1.0 mg/kg dose. A low dose (0.5 mg/kg) of CYCL was also administered as a pretreatment (not illustrated) and interacted with EKC in a pattern very similar to that noted with MTG pretreatment.

Since SKF has hallucinogenic properties and may be a selective agonist at sigma receptors, its effects on the FR-40 operant pattern were examined (Fig. 5). Once more the hallucinogenic profile of decreased reinforcers with a reciprocal increase in pause intervals was obtained. In this case pretreatment with 4 mg/kg NAL did not significantly influence the disruptive pattern of the drug. Pretreatment with MTG slightly antagonized the effects of SKF at several intermediate doses. Therefore, SKF does not appear to exert these disruptive effects via NAL-sensitive opioid receptors, but may act to some extent through 5-HT mechanisms.

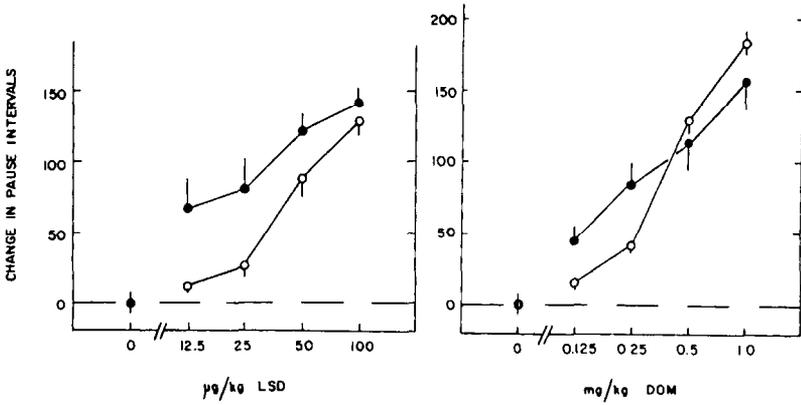


Fig. 1. Dose-response of LSD or DOM alone (open circles) or combined with 4 mg/kg naloxone (NAL) (closed circles) on FR-40 behavioral response pattern.

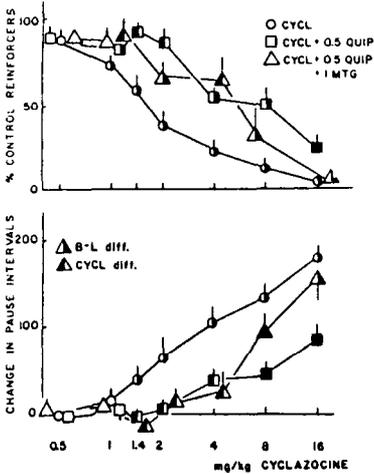


Fig. 2. Dose-response of cyclazocine (CYCL) alone, combined with 0.5 mg/kg quipazine (QUIP), or combined with 0.5 mg/kg QUIP and 1.0 mg/kg metergoline (MTG).

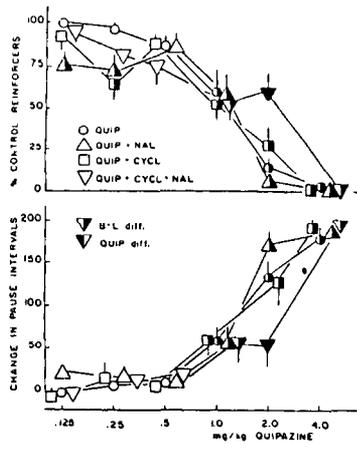


Fig. 3. Dose-response of quipazine (QUIP) alone, combined with 4 mg/kg naloxone (NAL), with 0.5 mg/kg cyclazocine (CYCL), or with both NAL and CYCL.

Pretreating with a low dose (0.5 mg/kg) of CYCL (results not illustrated) slightly attenuated the increase in pausing at the highest dose (16 mg/kg) of SKF, but otherwise had no appreciable effect.

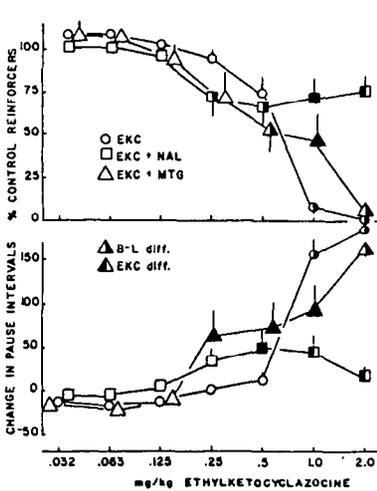


Fig. 4. Dose-response of ethylketocyclazocine (EKC) alone, combined with 4 mg/kg naloxone (NAL), or combined with 1 mg/kg metergoline (MTG).

