Callahan (1991, 1997) reported that coadministration of the
monoamine reuptake blockers can alter the DS effects of cocaine. Cunningham and Callahan (1991; 1994) indicated that inhibition of DA and 5-HT transport is responsible for the cocaine-enhancing effects of the monoamine reuptake blockers we examined. In contrast, NE reuptake apparently does not play a strong role, despite the finding that desipramine, talsupram and nortriptyline enhanced the DS effects of cocaine. However, pretreatment with the alpha-1 adrenergic antagonist prazosin failed to alter completely the ability of desipramine to enhance the DS effects of the low training dose of cocaine, but did produce dose-related decreases in the cocaine-enhancing effects of the beta adrenergic antagonist propranolol (10 mg/kg i.p.). These findings suggested that under some conditions, NE interactions can modulate the DS effects of cocaine. In all, the results confirm reports that monoamine reuptake blockers enhance the DS effects of cocaine, but indicate that 5-HT and DA can effectively modulate the DS effects of cocaine, but suggest that NE interactions may be relatively less important in the rat.

Whereas in vitro studies show that cocaine inhibits reuptake of NE, DA and 5-HT nonselectively (Koe, 1976; Reith et al., 1986), inhibition of DA reuptake is primarily responsible for cocaine's subjective effects in humans (Volkow et al., 1996, 1997). However, pretreatment with 5-HT/NE reuptake blockers can alter the DS effects of cocaine in rodents and nonhuman primates (Cunningham and Callahan, 1991; Spealman, 1993, 1995), reinforcing effects in rodents (Tella, 1995) and subjective effects in humans (Fischman et al., 1990; Walsh et al., 1994), which suggests that the indirect effects of cocaine on NE and 5-HT reuptake may be important in vivo. Although there is strong evidence that DA reuptake blockade plays a necessary and sufficient role (Girod et al., 1996; Silvia et al., 1997), these interaction studies indicate that NE and 5-HT may be important modulators of the behavioral effects of cocaine.

Results from several recent drug discrimination studies show convincingly that monoamine reuptake blockers enhance the behavioral effects of cocaine. Cunningham and Callahan (1991, 1997) reported that coadministration of the 5-HT reuptake inhibitor fluoxetine or the selective NE reuptake inhibitor desipramine produced leftward shifts in the drug-appropriate responding in rats trained to discriminate cocaine from saline in a two-lever drug discrimination paradigm. Spealman (1995) reported similar effects of the NE reuptake inhibitors talsupram and tomodexetine in squirrel monkeys trained to discriminate cocaine from saline; however, unlike results obtained in rats, the selective 5-HT reuptake inhibitor citalopram produced a rightward shift in the cocaine dose-response function (Spealman, 1993). This difference between species has not been explained adequately; yet taken in conjunction with findings that 1) fluoxetine does enhance the DS effects of a lower training dose of cocaine in squirrel monkeys (Schama et al., 1997), and 2) the rate-increasing effects of cocaine on schedule-controlled behavior in squirrel monkeys are attenuated by 5-HT reuptake inhibitors (Spealman, 1993; Howell and Byrd, 1995), monoamine reuptake blockers are indeed capable of altering behavioral effects of cocaine in both rats and nonhuman primates.

In addition to interaction experiments, several recent pharmacological characterizations of the DS effects of low doses of cocaine indicate that NE may play a more important
role than previously believed. That is, NE reuptake blockers (e.g., desipramine, nisoxetine or talipram) engender more complete substitution for the DS effects of a low training dose in either rats (Terry et al., 1994) or monkeys (Spealman, 1995), in contrast to findings obtained in animals trained with higher doses (Colpaert et al., 1979; Broadbent et al., 1991; Baker et al., 1993; Spealman, 1995). Additionally, the alpha-1 adrenergic antagonist prazosin produced rightward shifts in cocaine dose-response functions in monkeys trained to discriminate either low or high doses of cocaine from saline, although it has not been reported to antagonize the DS effects of cocaine in rats. It could be that species and/or training conditions are important determinants of the extent that NE is involved in the DS effects of cocaine. Nonetheless, taken together with findings that selective NE inhibitors enhance the DS effects of cocaine in rats and nonhuman primates, it is conceivable that NE may play a modulatory role in both species.

