Cocaine and Amphetamine Attenuate the Discriminative Stimulus Effects of Naltrexone in Opioid-Dependent Rhesus Monkeys

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ABSTRACT

This study tested the hypothesis that stimulants (indirect dopamine agonists) attenuate the discriminative stimulus of naltrexone in monkeys chronically treated with L-α-acetylmethadol (LAAM). Four rhesus monkeys (Macaca mulatta) received LAAM (1.0 mg/kg s.c.) twice daily and discriminated a withdrawal-precipitating dose of naltrexone (0.0178 mg/kg s.c.) from saline. Cocaine (0.1–1.78 mg/kg), amphetamine (0.32–1.78 mg/kg), haloperidol (0.01–0.1 mg/kg), sulpiride (1.0–10.0 mg/kg), propranolol (0.32–3.2 mg/kg), clonidine (0.001–0.1 mg/kg), desipramine (0.32–3.2 mg/kg), and imipramine (1.0–10.0 mg/kg) were given s.c. before cumulative doses of naltrexone. Cocaine and amphetamine antagonized the discriminative stimulus effects of naltrexone, each shifting the naltrexone dose-effect curve significantly (e.g., 100-fold) rightward or downward. In contrast, the dopamine antagonist haloperidol shifted the naltrexone dose-effect curve 5-fold leftward. Sulpiride, desipramine, clonidine, and propranolol had comparatively less effect on the naltrexone discriminative stimulus, whereas some doses of imipramine attenuated the naltrexone stimulus in a manner similar to that of cocaine and amphetamine. These results support the notion that multiple neurotransmitter systems are involved in the discriminative stimulus effects of opioid withdrawal. Furthermore, these data are consistent with reports that dopamine levels decrease during opioid withdrawal and provide evidence that enhancing dopamine or other monoamine levels may attenuate subjective effects of opioid withdrawal.

Changes within opioid systems in response to chronic opioid administration (homologous adaptations) undoubtedly play a major role in mediating withdrawal. However, changes also occur in other neurotransmitter systems (heterologous adaptations). For example, noradrenergic (Maldonado, 1997) and dopaminergic (Koob et al., 1989; Harris and Aston-Jones, 1994) systems seem to mediate different components of withdrawal. Decreases in dopamine in the nucleus accumbens have been suggested to mediate dysphoria during withdrawal (Koob et al., 1989; Rossetti et al., 1992), whereas increases in noradrenergic activity are thought to mediate somatic signs of withdrawal (Maldonado, 1997). This study focused on the role of dopamine and noradrenaline in the discriminative stimulus effects of opioid withdrawal.

Evidence in the literature implicates a role for noradrenergic systems in opioid withdrawal, suggesting the locus coeruleus as a primary site and noradrenaline as a primary mediator of somatic signs of withdrawal. For example, during withdrawal, locus coeruleus neuronal firing rates increase (Aghajanian, 1978). Involvement of noradrenergic systems was first suggested primarily because of the antiwithdrawal effects reported for clonidine. Clonidine alleviates some, but not all, withdrawal signs in humans (Charney et al., 1981; Jasinski et al., 1985), monkeys (Katz, 1986), and rats (Tseng et al., 1975). However, clonidine more effectively suppresses the observable, somatic signs of withdrawal rather than self-reported symptoms (Charney et al., 1981). Jasinski et al. (1985) reported that clonidine was more effective at reducing autonomic signs of withdrawal, whereas morphine was more effective at reducing subjective effects of withdrawal as reported on self-rating scales. In rats, clonidine decreases autonomic signs of withdrawal such as mean arterial blood pressure and heart rate, as well as intensity of somatic signs such as weight loss and wet-dog shakes. However, clonidine enhances other indicators of withdrawal in rats, such as escape behavior, teeth chattering, hyperactivity (Buccafusco et al., 1984), circling, rearing, and jumping (Kelsey et al., 1990) and does not alter decreases in spontaneous righting activity (van der Laan and de Groot, 1988). Administration of clonidine into the locus coeruleus attenuates several somatic signs of withdrawal such as diarrhea, ptosis, weight loss, and wet-dog shakes as well as reversing naloxone-precipitated withdrawal.

