**ABSTRACT**

The purpose of this investigation was to evaluate the discriminative stimulus effects of the mixed-opioid agonist/antagonist dezocine. In pigeons trained to discriminate 1.7 mg/kg dezocine from saline, a series of opioids with activity at the mu opioid receptor substituted completely for the dezocine stimulus with a rank order of potency similar to that obtained in other assays sensitive to the effects of mu agonists (i.e., fentanyl > [−]-cyclazocine > buprenorphine > l-methadone > nalbuphine > [−]-metazocine > morphine). (−)-N-allylnormetazocine and (+)-propoxyphene substituted partially for the dezocine stimulus, an effect obtained even when tested up to doses that suppressed responding. Naloxone (0.1 - 10 mg/kg) antagonized the stimulus effects of dezocine, (−)-propoxyphene and fentanyl in a dose-related manner, whereas doses of naloxone that antagonized fentanyl’s rate-decreasing effects failed to antagonize the rate-decreasing effects of dezocine and (+)-propoxyphene. A 10-mg/kg dose of the mu-selective, noncompetitive antagonist β-funaltrexamine was more effective against the stimulus effects of dezocine and nalbuphine than against morphine and fentanyl. As was observed with naloxone, β-funaltrexamine failed to antagonize dezocine’s rate-decreasing effects. The delta agonists BW373U86 and SNC80 substituted partially for the dezocine stimulus, and these effects were reversed by doses of the delta-selective antagonist naltrindole (0.1 and 1.0 mg/kg) that had no effect on the dezocine stimulus. Naltrindole also antagonized the rate-decreasing effects produced by BW373U86 and SNC80, but not those of dezocine. The kappa agonists bremazocine, spiradoline, U50,488 and U69,593 failed to substitute for the dezocine stimulus. The kappa-selective antagonist nornaltorphimine (1.0 mg/kg) failed to antagonize dezocine’s stimulus or rate-decreasing effects. The present findings indicate that dezocine shares similar stimulus effects with both mu and delta agonists, its stimulus effects are reversed by mu-selective antagonists, and its rate-decreasing effects are not mediated by activity at mu, kappa or delta opioid receptors.

**Discriminative Stimulus Effects of the Mixed-Opioid Agonist/Antagonist Dezocine: Cross-Substitution by Mu and Delta Opioid Agonists**

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Dezocine is a recently marketed opioid-analgesic that has a profile of pharmacological activity characteristic of a mixed-opioid agonist/antagonist (Malis et al., 1975; Rowlingson et al., 1983; O’Brien and Benfield, 1989). As with many mixed-opioid agonist/antagonists, dezocine can precipitate with a rank order of potency similar to that obtained in other assays sensitive to the effects of mu agonists (i.e., fentanyl > [−]-cyclazocine > buprenorphine > l-methadone > nalbuphine > [−]-metazocine > morphine). (−)-N-allylnormetazocine and (+)-propoxyphene substituted partially for the dezocine stimulus, an effect obtained even when tested up to doses that suppressed responding. Naloxone (0.1 - 10 mg/kg) antagonized the stimulus effects of dezocine, (−)-propoxyphene and fentanyl in a dose-related manner, whereas doses of naloxone that antagonized fentanyl’s rate-decreasing effects failed to antagonize the rate-decreasing effects of dezocine and (+)-propoxyphene. A 10-mg/kg dose of the mu-selective, noncompetitive antagonist β-funaltrexamine was more effective against the stimulus effects of dezocine and nalbuphine than against morphine and fentanyl. As was observed with naloxone, β-funaltrexamine failed to antagonize dezocine’s rate-decreasing effects. The delta agonists BW373U86 and SNC80 substituted partially for the dezocine stimulus, and these effects were reversed by doses of the delta-selective antagonist naltrindole (0.1 and 1.0 mg/kg) that had no effect on the dezocine stimulus. Naltrindole also antagonized the rate-decreasing effects produced by BW373U86 and SNC80, but not those of dezocine. The kappa agonists bremazocine, spiradoline, U50,488 and U69,593 failed to substitute for the dezocine stimulus. The kappa-selective antagonist nornaltorphimine (1.0 mg/kg) failed to antagonize dezocine’s stimulus or rate-decreasing effects. The present findings indicate that dezocine shares similar stimulus effects with both mu and delta agonists, its stimulus effects are reversed by mu-selective antagonists, and its rate-decreasing effects are not mediated by activity at mu, kappa or delta opioid receptors.