The purpose of our study was to characterize further recent findings that compounds with 5-HT and/or NE reuptake-blocking properties enhance the DS effects of cocaine (Cunningham and Callahan, 1991; Spealman, 1995; Callahan and Cunningham, 1997). These initial studies demonstrated clearly that monoamine reuptake inhibitors such as fluoxetine and desipramine enhance the DS effects of cocaine, but the relative importance of NE and 5-HT to the DS effects of cocaine has not been firmly established in the rat. Inasmuch as cocaine is considerably less potent than desipramine and fluoxetine in inhibiting 5-HT and NE reuptake (Koe, 1976; Hyttel, 1982), the fact that high doses of selective monoamine reuptake inhibitors are needed to enhance its DS effects (Cunningham and Callahan, 1991) makes it doubtful that these monoamines are involved when cocaine is given alone. Furthermore, although considered selective (Fuller, 1993), compounds such as fluoxetine and desipramine do have appreciable activity at other monoamine reuptake sites (Stanford, 1996). Thus, both 5-HT and NE reuptake blockade may be involved in the cocaine-enhancing effects of monoamine reuptake blockers, although the relative importance of different monoamines in modulating the DS effects of cocaine cannot be determined readily from the few compounds that have been examined to date in the rat. In our study the in vivo potencies of a large variety of monoamine reuptake inhibitors for enhancing the DS effects of cocaine were correlated with their potencies obtained from in vitro DA, NE or 5-HT reuptake-blocking studies. In this study a dose-dose discrimination procedure was used primarily because we expected compounds that substitute partially in cocaine-saline-trained animals to engender low-dose lever selection (Colpaert and Janssen, 1986; Kleven and Koek, 1997), a factor which makes it easier to detect the cocaine-enhancing effects of such compounds. We used this procedure recently to demonstrate that beta adrenergic antagonists enhance the DS effects of cocaine (Kleven and Koek, 1997).

Methods

Animals. Male Sprague-Dawley rats (Ico: OFA SD (I.O.P.S. Caw) Iffa Credo, St. Germain sur l’Arbresle, France), weighing between 240 and 260 g at the beginning of the studies, were used. Rats were housed in individual cages (Iffa Credo, 28 × 21 × 18 cm) with metal grid floors in air-conditioned rooms (21 ± 1°C; relative humidity 60 ± 5%) under a 12-hr light-dark cycle (lights on from 7:00 A.M. to 7:00 P.M.). Filtered (0.22 μ) water was freely available, but access to standard laboratory food (A04, Usine d’Alimentation Rationelle, Epinay sur Orge, France) was limited to 10 g per day, except during weekends when food was freely available between 5:00 P.M. Friday and 2:00 P.M. Sunday. Experiments were conducted between 9:00 A.M. and 5:00 P.M., Monday through Friday. Animals were cared for in accordance with guidelines set by the US Department of Health and Human Services for humane treatment of animals (Guide for the Care and Use of Laboratory Animals, US DHHS, PHS, National Institutes of Health publication no. 85–23, revised 1985), and the experiment protocol (assigned no. 009 by our local regulatory committee) was carried out in accordance with French law and the local ethical committee guidelines for animal research.

Apparatus. Experiments were conducted in standard operant conditioning chambers (model E10–12, Coulbourn Instruments, Lehigh Valley, PA) housed in light- and sound-attenuating enclosures that were ventilated by a fan, which also produced a masking noise. Each chamber contained a house light that was mounted above the food pellet receptacle located between two levers that were situated 2.5 cm above the grid floor. Food pellets (45 mg dustless pellets, Bioserv, Frenchtown, NJ) were delivered by a pellet dispenser (model E14–12, Coulbourn Instruments, Lehigh Valley, PA). Scheduling of reinforcement contingencies, reinforcement delivery and data recording were controlled by a SKED-11 system (State Systems, Kalamazoo, MI) implemented on a PDP-11 computer (Digital Equipment Corporation, Maynard, MA).

Discrimination procedure. All of the rats used in this study were trained initially to discriminate cocaine (10 mg/kg i.p.) from saline in a two-lever, food-reinforced FR10 drug discrimination paradigm by methods identical with those described recently (Koe et al., 1995; Kleven et al., 1997). Saline or cocaine (10 mg/kg) were administered 15 min before sessions during which responding on one of two levers, depending on pretreatment, was reinforced. Discrimination training was continued until fewer than three responses were made on the injection-inappropriate lever before the first food presentation during ten consecutive sessions (i.e., the FRF was less than 13).

Dose-dose discrimination training. On reaching the saline cocaine training criterion, rats were trained subsequently to discriminate a low dose (2.5 mg/kg) from the 10 mg/kg training dose using successive training periods wherein low doses of cocaine (0.63 or 2.5 mg/kg) were substituted for saline. That is, after first reaching the saline training criterion performance (FRF < 13 during ten consecutive sessions), the low training dose was 0.63 mg/kg, and after criterion performance was reached again it was changed to 2.5 mg/kg. Test sessions were conducted twice per week on Wednesdays and/or Fridays, although training continued on intervening days. During test sessions, the lever on which ten responses accumulated first was defined as the selected lever. After lever selection, the animal received the first food pellet, and subsequent reinforcement was made contingent on pressing the selected lever. A test session ended after 15 min. Testing was postponed to the next scheduled test day if, on either of the 2 most recent training days, the FRF value exceeded 15. Also, test data were discarded and the test condition later retested if the test session was followed by a training session of which the FRF value exceeded 15.

