Cocaine-Like Discriminative Stimulus Effects of Heroin: Modulation by Selective Monoamine Transport Inhibitors

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ABSTRACT

In previous studies, heroin was shown to engender cocaine-like discriminative stimulus (DS) effects; however, the mechanisms underlying the cocaine-like effects of heroin are unknown. The present study evaluated the extent to which the shared DS effects of heroin and cocaine involve common monoaminergic mechanisms of action. In squirrel monkeys discriminating cocaine (0.3 mg/kg) from saline, heroin engendered full or partial substitution for cocaine in three of four monkeys. Pretreatment with the selective dopamine transport inhibitor 1-(2-[(bis(4-fluorophenyl)methoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909) dose dependently enhanced the cocaine-like DS effects of heroin in these three monkeys as well as the DS effects of cocaine in all subjects. Neither talsupram, a noradrenergic transport inhibitor, nor prazosin, a noradrenergic antagonist selective for α1 receptors, systematically altered the cocaine-like DS effects of heroin at doses that enhanced (talsupram) or attenuated (prazosin) the DS effects of cocaine. Pretreatment with the serotonin uptake inhibitor citalopram similarly failed to alter the cocaine-like DS effects of heroin at doses that attenuated the DS effects of cocaine. Altogether, these findings suggest that heroin shares DS effects with cocaine in a subset of monkeys, and these cocaine-like effects are mediated at least in part by enhanced dopaminergic activity. Unlike the DS effects of cocaine itself, however, the cocaine-like DS effects of heroin do not appear to involve either noradrenergic or serotonergic mechanisms.

Research efforts focused on understanding “speedball” abuse (i.e., the concomitant use of stimulants and opioids; Kosten et al., 1986; Leri et al., 2003) have yet to reveal clear neuropharmacological mechanisms underlying this prevalent form of polydrug addiction. Preclinical investigations have implicated brain dopamine (DA) systems as important in modulating the abuse-related effects of stimulants and opioids when used singly (Koob and Bloom, 1988; Di Chiara and North, 1992), raising the possibility that speedballs engage their effects via a combined interaction at this neurotransmitter system (Spealman and Bergman, 1992; Rowlett et al., 1998). Evidence supporting this idea has come from experimental models in which stimulants and opioids elicit similar behavioral effects. For example, in drug discrimination procedures, which provide information relevant to understanding a drug’s interoceptive effects, stimulants and opioids often engender shared discriminative stimulus (DS) effects. In this regard, various opioid agonists have been shown to engender partial or full substitution for cocaine in the majority of monkeys trained to discriminate cocaine from vehicle (Mello et al., 1995; Negus et al., 1998; Rowlett et al., 2000, 2001). Because shared DS effects of drugs often correspond closely with overlapping mechanisms of action, these findings suggest commonalities in the neuropharmacological mechanisms underlying transduction of the DS effects of stimulants and opioids.

Biogenic amine neurotransmitters other than DA appear to play important modulatory roles in the transduction of the DS effects of cocaine. For example, norepinephrine transporter (NET) inhibitors have been shown to substitute at least partially for the DS effects of cocaine, whereas the α1 norepinephrine (NE) antagonist prazosin attenuated the DS effects of cocaine (Johanson and Barrett, 1993; Spealman, 1995). In contrast, serotonin transporter (SERT) inhibitors consistently have been shown to lack significant cocaine-like DS effects in monkeys (Kleven et al., 1990; Spealman, 1993; Schama et al., 1997). Variable effects of SERT inhibitors on the DS effects of cocaine in monkeys have been reported, with a study from our laboratory showing that the selective SERT inhibitor citalopram attenuated the DS effects of cocaine (Spealman, 1993; cf. Schama et al., 1997). Comparatively