**ABBREVIATIONS:** FR, fixed ratio; βFNA, β-funaltrexamine; nor-BNI, nornaltorphimine; ED, effective dose; CL, confidence limits.
sponding, dezocine decreases accuracy of responding in a dose-related manner (Moerschbaecher et al., 1987). Moreover, in rhesus monkeys responding on a shock titration procedure, doses of naloxone that antagonize the effects of morphine are only minimally effective against the effects of dezocine (Malis et al., 1975).

The purpose of the present study was to evaluate the discriminative stimulus effects of dezocine. To this end, pigeons were trained to discriminate a 1.7-mg/kg dose of dezocine from saline, and substitution tests were conducted with mu agonists (fentanyl, l-methadone, morphine, buprenorphine, butorphanol, nalbuphine, [\(+\)]-propoxyphene), kappa agonists (bremazocine, spiradoline, U50,488, U69,593) and delta agonists (BW373U86, SNC80). To evaluate further the receptor-mediated activity of dezocine, substitution tests were conducted with the stereoisomers of various opioids (cyclazocine, n-allylnormetazocine, metazocine) and antagonist tests were conducted with naloxone as well as a mu-selective (\(\beta\)FNA), kappa-selective (nor-BNI) and delta-selective (naltrindole) antagonist. Finally, to evaluate the pharmacological selectivity of the dezocine stimulus, substitution tests were conducted with selected nonopiod compounds (cocaine, oxotremorine, pentobarbital, chlorzepoxide, clonidine).

### Methods

#### Subjects.
Six experimentally naive, female, White Carneau pigeons maintained at approximately 85% of their free-feeding weights (400–500 g) were used. Each pigeon was housed individually with free access to grit and water in a colony maintained on a 12 hr light-dark cycle.

#### Apparatus.
Six operant conditioning chambers were used. The two operative response keys in each chamber were 2.5 cm in diameter and located 23 cm from the bottom of the front wall, centered approximately 12 cm apart. An aperture horizontally centered on the front wall 8 cm above the floor of the chamber allowed access to a hopper filled with mixed grain when the hopper was raised. The hopper, when raised, was illuminated by a 7-W white bulb. A white bulb mounted either 33 or 23 cm above the chamber floor provided ambient illumination. Each chamber was equipped with an exhaust fan for ventilation and white noise to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished through a microcomputer using software and interfacing supplied by MED Associates Inc. (Georgia, VT).

#### Discrimination training.
After the initial shaping of the key-peck response, food delivery (3-sec access to mixed grain) was made contingent on the completion of a FR 1 schedule. During each of the preliminary sessions, only one of the two response keys was illuminated red and this key alternated across sessions. Over several sessions, the number of responses required to produce food delivery was increased gradually to 20 (FR 20). When all pigeons responded reliably under this schedule, the two operative response keys were illuminated in red and pigeons received i.m. injections of either 1.0 mg/kg dezocine or saline (1 ml/kg), 10 min before the start of the session. The training dose of dezocine was subsequently increased to 1.7 mg/kg. A pseudo-random sequence was used to determine which injection was administered, with the restriction that the same injection was not given for more than two consecutive sessions. For three pigeons, responding was reinforced on the right key after administration of dezocine and the left key after the administration of saline. These contingencies were reversed for the other three pigeons. Although recorded, key-peck responses on the injection-inappropriate key had no programmed consequences. Sessions were initially 15 min in duration and conducted 5 days per week. After a mean of 32 sessions (range across pigeons of 16–48), a multiple trial procedure was implemented, with each trial consisting of a 10-min pretreatment interval followed by a 4-min interval in which responding on the injection-appropriate key was reinforced on an FR20 schedule. Each training session consisted of 1 to 3 training trials, and across 10 sessions the number of drug (or sham injections that followed drug injections) and saline trials was equal. For sessions in which the training dose of dezocine was administered before the first session, a sham injection preceded the second trial and at the end of this trial the session was terminated.