ABBREVIATIONS: MHPG, 3-methoxy-4-hydroxy-phenethyleneglycol; LAMM, L-α-acetylmethadol; FR, fixed ratio; CL, confidence limit; GBR 12909, 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine.

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increases in hippocampal 3-methoxy-4-hydroxy-phenethyl-ene glycol (MHPG; Taylor et al., 1988). Thus, the primary action of clonidine to relieve withdrawal seems to be through altering autonomic manifestations of withdrawal.

Evidence supports a role for mesolimbic dopamine mediating both somatic signs of withdrawal (Harris and Aston-Jones, 1994) and aversive symptoms of withdrawal (Koob et al., 1989). For example, extracellular concentrations of mesolimbic dopamine decrease substantially during both spontaneous (Acquas et al., 1991) and naloxone-precipitated withdrawal (Pothos et al., 1991; Rossetti et al., 1992). Activation of dopamine D2 receptors (but not D1; Pothos et al., 1991) in the nucleus accumbens reduces the severity of naloxone-precipitated withdrawal in rats. Furthermore, blockade of D2 receptors (Harris and Aston-Jones, 1994) but not opioid receptors (Maldonado et al., 1992) in the nucleus accumbens of morphine-dependent animals precipitates behavioral signs of withdrawal. Finally, dopamine antagonists such as haloperidol (Chahl et al., 1989) and raclopride (Brent and Chahl, 1993) exacerbate morphine withdrawal in guinea pigs. Although the relationship between the noradrenergic and dopaminergic systems during opioid withdrawal remains to be fully defined, evidence thus far points to a greater role for dopamine than noradrenaline in mediating subjective effects of withdrawal.

Drug discrimination is useful for studying dependence and withdrawal in laboratory animals (Gellert and Holtzman, 1979; France and Woods, 1987, 1989), in part because the discriminative stimulus of drugs in nonhumans is thought to be related to the subjective effects of drugs in humans (Preston and Bigelow, 1998). Animals maintained with chronic opioid administration can be trained to discriminate an opioid antagonist that precipitates withdrawal, such as naloxone or naltrexone. This type of discrimination is well established in rats (Gellert and Holtzman, 1979), pigeons (France and Woods, 1987), and nonhuman primates (France and Woods, 1989) and provides a method for measuring insurmountable stimuli of withdrawal in laboratory animals.

To address the hypothesis that decreased dopamine and increased noradrenergic neurotransmission regulate subjective effects of withdrawal, these experiments were designed to test the role of these systems in the discriminative stimulus effects of naltrexone-precipitated withdrawal. Monkeys chronically treated with LAAM discriminated a withdrawal-precipitating dose of naltrexone from saline. They were then tested with noradrenaline and dopamine uptake inhibitors as well as ligands selective for specific receptors of each system in combination with naltrexone.

**Materials and Methods**

**Subjects.** Four adult rhesus monkeys (*Macaca mulatta*, one male and three females, 5–8 kg) were housed individually in stainless steel cages with free access to water and maintained at 95% of free-feeding weight. Monkeys received chow (High Protein Monkey Diet; Harlan Teklad, Madison, WI) and fresh fruit daily during experimental sessions. All subjects were previously trained to respond under fixed ratio (FR) schedules (stimulus shock termination) and had received opioid agonists and antagonists in previous studies (Brandt and France, 1998). Animals used in these studies were maintained in accordance with the Institutional Animal Care and Use Committee, The University of Texas Health Science Center (San Antonio, TX) as well as the Guide for the Care and Use of Laboratory Animals [Institute of Laboratory Animal Resources on Life Sciences, National Research Council; Department of Health, Education, and Welfare, Publication No. (NIH) 85-23, revised 1996].

**Apparatus.** Monkeys were seated in primate chairs (model R001; Primate Products, Miami, FL) that provided restraint at the neck and shoulders. During experimental sessions monkeys were placed in ventilated, sound-attenuating operant chambers that contained two response levers and two red lights. Each chair was equipped with a pair of shoes containing brass electrodes to provide the capability of delivering a brief shock (250 ms, 3 mA) from a remote AC generator. Experimental procedures were controlled and data collected by a microprocessor and commercially available software (MED Associates, St. Albans, VT).