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ABBREVIATIONS: DA, dopamine; CI, confidence interval; DAT, dopamine transporter; DS, discriminative stimulus; GBR 12909, 1-(2-[(bis(4-fluorophenyl)methoxy)ethyl]-4-(3-phenylpropyl)piperazine; NE, norepinephrine; NET, norepinephrine transporter; SERT, serotonin transporter; 5-HT, 5-hydroxytryptamine; FR, fixed ratio.
little is known regarding the degree to which monoamine systems other than DA are involved in the DS effects of opioids. Platt et al. (1999), for example, demonstrated that neither the selective NET inhibitor talsupram nor the SERT inhibitor fluoxetine engendered significant levels of drug-appropriate responding in monkeys trained to discriminate morphine from vehicle. The ability of NET and SERT inhibitors to modulate the DS effects of opioids in monkeys is unknown at present.

Because NE and 5-HT systems appear to be involved in the transduction of the DS effects of cocaine, it is possible that these systems may play a similar role in or perhaps mediate the cocaine-like DS effects of opioids. The present study assessed the extent to which DA, NE, and 5-HT mechanisms are involved in the cocaine-like DS effects of heroin. The overall approach was based on previous studies from our laboratory that investigated the extent to which selective DA, NE, and 5-HT ligands modulated the DS effects of cocaine in squirrel monkeys (Spealman, 1993, 1995). Using similar drug discrimination techniques, selective DAT, NET, and SERT inhibitors [1-(2-bis[4-fluorophenyl]methoxy)ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909), talsupram, and citalopram, respectively] were evaluated for their ability to alter the cocaine-like DS effects of heroin. In addition, the ability of the NE receptor antagonist prazosin to attenuate the cocaine-like effects of heroin was assessed. To provide appropriate points of reference, parallel studies were conducted in the same monkeys to evaluate the effects of the monoamine transport inhibitors on the DS effects of cocaine itself.

**Materials and Methods**

**Subjects.** Four adult male squirrel monkeys (Saimiri sciureus) were studied in daily experimental sessions (Monday–Friday). Between sessions, the monkeys lived in individual home cages, where they had unlimited access to water. Each monkey was maintained at 85 to 90% of its free-feeding body weight (0.70–0.94 kg) by adjusting its access to food (Teklad monkey diet [Harlan Teklad, Madison, WI], fresh fruits, and vegetables) in the home cage. All monkeys previously had been trained to discriminate cocaine from vehicle and had been used in drug interaction studies with cocaine, GBR 12909, and heroin (Rowlett et al., 2001). All animals were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare publication no. NIH 85-23, as revised in 1996. Research protocols were approved by the Harvard Medical School Institutional Animal Care and Use Committee.

**Apparatus.** During experimental sessions, monkeys were seated in a Plexiglas chair identical to the one described by Rowlett et al. (2001). Two response levers (model 121-05; BRS/LVE, Laurel, MD) were mounted 15 cm apart on the wall of the chair in front of the monkey. A press of either lever with a minimum downward force of 0.25 newtons produced an audible click and was recorded as a response. Food pellets (Noyes, 190 mg, Formula L; Research Diets, Inc., New Brunswick, NJ) could be delivered to a tray located between the levers. Red lights, mounted at eye level above the levers, were illuminated during the session except during timeout periods (see below). The chair was enclosed in a ventilated, sound-attenuating chamber that was provided with white noise to mask extraneous sounds.

**Drug Discrimination Procedure.** Before the present study began, each monkey had been trained to discriminate 0.3 mg/kg cocaine from saline, and these training conditions continued during the present study. Briefly, after injections of cocaine, 10 consecutive responses (FR 10) on one lever produced food, whereas after injections of saline, 10 consecutive responses on the other lever produced food. Responses on the incorrect lever (e.g., the saline-associated lever when cocaine was injected) reset the FR requirement. Training sessions consisted of a variable number of components (n = 1–4) of the FR schedule. Each component ended after the completion of the tenth FR 10 or after 5 min had elapsed, whichever occurred first. A 10-min timeout period, during which the lights were off and responses had no programmed consequences, preceded each component. During most training sessions, saline was injected during timeout periods preceding the first n-1 components, and cocaine was injected before the last component of the session. Periodically, saline was injected before all components of a training session to prevent an invariant association between the fourth component and cocaine. Injections of cocaine or saline were made in a thigh or calf muscle of either leg during the 5th min of the 10-min timeout periods.