#### Substitution and antagonism tests.
The training conditions described above remained in effect until 1) the percentage of injection-appropriate responses before the completion of 20 responses on either key was ≥ 80% and 2) the percentage of the responses emitted during the entire session on the injection-appropriate key was ≥ 90%, over 10 consecutive sessions. This criterion was met in an average of 23 training sessions with a range of 14 to 41 across pigeons. Substitution tests were then conducted using a cumulative dosing procedure. In this procedure, the first dose of each test drug was administered 10 min before the start of the session and subsequent doses were administered at the beginning of each 10-min pretreatment interval such that each dose increased the total dose by 0.25 or 0.5 log unit. Sessions typically terminated when rates of responding decreased to less than 30% of saline control values or when all pigeons responded exclusively on the dezocine-appropriate key. Throughout a test session, the completion of 20 responses on either of the two response keys resulted in food delivery. Otherwise, conditions during testing were identical to those described during training sessions. During antagonism tests, naloxone and naltrindole were administered into the breast muscle on one side of the pigeon 10 min before the start of the session, followed immediately by the first dose of agonist on the opposite side of the breast muscle. During antagonism tests with \(\beta\)FNA, this antagonist was administered 2.5 hr before the session, and 10 min before the start of the session the first dose of the agonist was administered. Tests typically occurred on Tuesday and Fridays, while training sessions were continued on Mondays, Wednesdays and Thursdays. After the completion of all substitution and antagonism tests, a single dose of nor-BNI was administered, training was suspended, and after 9 days the dezocine dose-effect curve was redetermined.

#### Data analysis.
The percentage of responses on the injection-appropriate key and number of responses on both response keys were calculated during training and test sessions. Dose-effect curves were generated from data by expressing the percentage of responses on the dezocine-appropriate key or responses per second as a function of the dose of each drug examined. Complete substitution for the dezocine stimulus was defined as ≥ 80% drug-appropriate responding. For a number of the compounds tested, the dose that produced 50% dezocine-appropriate responding (i.e., ED\(_{50}\)) was derived by log-linear interpolation on the linear portion of the group dose-effect curve. Calculation of group ED\(_{50}\) values (and 95% CL) was based on observations for each subject at each dose. During antagonism tests, selective doses of naloxone, naltrindole and \(\beta\)FNA were administered in combination with various agonists. In these tests, when the dose-effect curve for the agonist was shifted to the right, a dose ratio was calculated by dividing the ED\(_{50}\) of the agonist in the presence of each dose of the antagonist by the ED\(_{50}\) of the agonist when administered alone. For combinations of naloxone and fentanyl, the three obtained dose ratios were then used to calculate apparent pA2 values (and 95% CL), which reflect the dose of the antagonist required to shift the fentanyl dose-effect curve 2-fold to the right (Pharmacological Calculation System, Version 4.1, Tallarida and Murray, 1987). Similarly, dose ratios and apparent pA2 value were obtained for naloxone against fentanyl’s rate-decreasing effects. For these calculations, the ED\(_{50}\) reflected the dose that decreased rates of responding to 50% of saline control values.

#### Drugs.
Dezocine HCl (Astra Pharmaceutical Products, Inc., Westborough, MA), naloxone HCl, oxotremorine sesquifumarate, chlorid-
azepoxide HCl, pentobarbital HCl, (+)-amphetamine HCl (all purchased from Sigma Chemical Co., St. Louis, MO), morphine sulfate, l-methadone HCl, buprenorphine HCl, (+) and (+)-n-allylnormetazocine HCl, (+) and (+)-metazocine fumarate, (+) and (+)-cyclazocine HCl, fentanyl citrate, norbinaltorphimine dihydrochloride, cocaine HCl, beta-funaltrexamine HCl (all supplied by the National Institute on Drug Abuse), bremazocine HCl, U50,488 methanesulfonate, spradoline mesylate, U69,593, naltrindole HCl, nalbuphine HCl, clonidine HCl, (+)-propoxyphene HCl (all purchased from Research Biochemicals Inc., Natick, MA), butorphanol HCl (generously supplied by Bristol-Meyers, Wallingford, CT), BW373U86 (generously supplied by Burroughs Wellcome, Research Triangle Park, NC) and SNC80 (purchased from Tocris Cookson, St. Louis, MO) were dissolved in saline. At the highest concentration of some drugs, a small amount of lactic acid was added to the solution to promote dilution.