Drug administration. All drugs were injected in a volume of 1 ml/100 g and doses are expressed as weight of the free base. For interaction studies in dose-dose trained rats, saline or drug was injected i.p. 30 min before the session, i.e., 15 min before administration of saline or cocaine (2.5 mg/kg i.p.). The order of treatment with individual drugs and doses was unsystematic.

Data analysis. Test sessions generated data on two variables: 1) the selected manipulandum, i.e., saline, drug, high-dose, or low-dose lever, representing the measure of discriminative responding and 2)
the response rate, i.e., the total number of responses made on either lever during the 15-min session, expressed as a percentage of the response rate during the most recently preceding saline or low-dose training session. Selection data were used to calculate the percentage of animals at each treatment condition selecting the 10 mg/kg cocaine-appropriate lever. Drug effects on this variable were analyzed by use of the Litchfield and Wilcoxon procedure (Tallarida and Murray, 1987), implemented with the research programming language, RS/1 (Bolt Beranek and Newman Inc., Cambridge, MA), to estimate ED50 values and 95% confidence limits. When less than two intermediate effects were observed, 0 and/or 100% effects were transformed by means of Berkson’s adjustment (Hubert, 1984) to permit evaluation of behavioral potencies and correlation analysis among behavioral potencies were conducted by use of Statview 4.5 (Abacus Concepts, Inc., Berkeley, CA). The in vitro biochemical potencies shown in table 1 were, unless noted otherwise, based on IC50 values from published monoamine uptake experiments in which cocaine was also studied (Hyttel, 1982; Hyttel and Larsen, 1985). In vitro data for all of the compounds, with the exception of cocaethylene, GBR 12935, metyrapone, cocaine and nisoxetine, were obtained from Hyttel (1982) or Hyttel and Larsen (1985); other sources were used for potencies of GBR 12935 (Matecka et al., 1996), cocaethylene (J. Ellsworth, personal communication), cocaine (Woodward et al., 1995) and methylenephedrine and nisoxetine (Koe, 1976). Because NE and/or 5-HT IC50 values for GBR 12935 and cocaine were not available, relative potencies were based on binding affinities (Ritz et al., 1987; Rothman et al., 1993).

Monoamine uptake inhibitors were grouped according to the classification scheme described by Koe (1976), modified to take into account the fact that absolute IC50 values can vary widely among different laboratories (Stanford, 1996). The grouping values for 1) 5-HT and DA: potent inhibitors, IC50 < 0.1 μM; strong inhibitors, IC50 0.1–1 μM; moderate inhibitors, IC50 1–5 μM; weak inhibitors, IC50 5–10 μM; “inactive” inhibitors, IC50 > 10 μM and 2) NE: potent inhibitors, IC50 < 0.01 μM; strong inhibitors, IC50 0.01–0.1 μM; moderate inhibitors, IC50 0.1–0.5 μM; weak inhibitors, IC50 0.5–1.0 μM; “inactive” inhibitors, IC50 > 1.0 μM were divided by their corresponding IC50 values for cocaine reported by Koe (1976): 5-HT (0.85 μM), NE (0.27 μM) and DA (1.7 μM). The resulting grouping criteria, expressed in terms relative to cocaine, were then applied to the in vitro potencies shown in table 1.

The DA reuptake blockers GBR 12935 and indatraline were excluded from the multiple regression analysis because their in vitro potencies were expected to deviate from their extremely high DA reuptake affinity in vitro (see “Discussion”), a finding that was confirmed by post hoc outlier analysis. For the remaining 16 compounds, outliers (desipramine and nisoxetine) were identified by use of externally studentized residuals (Snedecor and Cochran, 1967), i.e., where residuals are divided by the residual standard deviation obtained from the regression that omits the case (Data Desk, Data Descriptions Inc., Ithaca, NY). The level of statistical significance was adjusted to allow for the fact that the largest absolute deviations were selected (i.e., P = .05/n, in which n = the number of deviations).