**Drug Testing Procedure.** Drug test sessions were conducted once or twice per week with training sessions scheduled on intervening days. Test sessions were conducted only if ≥80% of responses were made on the injection-appropriate lever during at least four of the preceding five training sessions. Test sessions consisted of four FR components, each preceded by a 10-min timeout period. In each component, completion of 10 consecutive responses on either lever produced food. Dose-response functions were determined for test drugs using the cumulative dosing procedure described by Rowlett et al. (2001). Incremental doses were injected during the 5th min of the 10-min timeout periods that preceded sequential FR components, permitting a four-point cumulative dose-response function to be determined in a single session. Full dose-response functions were determined for cocaine (0.03–1.0 mg/kg) and heroin (0.03–0.1 mg/kg).

Periodically, the first injection in a cumulative dosing sequence was a saline injection.

In drug combination studies, GBR 12909 (3.0, 10 mg/kg), talsupram (3.0, 10 mg/kg), citalopram (3.0, 10 mg/kg), and prazosin (1.0, 1.8 mg/kg) were administered 30 min before the experimental session, based on previous experiments (Spealman, 1993, 1995; Rowlett et al., 2001). Pretreatments were followed by administration of cumulative doses of cocaine or heroin as described above. Each dose-response function in the drug combination studies was determined twice in each subject, and when warranted, five doses of a drug were studied by administering overlapping ranges of cumulative doses in separate testing sessions. Following two or three dose-response functions for a drug combination study, the dose-response function for cocaine or heroin alone was reetermined, and this dose-response function is presented with the results for the respective drug combination experiment.

**Analysis of Drug Effects.** The percentage of responses on the cocaine-associated lever was computed for individual subjects in each component of a test session by dividing the number of responses on that lever by the total number of responses on both levers and multiplying by 100. Because individual differences in the cocaine-like DS effects of heroin have been observed previously (Rowlett et al., 2001), the effects of heroin alone were assessed initially by evaluating the results of individual subjects followed by analysis of grouped data in the subset of monkeys showing cocaine-like DS effects of heroin. For analysis of drug interactions, mean percentage of cocaine-lever responding and standard error of the mean (S.E.M.) were calculated for the group of monkeys at each dose. Percentage of cocaine-lever responding was calculated for an individual monkey only if at least one FR 10 was completed during the component. The overall rate of responding in each component was computed by dividing the total number of responses in a component (regardless of lever) by the total component duration. Mean response rates ± S.E.M. were calculated for the group at each dose and compared with control values using Dunnett’s t-test (p < 0.05).

The doses of cocaine needed to engender 50% cocaine-appropriate responding (EDso) were estimated for individual subjects by linear
interpolation of the log dose-response functions, since in most cases
dose-response functions consisted of a dose at or near 0% drug-lever
responding and a dose at or near 100% drug-lever responding. Full
substitution for cocaine for an individual monkey or a group of
monkeys was concluded if the maximum percentage of drug-lever
responding was greater than or equal to 80% (i.e., the training
criterion for stimulus control). Partial substitution was concluded if
the percentage of drug-lever responding was greater than 50% but
less than 80%.