Results

Dezocine. Figure 1 shows the effects of dezocine on the percentage of dezocine-appropriate responding and rate of responding. When tested shortly after the acquisition of the discrimination, dezocine produced dose-dependent increases in the percentage of dezocine-appropriate responding with complete substitution (≥80% dezocine-appropriate responding) obtained at doses equal to and greater than 1.0 mg/kg. The highest dose of dezocine tested (3.0 mg/kg) decreased responding to less than 3% of saline control levels in three pigeons, decreased responding in one pigeon to 54% of saline control levels and had little effect on responding in the two others. The dose-effect curve for dezocine’s stimulus effects determined after approximately 12 mo of training and testing was similar to that obtained initially (compare ED_{50} values in table 1). During this latter determination, however, the 3.0-mg/kg dose of dezocine had little systematic effect on responding, whereas the 10-mg/kg dose eliminated responding in three pigeons and did not alter responding in the other three (data not shown).

Mu agonists. Figure 1 also shows that l-methadone, fentanyl, morphine, buprenorphine, butorphanol and nalbuphine produced dose-related increases in dezocine-appropriate responding, and in each of the pigeons tested at least one dose of these compounds substituted completely for the dezocine stimulus. Differences were observed for these compounds in terms of the relationship between doses that substituted for the dezocine stimulus and those that decreased responding. For example, with fentanyl, morphine and buprenorphine complete substitution was obtained at doses that had little effect on response rates, whereas complete substitution with butorphanol, l-methadone and nalbuphine was obtained at doses that decreased response rates to 67, 59 and 19% of saline control levels, respectively. (+)-Propoxyphene also produced dose-related increases in dezocine-appropriate responding, although complete substitution was obtained in only four of six pigeons tested. At the highest dose tested, (+)-propxyphene decreased rate of responding to 35% of saline control levels.

![Fig. 1. Effects of dezocine, l-methadone, fentanyl, morphine, buprenorphine, butorphanol, nalbuphine and (+)-propxyphene on percentage of dezocine-appropriate responding (top panels) and rate of responding (bottom panels) in pigeons (n = 5–6) trained to discriminate 1.7 mg/kg dezocine from saline. Data in the top panels reflect the mean percentage of dezocine-appropriate responding obtained across the entire session; data were excluded from this analysis when an individual pigeon failed to complete at least 20 responses on either response key. Data in the bottom panels reflect mean rate of responding obtained during the entire session, and are expressed as responses per second. Vertical lines on data points represent the S.E.; when not indicated, the S.E. fell within the data point.](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED_{50} (mg/kg)</th>
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<tbody>
<tr>
<td>Dezocine</td>
<td></td>
</tr>
<tr>
<td>0 mo</td>
<td>0.38 (0.27–0.53)</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.46 (0.24–0.87)</td>
</tr>
<tr>
<td>l-Methadone</td>
<td>0.12 (0.04–0.34)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.009 (0.004–0.018)</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.72 (0.42–1.24)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.033 (0.020–0.056)</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.029 (0.021–0.042)</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>0.40 (0.13–1.15)</td>
</tr>
<tr>
<td>(+)-Propoxyphene</td>
<td>3.0 (1.1–8.2)</td>
</tr>
<tr>
<td>(-)-Cyclazocine</td>
<td>0.012 (0.004–0.048)</td>
</tr>
<tr>
<td>(-)-Metazocine</td>
<td>0.66 (0.50–0.89)</td>
</tr>
<tr>
<td>BW373U86</td>
<td>0.087 (0.031–0.250)</td>
</tr>
<tr>
<td>SNC80</td>
<td>0.54 (0.32–0.91)</td>
</tr>
</tbody>
</table>
Stereoselectivity. As shown in figure 2, the (-)-isomers of cyclazocine and metazocine produced dose-related increases in the percentage of dezocine-appropriate responding. At least one dose of these compounds substituted completely for the dezocine stimulus in all pigeons, and this effect was obtained at doses that had little effect on rate of responding. When tested up to doses that decreased responding to less than 20% of saline control values, the (-)-isomer of n-allylnormetazocine substituted partially for the dezocine stimulus with complete substitution obtained in only three of six pigeons tested. In contrast to their (-)-isomers, the (+)-isomers of n-allylnormetazocine, cyclazocine and metazocine produced predominantly saline-appropriate responding and decreased rates of responding in a dose-related manner.