**Behavioral Procedure.** Monkeys received 1.0 mg/kg s.c. LAAM twice daily, 8 to 9 h apart. This treatment has been shown to be adequate for producing physical dependence (Brandt and France, 1998). Experimental sessions began 7 h after the first daily injection of LAAM. Training and testing procedures have been reported previously (Brandt and France, 1998). Each session consisted of two to eight 15-min cycles with each cycle beginning with a 10-min timeout, during which the chamber was dark and lever presses had no programmed consequence. This was followed by a 5-min response period during which monkeys could respond under an FR5 schedule of stimulus-shock termination with shocks scheduled to occur every 15 s. Both red lights were illuminated at the beginning of the 15-s period and monkeys could postpone scheduled shock for 30 s by completing five consecutive responses on the correct lever. The correct lever was determined by an injection of either 0.1 ml/kg saline or 0.0178 mg/kg naltrexone administered during the 1st min of the cycle. The right lever was correct after saline and the left lever was correct after naltrexone for two monkeys, whereas the right lever was correct after naltrexone and the left lever was correct after saline for the other two monkeys. Responses on the incorrect (injection-inappropriate) lever reset the response requirement on the correct lever.

Test drugs were administered every 2nd or 3rd day as long as behavior was under adequate stimulus control during intervening training sessions according to the following criteria: at least 80% of responses on the injection-appropriate lever and fewer than five responses on the injection-inappropriate lever before the first reinforcer. Parameters for test sessions were the same as for training sessions except that five consecutive responses on either lever postponed scheduled shock. After injection of the test compound at the beginning of the first cycle, increasing doses of naltrexone were administered at the beginning of subsequent cycles, up to doses that produced at least 80% responding on the naltrexone lever or to a cumulative dose of 1.0 mg/kg. Tests were conducted with the following drugs: cocaine (0.1–1.78 mg/kg), amphetamine (0.032–1.78 mg/kg), haloperidol (0.01–0.1 mg/kg), sulpiride (1.0–10.0 mg/kg), propranolol (0.32–3.2 mg/kg), clonidine (0.001–0.1 mg/kg), desipramine (0.32–3.2 mg/kg), and imipramine (1.0–10.0 mg/kg).

**Drugs.** All drugs were administered s.c. in a volume of 0.1 to 1.0 ml. The compounds studied were d-amphetamine sulfate, cocaine hydrochloride, naltrexone hydrochloride, and LAAM (The Research Technology Branch, National Institute on Drug Abuse, Rockville, MD); and clonidine hydrochloride, desipramine hydrochloride, haloperidol, imipramine hydrochloride, DL-propranolol hydrochloride, and (±)-sulpiride (Sigma-Aldrich, St. Louis, MO). LAAM was dissolved in a vehicle containing 77.5% sterile water, 15% Emulphor, and 7.5% ethanol; heated; and sonicated. All other drugs were dissolved in sterile water, heated, and/or sonicated as needed.
Results

Naltrexone Dose-Effect Curves. Naltrexone dose-effect curves were determined periodically (every 2–4 weeks) throughout the course of the experiment to monitor the sensitivity of the monkeys to the training drug. The dose-effect curves that were determined at the beginning and at the end of the experiment are shown for each monkey in Fig. 1. Monkeys generally responded at least 80% on the drug-appropriate lever at doses of 0.01 to 0.032 mg/kg naltrexone. Individual ED₅₀ values for each animal are presented in Table 1. The overall sensitivity of monkeys to naltrexone remained stable throughout the course of the experiment, with the overall average ED₅₀ (95% C.Ls) for naltrexone being 0.0058 mg/kg (0.0043–0.0078). Over the range of naltrexone doses studied, the rate of responding remained stable (Table 2).

Stimulants before Naltrexone. Pretreatment with cocaine attenuated the discriminative stimulus effects of naltrexone (Fig. 2; Table 1), although there was variation in sensitivity among the four monkeys. For example, in monkey OP 1.0 mg/kg cocaine shifted the naltrexone dose-effect curve 3.6-fold to the right. The same dose, in monkey CL, shifted the naltrexone dose-effect curve 20-fold to the right. Moreover, in monkeys XE and KA, doses of 0.32 to 1.0 mg/kg cocaine markedly attenuated the discriminative stimulus effects of naltrexone as evidenced by predominantly vehicle-lever responding up to a dose of naltrexone (1.0 mg/kg) 100-fold larger than the dose that occasioned drug-lever responding under control conditions. A larger dose (1.78 mg/kg) of cocaine markedly disrupted lever pressing in monkey OP (data not shown).