Reliable effects of drug pretreatments were determined by com-
puting 95% CI for the mean ED_{50} values obtained in the presence
and absence of the particular pretreatment. A reliable effect of the
pretreatment drug on the DS effects of cocaine or the cocaine-like
effects of heroin was concluded if the 95% CIs did not overlap. To
determine the extent to which drug combinations resulted in effects
that differed from dose additivity, isobolographic analyses were con-
ducted as described by Rowlett et al. (2001), adapted from Gessner
(1974). Dose additivity is defined as the combined effect occurring
when dose combinations of two drugs produce effects equal to the
effect produced by the sum of the individual doses. For each drug
combination, a theoretical line of dose additivity was plotted in a
two-dimensional graph as a diagonal line between the ED_{50} values
for each drug alone. The ED_{50} value of the combinations was divided
by predicted ED_{50} values and compared with the population value of
1.0 using one-sample t tests (Rowlett and Woolverton, 1995; Rowlett
et al., 2001).

**Drugs.** Cocaine hydrochloride, heroin (base form), GBR 12909
dihydrochloride, talsupram hydrochloride, citalopram hydrobro-
mide, and prazosin hydrochloride were provided by the National
Institute on Drug Abuse (Bethesda, MD) or were purchased from
commercial sources (Research Biochemicals, Natick, MA; Tocris
Cookson, Ballwin, MO). Drugs were dissolved in sterile distilled
water containing 95% ethanol, 1 N acetic acid, or 0.1 N HCl as
required and were diluted to the desired concentrations with 0.9%
saline solution. All drugs were injected via the intramuscular route
(calf or thigh muscle) in a maximum volume of 0.5 ml/kg. The vehicle
for drug injections had ethanol concentrations less than 1.0%, with
pH values between 5.0 and 7.0.

**Results**

**Effects of Cocaine and Heroin.** Cumulative doses of
cocaine increased the percentage of drug-lever responding in
each monkey from predominantly saline-like levels (at or
near 0%) to drug-like levels (80–100%) as the dose was in-
creased (Fig. 1, top left panel). At cocaine doses up to the
training dose (0.3 mg/kg), rates of responding were increased,
whereas the next higher dose (1.0 mg/kg) tended to suppress
response rates to or below saline levels (Fig. 1, bottom left
panel).

Heroin had qualitatively different effects in the individual
subjects (Fig. 1, top right panel). In two of four monkeys
(S-479 and S-329), heroin engendered dose-related increases
in the percentage of responses on the cocaine-associated le-
ver, reaching maximums of 95 to 100% cocaine-lever re-
sponding (i.e., full substitution for cocaine for individual
monkeys). In a third monkey (S-120), heroin engendered
appreciable levels of drug-lever responding; however, the
maximum level was lower than observed for monkeys S-479
and S-329 (74% cocaine-lever responding; partial substitu-
tion for cocaine). In monkey S-94, heroin did not engender
substantial cocaine-lever responding regardless of dose. This
monkey was excluded from subsequent experiments, since
the overall aim was to examine the underlying mechanisms
that determined the cocaine-like DS effects of heroin. In
three of four monkeys, at least one dose of heroin decreased
the overall rate of responding (Fig. 1, bottom right panel).

**Combination Studies with GBR 12909.** When GBR
12909 (3.0 or 10 mg/kg) was administered prior to cumulative
doses of heroin, the cocaine-like DS effects of heroin were
enhanced, with leftward shifts in the heroin dose-response
function (Fig. 2). Isobolographic analysis showed that the
mean ED_{50} values were reduced in an additive manner. This
result was confirmed by the one-sample t test analysis com-

![Fig. 1. Percentage of drug-lever responding and response rates for cocaine and heroin in squirrel monkeys trained to discriminate 0.3 mg/kg co-
caine from vehicle. Data are the results from tests in individual subjects. Dashed lines rep-
resent full substitution for the cocaine stimulus (≥80% cocaine-lever responding).](image-url)
paring the ratio of observed to predicted ED$_{50}$ values with a predicted population ratio of 1.0 (Table 1). Average rates of responding following combination of GBR 12909 and heroin were nearly identical to those obtained with heroin alone (data not shown).