Antagonism by naloxone. Figure 3 shows the effects of dezocine, fentanyl and (+)-propoxyphene alone and in combination with selected doses of naloxone on percentage of dezocine-appropriate responding and rate of responding. Across the dose range tested, naloxone shifted the dose-effect curve for the stimulus effects of dezocine to the right and downward in a dose-related manner. At 1.0 mg/kg naloxone, the ED$_{50}$ for dezocine was increased by 1.0 log unit. Because all doses of dezocine produced exclusively saline-appropriate responding when administered in combination with 10 mg/kg naloxone, an ED$_{50}$ could not be calculated. Similarly, the 1.0- and 10-mg/kg doses of naloxone flattened the (+)-propoxyphene curve such that even the highest dose tested (10 mg/kg) produced predominantly saline-appropriate responding. In contrast to their stimulus effects, naloxone failed to antagonize the rate-decreasing effects of either dezocine or (+)-propoxyphene, and in some instances shifted the dose-effect curves for these drugs to the left. For example, doses of dezocine and (+)-propoxyphene that had no effect on rate of responding when administered alone, markedly suppressed responding when administered with the 10 mg/kg-dose of naloxone.

Naloxone shifted the dose-effect curves for fentanyl’s stimulus and rate-decreasing effects to the right in a dose-related and parallel manner. At the 1.0-mg/kg dose of naloxone, for example, the dose-effect curves for fentanyl’s stimulus and rate-decreasing effects were shifted to the right by 1.4 and 0.9 log units, respectively. Against the fentanyl stimulus, the apparent pA2 value (95% C.L.) obtained for naloxone was 7.11 (6.86–7.37) and the slope of the Schild regression line (see insert in fig. 3) was -0.91 (0.01). Against fentanyl’s rate-decreasing effects, the apparent pA2 value for naloxone was 6.1 (0.96–11.24) and the slope of the Schild regression line was -0.77 (0.33).

Antagonism by βFNA. Figure 4 shows the effects of dezocine, nalbuphine, fentanyl and morphine when administered alone and in combination with a 10-mg/kg dose of βFNA on percentage of dezocine-appropriate responding and rate of responding. Pretreatment with βFNA shifted the dose-effect curve for dezocine’s stimulus effects to the right and downward, increasing the ED$_{50}$ by 0.63 log units and decreasing the maximal effect from 100 to 62% dezocine-appropriate responding. In contrast, βFNA did not alter the dose-effect curve for dezocine’s rate-decreasing effects. βFNA also antagonized the stimulus and rate-decreasing effects produced by nalbuphine, increasing the ED$_{50}$ by 1.0 and 1.2 log units, respectively. Pretreatment with βFNA did not systematically alter the dose-effect curves for fentanyl’s stimulus or rate-decreasing effects. Although βFNA failed to alter the dose-effect curve for morphine’s stimulus effects, it did antagonize the rate-decreasing effects produced by the high doses of morphine.