Similar effects were obtained with amphetamine in combination with naltrexone (Fig. 3), with variations in sensitivity among animals. A dose of 1.0 mg/kg amphetamine shifted the naltrexone dose-effect curve 3-fold rightward in monkey OP; the same dose resulted in an insurmountable attenuation of the naltrexone discriminative stimulus in the remaining three monkeys up to a dose of 1.0 mg/kg (Fig. 3; Table 1). Because monkey OP seemed to be less sensitive to the effects of amphetamine, compared with other monkeys, a dose of 1.78 mg/kg amphetamine was tested only in monkey OP and this dose completely blocked drug-lever responding up to a dose of 1.0 mg/kg naltrexone in this subject. With the exception of 1.78 mg/kg cocaine in monkey OP, both cocaine and amphetamine had moderate rate-increasing effects (Table 2). With the exception of 0.32 mg/kg amphetamine in monkey OP (19.6% naltrexone-lever responding), subjects responded exclusively on the saline-associated lever after acute injections of these test compounds (data not shown).

Dopamine Receptor Antagonists before Naltrexone. Pretreatment with the nonselective dopamine receptor antagonist haloperidol shifted the naltrexone dose-effect curve 3- to 5-fold to the left in each monkey. Although there was some variability among monkeys in their response to 0.01 mg/kg haloperidol, a dose of 0.032 mg/kg significantly and consistently decreased the ED₅₀ for naltrexone in all four monkeys (Fig. 4; Table 1). Rates of lever pressing were decreased after 0.01 or 0.032 mg/kg haloperidol (Table 2). The largest dose of haloperidol tested (0.1 mg/kg) markedly disrupted lever pressing in the two monkeys studied at this dose (data not shown; OP and CL).

In contrast, the D₂-selective antagonist sulpiride did not have a consistent effect on the naltrexone discrimination dose-effect curve among monkeys (Fig. 5), generating a small (≈3-fold) shift rightward only in monkeys OP and CL (Table 1). Up to a dose of 10.0 mg/kg, sulpiride did not affect rates of lever pressing (Table 2). When administered alone, neither haloperidol nor sulpiride occasioned any naltrexone-lever responding (data not shown).

Noradrenaline Receptor Agonists and Antagonists before Naltrexone. Treatment with the β-adrenergic antagonist propranolol (Fig. 6) or the α₂-adrenergic agonist clonidine (Fig. 7) had small, although in some cases significant, effects on the sensitivity of monkeys to the discriminative stimulus effects of naltrexone. The two smallest doses (0.32 and 1.0 mg/kg) of propranolol shifted the naltrexone dose-effect curve up to 3-fold leftward in monkeys OP and CL, with a larger dose (3.2 mg/kg) shifting the dose-effect curve up to 3-fold rightward in monkeys CL, XE, and KA (Fig. 6; Table 1). Similarly, depending on dose, clonidine shifted the naltrexone dose-effect curve slightly (≈3-fold) leftward (e.g., 0.032 mg/kg in OP and CL) or...
rightward (e.g., 0.0032 mg/kg in KA). In the one monkey in which 0.1 mg/kg clonidine was studied (KA), this dose markedly disrupted lever pressing and caused profound sedation (data not shown). With the exception of slightly reduced rates of responding after administration of 0.032 mg/kg clonidine, other doses of clonidine and propranolol did not affect response rate (Table 2). Moreover, neither of these compounds occasioned any responding on the naltrexone lever (data not shown).