When doses of GBR 12909 (3.0 or 10 mg/kg) were administered prior to cumulative doses of cocaine, the dose-response function for the percentage of responses on the drug lever was shifted to the left in a dose-dependent manner (Fig. 2). Isobolographic analysis showed that the mean ED$_{50}$ values were reduced but did not differ reliably from additivity as evident by nonsignificant one-sample $t$ tests comparing the observed/predicted ED$_{50}$ values to a predicted population ratio of 1.0 (Table 1). As with the combination of GBR 12909 and heroin, combining GBR 12909 with cocaine did not systematically alter rates of responding (data not shown).

**TABLE 1**
Isobolographic analyses of heroin and cocaine combined with GBR 12909 in cocaine-trained squirrel monkeys ($N = 3$)

<table>
<thead>
<tr>
<th></th>
<th>Predicted$^a$ (Mean ± S.E.M.)</th>
<th>Observed Ratio$^b$</th>
<th>$t$ Value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBR 12909 + heroin</td>
<td>0.015 ± 0.002</td>
<td>0.017 ± 0.002</td>
<td>1.12</td>
</tr>
<tr>
<td>10</td>
<td>0.007 ± 0.002</td>
<td>0.009 ± 0.002</td>
<td>1.30</td>
</tr>
<tr>
<td>GBR 12909 + cocaine</td>
<td>0.069 ± 0.011</td>
<td>0.084 ± 0.011</td>
<td>1.22</td>
</tr>
<tr>
<td>10</td>
<td>0.055 ± 0.010</td>
<td>0.039 ± 0.010</td>
<td>0.71</td>
</tr>
</tbody>
</table>

$^a$ Values obtained from linear regression analysis of the additivity lines obtained from isobolographic plots.

$^b$ Ratio is Observed ED$_{50}$ divided by the Predicted ED$_{50}$.

$^c$ $t$ values were obtained from one-sample $t$ tests comparing the ratio values to the predicted population mean ratio based on no difference from additivity (1.0). $t_{crit} = 4.30, P = 0.05$, two-tailed.

**Combination Studies with Talsupram and Prazosin.**
The NET inhibitor talsupram did not systematically alter the cocaine-like DS effects of heroin regardless of dose (Fig. 3; Table 2). In general, combining talsupram with heroin had few effects on rates of responding, except that the combination of 0.1 mg/kg heroin and 10 mg/kg talsupram reduced responding to approximately 10% of response rates obtained during vehicle tests (Table 3).

In contrast to combining talsupram with heroin, combinations of talsupram and cocaine shifted the dose-response function for percentage of drug-lever responding to the left at both 3.0 and 10 mg/kg talsupram (Fig. 3). Compared with cocaine alone, the ED$_{50}$ values for cocaine plus both doses of talsupram were reliably decreased by approximately 3-fold (Table 2). Talsupram at both doses had no systematic effect.
of heroin (Fig. 4; Table 2). Because this dose of prazosin had no effect on drug-lever responding or rates of responding, a higher dose (1.8 mg/kg) was evaluated. This higher dose also did not alter the cocaine-like DS effects of heroin at the two doses tested. When tested alone, this dose of prazosin reduced rates of responding to approximately 26% of saline levels and engendered marked reductions in responding when combined with heroin. Prazosin could only be tested up to 0.01 mg/kg heroin without eliminating responding completely (Table 3; Fig. 4).

In contrast to the results with heroin, 1.0 mg/kg prazosin shifted the cocaine dose-response function to the right in an approximately parallel fashion (Fig. 4). The ED$_{50}$ for the DS effects of cocaine was increased reliably (approximately 5-fold) by 1.0 mg/kg prazosin (Table 2). This dose of prazosin had no consistent effect on rates of responding, either alone or combined with cocaine.