Kappa agonists and antagonists. Figure 5 shows the effects of dezocine alone and 8 days after administration of 1.0 mg/kg nor-BNI on percentage of dezocine-appropriate responding and rate of responding. At the time point tested, nor-BNI did not alter dezocine’s stimulus or rate-decreasing effects. Figure 5 also shows the effects of bremazocine, U69,593, U50,488 and spiradoline on percentage of dezocine-appropriate responding and rate of responding. Up to doses that decreased rates of responding to less than 20% of saline control levels, these compounds produced predominately sa-

![Fig. 2. Effects of the (+)- and (-)-isomers of cyclazocine, metazocine and n-allylnormetazocine on percentage of dezocine-appropriate responding (top panels) and rate of responding (bottom panels) in pigeons (n = 5–6) trained to discriminate 1.7 mg/kg dezocine from saline. For percentage dezocine-appropriate responding, data are not displayed at 1.0 mg/kg (-)-cyclazocine, where only one pigeon responded. Other details are as described in figure 1.](image)
line-appropriate responding. At least one dose of U50,488 did, however, substitute for the dezocine stimulus in one of five pigeons and for spiradoline in two of six pigeons, whereas with bremazocine and U69,593 complete substitution was not obtained at any dose in any of the pigeons.

**Delta agonists and antagonists.** Figure 6 shows the effects of dezocine, BW373U86 and SNC80 alone and in combination with naltrindole. At the doses tested, naltrindole failed to antagonize dezocine’s stimulus or rate-decreasing effects. When administered alone, BW373U86 produced dose-related increases in the percentage of dezocine-appropriate responding with complete substitution obtained in three of six pigeons tested. Based on the ED_{50}, the 0.1- and 1.0-mg/kg doses of naltrindole shifted the BW373U86 dose-effect curve to the right by 1.0 and 1.94 log units, respectively. In all three of the pigeons that BW373U86 failed to substitute for the dezocine stimulus when administered alone, complete substitution was obtained when high doses (1.0 and 3.0 mg/kg) of BW373U86 were administered in combination with naltrindole. Naltrindole also shifted the dose-effect curve for BW373U86’s rate-decreasing effects to the right in a dose-related manner. For example, whereas the 0.1-mg/kg dose of naltrindole increased the ED_{50} for BW373U86’s rate-decreasing effects by 1.5 log units, when tested in combination with 1.0 mg/kg naltrindole even doses as high as 17.5 mg/kg BW373U86 had no effect on responding.

SNC80 also produced dose-related increases in the percentage of dezocine-appropriate responding with complete substitution obtained in four of five pigeons tested. The 0.1 mg/kg naltrindole antagonized the stimulus effects produced by SNC80, resulting in a rightward shift of the dose-effect curve. However, even at the highest dose of SNC80 tested (10 mg/kg), the maximal level of substitution did not exceed 50% dezocine-appropriate responding. SNC80 also produced dose-related decreases in responding, and this effect was antago-
nized by naltrindole. Due to changes in the slopes of the SNC80 dose-effect curve, the magnitude of this effect could not be quantified.

Nonopioids. Figure 7 shows the effects of cocaine, oxotremorine, (-)-amphetamine, pentobarbital, cloridiazepoxide and clonidine on percentage of dezocine-appropriate responding and rate of responding. Across the dose ranges tested, these compounds produced predominantly saline-appropriate responding and decreased responding in a dose-related manner. At the highest dose of each compound tested, responding was decreased to less than 20% of saline control values.

**Discussion**

The present study demonstrated that the mixed-opioid agonist/antagonist dezocine could serve as a discriminative stimulus and the rate at which this discrimination was established was comparable to that obtained with other mu agonists (e.g., morphine, fentanyl, butorphanol) in pigeons trained in two-choice, drug-discrimination tasks (Herling et al., 1980; Koek and Woods, 1989; Picker et al., 1996). The dose selected for study, 1.7 mg/kg, was probably the highest dose that could be established as a discriminative stimulus using these procedures, in that a dose 0.25 larger (i.e., 3.0 mg/kg) eliminated or markedly decreased responding in the majority of pigeons tested.