The noradrenergic uptake inhibitor desipramine had similarly small and variable effects among the four monkeys (Fig. 8; Table 1). With the exception of 0.32 mg/kg in monkey XE, sensitivity to naltrexone did not vary by more than 3-fold after pretreatment with desipramine. The effects of pretreatment with imipramine were also variable among the four monkeys, although in two monkeys (XE and KA) imipramine markedly attenuated the naltrexone discriminative stimulus (Fig. 9; Table 1). A dose of 3.2 mg/kg imipramine in monkey XE and a dose of 10.0 mg/kg imipramine in monkey KA insurmountably attenuated the discriminative stimulus effects of naltrexone up to a cumulative dose of 1.0 mg/kg. Neither imipramine nor desipramine consistently altered rates of lever pressing (Table 2). With the exception of 10.0 mg/kg imipramine in monkeys OP and CL (21.4 and 1.9% naltrexone-lever responding, respectively), subjects responded exclusively on the saline-associated lever after acute injections of these test compounds (data not shown).

**Discussion**

Results of this study demonstrate that cocaine and amphetamine attenuate the discriminative stimulus effects of naltrexone in opioid-dependent rhesus monkeys. The discriminative stimulus of naltrexone in LAAM-treated monkeys has been shown to be related to and predictive of withdrawal (Brandt and France, 1998). Furthermore, the discriminative stimulus effects of naltrexone have been clearly shown to be mediated primarily by $\mu$-opioid receptors in monkeys treated with LAAM (Brandt and France, 1998) or morphine (France and Woods, 1989). However, a growing body of literature indicates the involvement of other neurotransmitter systems in mediating different specific components of withdrawal.

As suggested by the results of tests with specific dopaminergic and noradrenergic antagonists, the effects of cocaine and amphetamine in attenuating antagonist-precipitated withdrawal do not seem to be mediated primarily by norad-
TABLE 2
Effects of test drugs alone or in combination with increasing doses of naltrexone on response rates given as the responses per second averaged among three to four monkeys, except at higher doses of naltrexone (0.032–1.0 mg/kg), where n = 1–4. At ≥80% responding on the drug lever, naltrexone dosing was terminated irregardless of rate.
Data are presented as means ± S.D.

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<th>Naltrexone (mg/kg)</th>
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<th>0.001</th>
<th>0.0032</th>
<th>0.01</th>
<th>0.032</th>
<th>0.10</th>
<th>0.32</th>
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<td>Saline</td>
<td>1.54 ± 0.38</td>
<td>1.61 ± 0.33</td>
<td>1.64 ± 0.43</td>
<td>1.55 ± 0.55</td>
<td>1.97 ± 0.30</td>
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<tr>
<td>Cocaine 0.1</td>
<td>1.96 ± 0.36</td>
<td>1.62 ± 0.30</td>
<td>1.61 ± 0.46</td>
<td>1.66 ± 0.58</td>
<td>1.36 ± 0.16</td>
<td>1.29 ± 0.0*</td>
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<tr>
<td>Cocaine 0.32</td>
<td>1.83 ± 0.37</td>
<td>1.71 ± 0.36</td>
<td>1.71 ± 0.37</td>
<td>1.81 ± 0.64</td>
<td>2.20 ± 0.05</td>
<td>2.37 ± 0.0*</td>
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<tr>
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<td>1.58 ± 0.62</td>
<td>1.58 ± 0.69</td>
<td>1.70 ± 0.45</td>
<td>1.94 ± 0.64</td>
<td>1.49 ± 0.77</td>
<td>2.06 ± 0.09</td>
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<td>1.95 ± 0.41</td>
<td>1.85 ± 0.43</td>
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<td>1.99 ± 0.60</td>
<td>2.22 ± 0.64</td>
<td>2.80 ± 0.0*</td>
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<td>1.96 ± 0.67</td>
<td>1.93 ± 0.78</td>
<td>2.24 ± 0.77</td>
<td>2.42 ± 0.97</td>
<td>3.13 ± 0.0*</td>
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<td>Amphetamine 1.0</td>
<td>1.44 ± 0.27</td>
<td>1.23 ± 0.34</td>
<td>1.84 ± 0.45</td>
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<td>1.62 ± 0.29</td>
<td>1.88 ± 0.54</td>
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<td>1.26 ± 0.41</td>
<td>1.26 ± 0.84</td>
<td>0.44 ± 0.17</td>
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<td>1.11 ± 0.21</td>
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<td>Imipramine 3.2</td>
<td>1.45 ± 0.15</td>
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<td>1.22 ± 1.04</td>
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* When S.D. = 0, then n = 1 for that dose of naltrexone.