**Combination Studies with Citalopram.** The SERT inhibitor citalopram did not alter the cocaine-like DS effects of heroin (Fig. 5; Table 2). The effects of 10 mg/kg citalopram on the cocaine-like effects of 0.1 mg/kg heroin could not be assessed due to this citalopram dose completely eliminating responding in all subjects. At a lower dose of heroin (0.03 mg/kg), 10 mg/kg citalopram reduced rates of responding to 50% of vehicle control levels (Table 3); nonetheless, this dose of citalopram did not alter cocaine-lever responding (Fig. 5).

The 10 mg/kg, but not 3.0 mg/kg dose of citalopram shifted the cocaine dose-response function for drug-lever responding to the right and down (Fig. 5). Maximum drug-lever responding engendered by cocaine at the higher dose of citalopram was below 50%, precluding the calculation of ED$_{50}$ values. The combination of the higher dose of citalopram with 1.0 mg/kg cocaine suppressed response rates to approximately 50% of vehicle control levels.

**Discussion**

**Cocaine-like Effects of Heroin.** The findings of the present study confirm that heroin has full or partial cocaine-like DS effects in a sizeable proportion of subjects trained to discriminate cocaine, an observation consistent with other studies (e.g., Mello et al., 1995; Negus et al., 1998; Rowlett et al., 2000, 2001). These results suggest that although heroin and cocaine are pharmacologically distinct, they can share interoceptive effects in cocaine-trained monkeys. The factors

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Dose</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.035 ± 0.011</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td>+ 3.0 Citalopram</td>
<td>0.036 ± 0.011</td>
<td>0.059 ± 0.013</td>
</tr>
<tr>
<td>+ 10 Citalopram</td>
<td>0.052 ± 0.020</td>
<td>0.054 ± 0.009</td>
</tr>
<tr>
<td>+ 1.8 Prazosin</td>
<td>0.023 ± 0.012</td>
<td>0.48 ± 0.09</td>
</tr>
</tbody>
</table>

This dose of prazosin had a

- Fig. 4. Percentage of drug-lever responding after administration of heroin (left panel) or cocaine (right panel), alone and after pretreatments with the α-1 antagonist prazosin in cocaine-trained squirrel monkeys. Other details as described in Fig. 2.
- Fig. 5. Percentage of drug-lever responding after administration of heroin (left panel) or cocaine (right panel), alone and after pretreatments with the serotonin transport inhibitor citalopram in cocaine-trained squirrel monkeys. Other details as described in Fig. 2.

**TABLE 2**

Mean ED$_{50}$ values (± S.E.M.) for the discriminative stimulus effects of heroin and cocaine, alone and combined with noradrenergic and serotonergic drugs, in cocaine-trained squirrel monkeys ($N = 3$)

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Dose</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Saline</td>
<td>0.84 ± 0.44</td>
</tr>
<tr>
<td>+ 10 Talsupram</td>
<td>Saline</td>
<td>0.70 ± 0.31</td>
</tr>
<tr>
<td>+ 1.8 Prazosin</td>
<td>Saline</td>
<td>0.065 ± 0.010</td>
</tr>
<tr>
<td>+ 10 Citalopram</td>
<td>Saline</td>
<td>0.68 ± 0.22</td>
</tr>
<tr>
<td>+ 1.8 Citalopram</td>
<td>Saline</td>
<td>0.35 ± 0.20</td>
</tr>
</tbody>
</table>

* P < 0.05, Dunnett's test vs. saline control.

on rates of responding after injections of cocaine (data not shown).

Pretreatment with the α-1 NE antagonist prazosin (1.0 mg/kg) did not significantly alter the cocaine-like DS effects of heroin (Fig. 4; Table 2). Because this dose of prazosin had

- Nonoverlapping 95% CI compared with “no pretreatment” condition.
- ED$_{50}$ could not be calculated because 50% drug-lever responding was not obtained or was the maximum effect obtained.
- NT, not tested.
contributing to the individual differences in the ability of heroin to engender cocaine-like effects are unclear at present. As reported previously, the pattern of heroin substitution for cocaine did not correlate with any experiential factors associated with individual monkeys, such as experimental history or training dose (Rowlett et al., 2001).