A major goal of the present investigation was to evaluate the mechanisms mediating dezocine’s discriminative stimulus effects. Several lines of evidence suggested that the dezocine stimulus was mediated by activity at the mu opioid receptor. For example, a series of mu agonists, which included the high-efficacy agonists fentanyl, l-methadone and morphine and the low-efficacy agonists (-)-metazocine, (-)-cyclazocine, buprenorphine, butorphanol and nalbuphine substituted completely for the dezocine stimulus. Moreover, the rank order of potency for the dezocine-like stimulus effects of these opioids (i.e., fentanyl >(-)-cyclazocine >buprenorphine = butorphanol >l-methadone >nalbuphine >(-)-metazocine >morphine) was similar to that found in drug discrimination procedures using mu agonists as the training stimuli (Young et al., 1984; Picker et al., 1993, 1996), in tissue preparations (Miller et al., 1986), in assays of antinociception (Hayes et al., 1987; Paronis and Holtzman,
The stimulus effects produced by dezocine were also reversed by a 10-mg/kg dose of the mu-selective antagonist βFNA, but not by delta-selective doses of naltirindole (Comer et al., 1993) or a kappa-selective dose of nor-BNI (Jewett and Woods, 1995). Previous studies also indicate that βFNA is more effective as an antagonist of the effects of mu agonists than kappa and delta agonists (Hayes et al., 1986; Dykstra et al., 1987; Zimmerman et al., 1987; Heyman et al., 1989), which suggests further that activity at the mu opioid receptor underlies the stimulus effects of dezocine. The 10-mg/kg dose of βFNA also antagonized the dezocine-like stimulus effects produced of nalbuphine, but not those produced morphine or fentanyl. That βFNA was effective against the stimulus effects of dezocine and nalbuphine but not morphine and fentanyl is consistent with previous findings indicating that noncompetitive antagonists are more potent as antagonists of lower- than higher-efficacy mu agonists (e.g., Hayes et al., 1986; Zimmerman et al., 1987; Adams et al., 1990). Similarly, in pigeons a 10-mg/kg dose of βFNA was more effective as an antagonist of the morphine-like stimulus effects produced by various mixed-opioid agonist/antagonists than morphine (Morgan and Picker, 1995). As observed in the present investigation, this dose of βFNA failed to antagonize the morphine-like stimulus effects of fentanyl, which suggests further that the failure of βFNA to antagonize the dezocine-like stimulus effects of morphine and fentanyl in the present investigation most likely reflects their high intrinsic efficacy at the mu opioid receptor.

Although the dezocine stimulus was also sensitive to antagonism by naloxone, the lowest dose of naloxone (1.0 mg/kg) required to antagonize the dezocine stimulus was 10-fold larger than that required to antagonize the dezocine-like stimulus effects produced by fentanyl and larger than that required to antagonize the stimulus effects of morphine and fentanyl (Wessinger and McMillan, 1986; Picker et al., 1993). Similarly, in squirrel monkeys the morphine-like stimulus effects produced by dezocine were reversed by doses of naloxone considerably greater than those required to antagonize the morphine stimulus (Schaefer and Holtzman, 1981). It is not clear as to the factors that account for this differential sensitivity to antagonism by naloxone.

Differences were also apparent in the effects of the largest dose of naloxone tested (10 mg/kg) on the stimulus effects of dezocine and fentanyl. Indeed, this dose of naloxone shifted the fentanyl dose-effect curve to the right in a parallel manner and flattened the dezocine dose-effect curve such that all doses of dezocine tested produced only saline-appropriate responding. It is possible that dezocine’s nonopioid-mediated rate-decreasing effects (see below) account for the failure of naloxone to shift the dose-effect curve for dezocine’s stimulus effects to the right in a parallel manner as would be predicted from a competitive interaction at the opioid receptor. For example, had the 10-mg/kg dose of naloxone shifted the dose-effect curve for dezocine’s stimulus effects to the right by the same extent as that observed with fentanyl, it would have required testing doses of dezocine between 10 and 100 mg/kg. However, because naloxone failed to antagonize dezocine’s rate-decreasing effects, even doses as low as 10 mg/kg dezocine eliminated responding in some pigeons and markedly suppressed responding in others.