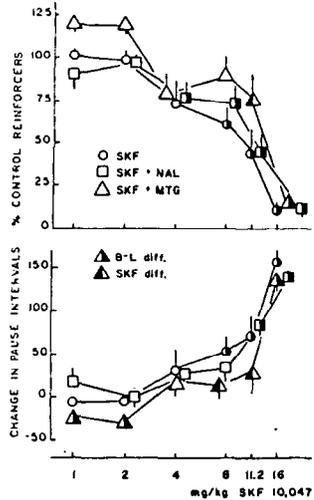


Fig. 5. Dose-response of SKF 10,047 (SKF) alone, combined with 4 mg/kg naloxone (NAL), or combined with 1 mg/kg metergoline (MTG).

DISCUSSION

The shifts of the dose-response curves of LSD, DOM (Fig. 1 and mescaline (Commissaris et al., 1980) to the left by pretreatment with 4 mg/kg NAL were not parallel, suggesting that the opioid interaction is modulatory and not exerted at the same receptors as those affected by the hallucinogens. Similar results were found for LSD and DMT by Ruffing and Domino (1981). Additionally, they observed antagonism of the operant behavioral disruption of hallucinogens by pretreating with low doses of morphine or methadone. The dose of NAL required to produce these interactions (2-8 mg/kg) is in the range optimal for kappa receptor antagonism rather than that which is optimal for mu antagonism (0.2-1.0 mg/kg).

Disruption of the FR-40 operant pattern by these hallucinogenic drugs is characterized by dose-related decreases in responses (reinforcers earned) correlated with increases in pause intervals (10-sec intervals without a

response) over the entire dose-response curve (Rech and Commissaris, 1982). This pattern of impairment is not observed with many other psychoactive drugs (chlorpromazine, d-amphetamine, pentobarbital), but is seen with other 5-HT agonists, such-as QUIP and lisuride. The operant behavioral effects of hallucinogens and non-hallucinogenic 5-HT agonists are attenuated by pretreating with MTG and other 5-HT antagonists, but the rate-decreasing effect of the other classes of psychoactive agents is not affected by these pretreatments. However, the opioid mixed agonist-antagonist CYCL was found to disrupt the FR-40 operant pattern in the same way as the hallucinogens did, i.e., a decrease in reinforcers correlated with a reciprocal increase in pause intervals (Henck et al., 1983). Furthermore, this impairment was partly antagonized by pretreating with NAL, MTG, or a combination of the two.

The behavioral effects of CYCL were attenuated by a low dose of QUIP (Fig. 2). This antagonism may relate in part to the opioid-like effects of QUIP (Minnema et al., 1980; Samanin et al., 1976). However, 5-HT influences may also pertain, since combined pretreatment with QUIP and MTG reversed the protection by QUIP at the higher doses of CYCL. QUIP itself, at higher dose levels, caused a decrement in FR-40 responding (Fig. 3), which was little affected by pretreatment with NAL or a low dose of CYCL. Nevertheless, the combined pretreatment with NAL and CYCL reversed both the decrease in reinforcers and the increase in pausing caused by the 2 mg/kg dose of QUIP. It seems likely that both opioid and 5-HT mechanisms are involved in this complex interaction.

If the CYCL effects on FR-40 behavior act in part through kappa opioid receptors, the more selective kappa agonist EKC might show similar effects. However, interactions of EKC with NAL or MTG were quite complex (Fig. 4). The slight potentiation of lower doses of EKC by NAL may relate to subtle opioid influences at other than kappa receptors. The prominent protection by NAL against higher doses of EKC probably does involve kappa receptors. The fact that MTG pretreatment enhanced the disruptive effects of low doses of EKC but attenuated those from a higher dose suggests that EKC interacts in a complex manner with 5-HT mechanisms that influence this behavior.

Lastly, the actions of SKF (Fig. 5) must be mediated via mechanisms different from those involved in the effects of indole and phenethylamine hallucinogens and QUIP and CYCL. NAL had no effect on the SKF dose-response pattern in keeping with a mechanism involving sigma receptors, which are considered NAL-insensitive (Simon and Hiller, 1978). MTG pretreatment exerted only a slight protection against the behavioral decrement caused by SKF, indicating that the latter drug does not act primarily via 5-HT receptors.

The results of this study show that the opioids CYCL and EKC produce their disruption of operant behavior by interacting, at least in part, with 5-HT and NAL-sensitive opioid systems. Thus, they appear to exert their effects in a manner related to the actions of indole and phenethylamine hallucinogens. On the contrary, the effects of SKF appear to be mediated mainly through mechanisms different from those of the indole and phenethylamine hallucinogens.

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ACKNOWLEDGMENTS

This research was supported by Grant DA-01836 from the National Institute on Drug Abuse and Training Grant 07392 from the National Institute of General Medical Sciences. Katharine Stoudt and Kim Whitehouse assisted in testing animal behavior and in statistical analysis of data.

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