Fig. 2. Discriminative stimulus effects of naltrexone alone and in combination with cocaine (0.1, 0.32, and 1.0 mg/kg). Saline or drug (cocaine) was administered in the first cycle followed by increasing doses of naltrexone in subsequent cycles. The control curve (filled circles) represents the average (+ S.E.) curve generated from 9 to 11 naltrexone dose-effect curves determined for each monkey over the course of the experiment. See Fig. 1 for additional details.

dopamine is a primary mediator of the effects of both cocaine and amphetamine, the data presented herein agree with other evidence in the literature that collectively indicate that dopaminergic systems are integrally involved in mediating opioid withdrawal (Acquas et al., 1991; Harris and Aston-Jones, 1994). Moreover, the ability of a dopamine receptor

renergic systems, as has been proposed by others. Kosten (1990) reported that opioid-withdrawal signs are less severe in both humans and rats in the presence of cocaine. Because
antagonist, haloperidol, to enhance the naltrexone discrimi-
native stimulus (i.e., shift the naltrexone dose-effect curve to
the left) in opioid-dependent monkeys further implicates the
involvement of dopamine in opioid withdrawal.

Albeit by slightly different mechanisms, both cocaine and
amphetamine act at monoamine transporters to increase ex-
tracellular concentrations of dopamine, noradrenaline, and
serotonin (Koe, 1976). Because of an abundant literature
implicating noradrenaline in opioid withdrawal (for review,
see Maldonado, 1997), and because cocaine and amphetamine
can enhance noradrenaline in brain, it has been suggested that
the effect of cocaine in attenuating opioid withdrawal might be
due to increased concentrations of noradrenaline acting at \( \alpha_2 \)
adrenergic receptors (Kosten, 1990). For example, spontaneous
firing of locus coeruleus neurons was inhibited by peripherally
administered cocaine, and this effect was reversed by piperox-
ane (Pitts and Marwah, 1986). Clonidine, which activates pre-
synaptic \( \alpha_2 \)-adrenergic receptors that inhibit locus coeruleus
activity (Korf et al., 1973), has been shown to attenuate with-
drawal signs in rats (Holtzman, 1985) as well as some (Jasinski
et al., 1985) but not all (Jasinski et al., 1985) withdrawal signs
in humans. Although clonidine reduces some withdrawal signs
in rats it has also been reported to exacerbate others (Tseng et
al., 1975). Consistent with data obtained in rats (Holtzman,
1985), clonidine did not attenuate the discriminative stimulus
of naltrexone in opioid-dependent monkeys, suggesting that
clonidine might act specifically to reduce physiological signs of
withdrawal rather than interoceptive effects of withdrawal that
mediate the discriminative stimulus or subjective effects.

Dopamine is an important neurotransmitter in the reward-
ing effects of cocaine and amphetamine and dopamine con-
centrations in brain decrease during naloxone-precipitated
withdrawal (Pothos et al., 1991; Rossetti et al., 1992); thus, it
is possible that psychostimulants attenuate the discriminative
stimulus of naltrexone by increasing dopaminergic transmis-
sion. Furthermore, it has been proposed that the aversive subjective effects of withdrawal might result from
decreased dopaminergic activity (Acquas et al., 1991; Ros-
setti et al., 1992). The effect of haloperidol, to shift the nal-
The results obtained with other noradrenergic compounds, such as propranolol, desipramine, and imipramine, suggest that the effects of cocaine and amphetamine under these conditions require the activation of more than one neurotransmitter system. Desipramine, which is more selective than imipramine for the noradrenaline transporter, had very little effect on the naltrexone stimulus. In contrast, propranolol and imipramine had more robust effects, shifting the naltrexone dose-effect curve further to the right and down in some monkeys, and in a manner similar to that of cocaine and amphetamine. Both propranolol and imipramine have some affinity for serotonin as well as noradrenaline transporters or receptors. For example, propranolol, which can reduce cocaine withdrawal in humans (Kampman et al., 2001), binds to serotonin 1A and 1B receptors (Pierson et al., 1989). Moreover, imipramine has greater affinity for the serotonin transporter than does desipramine (for review, see Humble, 2000). Among other compounds, imipramine yielded data that were most similar to those obtained with cocaine and amphetamine, further suggesting that an amalgamation of neurotransmitter systems is involved in the capacity of stimulants to attenuate the discriminative stimulus effects of naltrexone.