Although delta-selective doses of naltirindole (Comer et al., 1993) failed to antagonize the dezocine stimulus, the stimulus effects of dezocine were shared, in part, by the delta agonist BW373U86 and its chemically modified enantiomer SNC80 (Chang et al., 1993; Bilsky et al., 1995; Negus and Picker, 1996). This latter finding is consistent with studies indicating that in pigeons BW373U86 substitutes partially or completely for the stimulus effects of fentanyl, morphine and butorphanol and suggests further that activation of delta opioid receptors can produce mu opioid-like stimulus effects.

**Figure 7.** Effects of cocaine, oxotremorine, (+)-amphetamine, pentobarbital, chlordiazepoxide and clonidine on percentage of dezocine-appropriate responding (top panel) and rate of responding (bottom panel) in pigeons (n = 5–6) trained to discriminate 1.7 mg/kg dezocine from saline. For percentage dezocine-appropriate responding, data are not displayed at 5.6 mg/kg (+)-amphetamine, 10 mg/kg chlordiazepoxide, 5.6 mg/kg cocaine, 17.5 mg/kg pentobarbital and 0.1 mg/kg clonidine, where only one pigeon responded. Other details are as described in figure 1.
(Comer et al., 1993; Negus et al., 1996; Negus and Picker, 1996; Picker et al., 1996). That the dezocine-like stimulus effects produced by BW373U86 and SNC80 were antagonized by 0.1 and 1.0 mg/kg naltrindole indicates that these effects were most likely mediated by activity at the delta receptor. Similarly, in pigeons these doses of naltrindole also antagonize the stimulus effects of BW373U86 and DPDPDE (Comer et al., 1993; Hewlett et al., 1996), but not those of butorphanol, morphine or fentanyl (Comer et al., 1993; Negus et al., 1996; Picker et al., 1996). That BW373U86 does not produce appreciable levels of substitution for the stimulus effects of etonitazene in monkeys or morphine in rats (Negus et al., 1994; Negus and Picker, 1996; Craft et al., 1996), suggesting that species may play an important role in the cross-substitution patterns produced by mu and delta agonists.

The discriminative stimulus effects of dezocine were not shared by the kappa agonists bremazocine, U69,593, U50,488 and spiradoline, a finding consistent with dezocine’s low affinity for the kappa opioid receptor (Chen et al., 1992) and its failure to substitute for the stimulus effects of kappa agonists (Young et al., 1984; Picker, 1995). Moreover, these findings extend previous observations indicating that mu and kappa agonists do not typically display cross-substitution in pigeons (e.g., Comer et al., 1993; Brandt and France, 1996). As with the kappa agonists, the nonopioid octreotide, clonidine, clodiazepoxide, pentobarbital, cocaine and (+)-amphetamine failed to substitute for the dezocine stimulus, indicating that the dezocine stimulus was pharmacologically selective.

In contrast to dezocine’s stimulus effects, even doses as high as 10 mg/kg naloxone failed to antagonize dezocine’s rate-decreasing effects. Moreover, in some instances doses of dezocine that had no effect on rate of responding when administered alone, markedly suppressed responding when administered with 10 mg/kg naloxone. That the doses of naltrindole that antagonized the rate-decreasing effects of bremazocine but not dezocine’s rate-decreasing effects as evidenced by the finding that doses of naltrindole that antagonized the rate-decreasing effects of BW373U86 and SNC80 had no effect of dezocine’s rate-decreasing effects. Taken together, these findings indicate that a nonopioid component of action contributed to dezocine’s rate-decreasing effects. These findings also extend previous observations that the rate-decreasing effects of some mixed-opioid agonist/antagonists are not mediated by activity at opioid receptors and that these effects may vary across species (e.g., Leander and McMillan, 1977; Izenwasser et al., 1996). For example, naloxone and naltrexone have been reported to be effective in antagonizing the rate-decreasing effects of dezocine, profadol and (+)-propoxyphene in rats but not in pigeons (Holtzman, 1974; Leander, 1982; Walker et al., 1996; present investigation).

In summary, the present findings indicate that dezocine shares similar stimulus effects with both mu and delta agonists and its rate-decreasing effects are not mediated by activity at mu, kappa or delta opioid receptors. In addition, the relative intrinsic efficacy of dezocine at the mu opioid receptor appears to be less than that of morphine and fentanyl.

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References


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