Heroin and related opioid agonists also can be trained as discriminative stimuli, and several reports have evaluated the ability of stimulant-type drugs to engender heroin-like effects. For example, Lamas et al. (1998) demonstrated that cocaine lacked heroin-like DS effects in rats, although heroin partially substituted for cocaine as found in the present study. In a recent report, Platt et al. (2001) showed that cocaine did not engender drug-lever responding in rhesus monkeys trained to discriminate intravenous injections of heroin. Together with the present findings, these results suggest that the extent to which heroin and cocaine share DS effects depends critically on the training drug, with heroin more likely to engender cocaine-like effects than cocaine to engender heroin-like effects.

**Role of the Dopamine Transporter.** Based on the finding that μ opioid agonists stimulate DA overflow in mesocorticolimbic brain regions (for review, see Leri et al., 2003), we postulated that activation of DA systems may represent a common substrate underlying the shared DS effects of cocaine and heroin (Rowlett et al., 2001). To examine this possibility, interaction studies were conducted with heroin in combination with the selective DAT inhibitor, GBR 12909. Pretreatments with GBR 12909 enhanced the cocaine-like DS effects of heroin in an additive manner, as revealed by isobolographic analysis. This analysis also revealed that the combined effects of cocaine with GBR 12909 were additive, and these similar findings suggest that the cocaine-like DS effects of heroin are mediated by a common action at DA systems.

In rhesus monkeys trained to discriminate heroin, GBR 12909 did not engender heroin-like DS effects in any monkey (Platt et al., 2001). Thus, in contrast to the cocaine-like effects of heroin, there appears to be no prominent role for the DAT system in the DS effects of heroin in heroin-trained subjects. To our knowledge, no studies are available in which GBR 12909 or other selective DAT inhibitors were evaluated for their ability to modulate the DS effects of heroin in heroin-trained subjects.

Another approach to studying DA systems is to investigate the extent to which DA antagonists attenuate the DS effects of heroin or other opioids. Clear-cut antagonism of the DS effects of heroin has not been demonstrated (Lamas et al., 1998; Platt et al., 1999). The lack of a role for the DAT or DA receptors in heroin-trained subjects contrasts with the results of the present study, suggesting a differential role of DA neurotransmission in the DS effects of heroin in cocaine-versus heroin-trained subjects. There remains a possibility, however, that interactions between the opioid and DA systems in heroin-trained subjects may be unique to a specific DA receptor subtype. For example, Cook and Picker (1998) demonstrated an attenuation of the DS effects of a μ agonist by the D3 subtype-preferring agonist 7-OH-DPAT (7-hydroxy-2-dipropylaminotetralin).

In addition to DS effects, enhancement of other abuse-related effects of cocaine and heroin when combined has been reported. For example, combinations of cocaine and heroin result in enhanced self-administration compared with the individual drugs (e.g., Rowlett and Woolverton, 1997). The role of the DAT in this enhancement of self-administration is unknown, although combination of cocaine and heroin enhances extracellular levels of DA in the nucleus accumbens (Hemby et al., 1999), a brain region thought to play a key role in the abuse-related effects of both stimulants and opioids.

**Role of Norepinephrine Transporters and α-1 Receptors.** In recent years, there has been an increasing appreciation of the role of other monoaminergic neurotransmitters in modulating the effects of cocaine, based in large part on the observation that cocaine binds with relatively high affinity to NE and 5-HT transporters. For example, in a previous report using experimental procedures similar to the present study, NET inhibitors engendered cocaine-like DS effects and enhanced the cocaine-like DS effects of GBR 12909, whereas prazosin attenuated the DS effects of cocaine (Spealman, 1995). Consistent with these findings, talsupram enhanced the DS effects of cocaine in the present study, whereas prazosin attenuated the DS effects of cocaine. In contrast, a similar pattern of effects for talsupram and prazosin was not evident when these drugs were administered prior to determinations of the serotonin dose-response function, providing no evidence of a role for NET and α-1 receptors in the cocaine-like DS effects of heroin.