Although inhibition of dopamine uptake at the dopamine transporter is considered to be an important mechanism in the reinforcing effects of cocaine, other selective compounds for this transporter (e.g., GBR 12909) do not always exhibit equivalent discriminative stimulus (Tella and Goldberg, 2001) or reinforcing effects (Tella et al., 1996). Differences in behavioral effects among dopamine uptake inhibitors might indicate that “secondary” actions of less selective compounds are necessary for certain effects. For cocaine, increased levels of serotonin (Ritz and Kuhar, 1989) and noradrenaline (Rothman et al., 2001) as well as dopamine seem to be involved in the expression of some behavioral effects (e.g., discriminative stimulus, reinforcing and subjective effects). Collectively, the data presented herein and elsewhere (Ritz and Kuhar, 1989; Rothman et al., 2001) indicate that there might be more than one amalgamation of actions that achieves the same behavioral outcome. The notion of multiple (heterologous) mechanisms is consistent with the relative ineffectiveness in this study of more specific compounds (sulpiride and desipramine) compared with less specific compounds (propranolol and imipramine).

Stimulants such as cocaine and amphetamine can elicit perseverant responding, whereby the same response occurs repeatedly regardless of programmed contingencies (e.g., absence of reinforcers). In monkeys, amphetamine can induce perseverant behavior that is blocked by haloperidol, indicating a role for dopamine in this effect (Ridley et al., 1981). However, amphetamine-induced disruptions in performance are markedly diminished by extensive training, perhaps because of increased stimulus control over responding (Glick and Jarvik, 1969). In the present study monkeys were under excellent stimulus control as evidenced by the extremely small confidence limits for the control naltrexone dose-effect curve. Moreover, imipramine, which has selectivity for noradrenaline and serotonin transporters, had effects in some monkeys that were qualitatively and quantitatively similar to those obtained with cocaine, suggesting that a nonselective induction of perseverant responding is not likely to have contributed to the effects obtained in this study.

Combinations of two or more drugs can generate novel effects that are not necessarily predicted from the known pharmacology of each compound alone. With regard to drug discrimination, it has been hypothesized that perceptual masking might occur whereby one compound exerts distinctive stimulus effects that render an otherwise readily identified training compound no longer detectable (Colpaert, 1977). Masking has generally been ignored or assumed irrelevant in most drug-discrimination studies (Overton, 1984);
however, dopaminergic compounds have been suggested to alter the morphine discriminative stimulus under some conditions by masking (Gauvin and Young, 1989). Although the effects of cocaine and amphetamine on the naltrexone discriminative stimulus in opioid-dependent monkeys might reflect perceptual masking, if this procedure was generally susceptible to masking then it might be expected that a similar effect would be obtained with a wider variety of compounds. In fact, the only other drugs that attenuate this effect of naltrexone are μ-opioid agonists.

It is clear that the primary dependent variable in this study (i.e., naltrexone discriminative stimulus in opioid-dependent monkeys) is mediated primarily by the receptor system for which naltrexone and LAAM have selectivity (i.e., μ-receptors); however, it also seems that this variable can be modulated by an amalgamation of receptor systems (in this case monoamines), which either subserve or contribute to the primary receptor system response. Because opioid withdrawal, whether naltrexone-precipitated or spontaneous, initiates a cascade of events involving a variety of neurotransmitter systems, it follows that perturbing these systems might attenuate or enhance (as the case may be) the withdrawal-associated discriminative stimulus. Finally, nonsystematic observations in these opioid-dependent monkeys suggest that the effects of some drugs (e.g., amphetamine, clonidine) on the naltrexone discriminative stimulus do not predict their effects on other measures of withdrawal. This apparent disconnect between the discriminative stimulus and observable signs of withdrawal supports the notion that these two manifestations of withdrawal are mediated, in part, by different neurotransmitter systems.

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