Little information is available regarding the role of NE systems in modulating the DS effects of heroin in heroin-trained subjects. However, using morphine instead of heroin as the training drug, Platt et al. (1999) demonstrated that talsupram did not engender morphine-like DS effects in monkeys, and Hughes et al. (1996) found no evidence for involvement of α-1 receptors in the DS effects of morphine in rats. These findings clearly suggest that the NE system likely plays no prominent role in the DS effects of heroin-like drugs. Given the widespread use of the α-2 agonist clonidine in the treatment of heroin withdrawal, it is possible that α-2 receptors are involved in the cocaine-like effects of heroin; however, Hughes et al. (1996) found no evidence for α-2 receptor involvement in the DS effects of morphine.

Although the NE system appears to play a modulatory role in the DS effects of cocaine, involvement of NE in other abuse-related effects of cocaine is less clear. For example, early research suggested that the NE system was not involved in cocaine self-administration (e.g., Woolverton, 1987), although more recent evidence suggests that under certain conditions, NET inhibition may play a modulatory role in cocaine self-administration (for review, see Rocha, 2003). Less information is available regarding self-administration of heroin and NE systems; for example, an early study showed that morphine self-administration was attenuated by NE depletion (Davis et al., 1975). Regardless, the results of the present study suggest that the abuse-related effects of cocaine and heroin do not involve a common substrate at brain NE systems.

**Role of the Serotonin Transporter.** Serotonergic systems also have been found to modulate the DS effects of cocaine in monkeys in an inhibitory fashion. For example, the DS effects of cocaine were attenuated by the selective SERT inhibitor citalopram (Spealman, 1993, 1995), and this suppression of the DS effects of cocaine also was evident in the present study. The same pretreatment doses of citalopram, however, did not attenuate the cocaine-like DS effects of...
heroin. Although our results do not support a role for the SERK in modulating the shared DS effects of heroin and cocaine, these findings do not rule out the possibility of a role of specific 5-HT receptor subtypes. For example, the selective 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin) attenuated the DS effects of morphine in morphine-trained rats (Powell et al., 1994), suggesting an inhibitory influence of 5-HT_{1A} receptor stimulation on the interoceptive effects of morphine. Although 5-HT_{1A} receptor stimulation likely occurs indirectly via blockade of the SERK, the possibility of involvement of specific 5-HT receptor subtypes deserves additional evaluation.

Although SERK inhibition differentially attenuated the DS effects of cocaine and not the cocaine-like effects of heroin, SERK inhibitors have been shown to attenuate self-administration of both cocaine and the µ agonist morphine (Higgins et al., 1994; Czoty et al., 2002). Moreover, SERK inhibition resulted in a decrease in extracellular DA levels following cocaine administration (Czoty et al., 2002), whereas 5-HT receptor activation reduces morphine-induced increases in DA neurotransmission in the nucleus accumbens (e.g., Porras et al., 2002). Altogether, these findings raise the possibility that the SERK may play a differential role in the DS versus reinforcing effects of cocaine and heroin.

**Summary.** The results of the present study suggest that monoaminergic mechanisms differentially underlie the DS effects of heroin and cocaine. Specifically, the DA system is implicated in the shared DS effects of heroin and cocaine, whereas NE and 5-HT systems play a role in the DS effects of cocaine, but not the cocaine-like effects of heroin. Based on these and previous findings, it appears that the DAT system may play a more prominent role in the DS effects of heroin in cocaine-trained subjects than in heroin-trained subjects. Depending on the generality of these observations, a clear implication of these findings is that successful pharmacotherapies for speedball abuse may be effective if targeting the DAT.

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**References**


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