**Drugs.** The drugs used in this study were alaproclate HCl (MW 292.2), GBR 12935 di-HCl (MW 487.5), 6-chloro-APB HCl (MW 370.7), cocaethylene HCl (MW 289.8), 8-OH-DPAT HBr (MW 328.3), cocaine (MW 289.4), mazindol (MW 284.7), nomifensine maleate (MW 354.4), nisoxetine HCl (MW 307.8), (-)-propranolol HCl (MW 295.8) (all from Research Biochemicals Int., Natick, MA), bupropion HCl (MW 240.2), nortriptyline HCl (MW 298.9), prazosin HCl (MW 419.9), procaine HCl (MW 276.2) (Sigma), desipramine HCl (also designated desmethylimipramine; MW 302.8), caffeine (MW 194.2), nortriptyline HCl (MW 298.9), prazosin HCl (MW 419.9), procaine HCl (MW 276.2) (all from Sigma, Fresenius, France); fluoxetine HCl (MW 345.8) and paroxetine HCl (MW 374.9) (J.-L. Maurel, Centre de Recherche Pierre Fabre, Castres, France); imipramine HCl (MW 316.9) (Interchim, Paris, France); cocaethylene HCl (MW 389.8) and talsupram HCl (MW 348.0) (Lundbeck A/S, Copenhagen-Valby, Denmark); methylenephedrine HCl (MW 269.9) (Ciba-Geigy Co., Basel, Switzerland); and cocaine HCl (MW 339.8) (Coopération Pharmaceutique Française, Melun, France). All drugs, with the exception of paroxetine, mazindol and nomifensine, were dissolved and administered in distilled water; paroxetine was prepared as a suspension in aqueous Tweens 80 (2 drops/10 ml distilled water).

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED50 μmol/kg</th>
<th>Relative Behavioral Potency</th>
<th>Relative in Vitro Potency</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obtained</td>
<td>Predicted</td>
<td>5-HT</td>
<td>NE</td>
</tr>
<tr>
<td>5-HT/NE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2.2</td>
<td>0.39</td>
<td>0.49</td>
<td>0.0012</td>
</tr>
<tr>
<td>Citalopram</td>
<td>8.1</td>
<td>1.4</td>
<td>1.8</td>
<td>0.0069</td>
</tr>
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<td>Fluoxetine</td>
<td>11</td>
<td>1.9</td>
<td>1.1</td>
<td>0.027</td>
</tr>
<tr>
<td>Alaproclate</td>
<td>14</td>
<td>2.5</td>
<td>3.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Desipramine</td>
<td>2.3</td>
<td>0.39</td>
<td>2.2*</td>
<td>0.81</td>
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<tr>
<td>Talsupram</td>
<td>12</td>
<td>2.0</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>16</td>
<td>2.8</td>
<td>2.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Imipramine</td>
<td>20</td>
<td>3.5</td>
<td>2.1</td>
<td>0.13</td>
</tr>
<tr>
<td>Nisoxetine</td>
<td>38</td>
<td>6.6</td>
<td>1.2*</td>
<td>1.4</td>
</tr>
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<td>DA/5-HT/NE</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Mazindol</td>
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<td>0.20</td>
<td>0.19</td>
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<td>Indatraline</td>
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<td>0.64</td>
<td>0.027*</td>
<td>0.0018</td>
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<td>Nomifensine</td>
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<td>0.90</td>
<td>0.69</td>
<td>3.2</td>
</tr>
<tr>
<td>Cocaine</td>
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<td>1.0</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Methylenephedrine</td>
<td>7.8</td>
<td>1.4</td>
<td>3.2</td>
<td>95</td>
</tr>
<tr>
<td>GBR-12935</td>
<td>12</td>
<td>2.1</td>
<td>0.26*</td>
<td>0.95</td>
</tr>
<tr>
<td>Cocaine</td>
<td>18</td>
<td>3.2</td>
<td>2.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>24</td>
<td>4.2</td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>Procaine</td>
<td>317</td>
<td>55</td>
<td>39</td>
<td>1971*</td>
</tr>
</tbody>
</table>

* Behavioral potency relative to cocaine for enhancement of the discriminative stimulus effects of 2.5 mg/kg cocaine.

b Behavioral potency relative to cocaine for enhancement of the DA response rate, i.e., the total number of responses made on either lever during the 15-min session expressed as a percentage of the response rate during the most recently preceding saline or low-dose training session. Selection data were used to calculate the percentage of animals at each treatment condition selecting the 10 mg/kg cocaine-appropriate lever.

### Footnotes

- a Significant deviation (P < .05) from obtained relative behavioral potency.
- b Relative potencies based on binding results.
- c Relative potencies based on IC50 values from published sources.
water); and mazindol and nomifensine were dissolved in distilled water to which a small amount of acetic acid was added and the pH adjusted to 5 to 7 with 4% NaOH.

**Results**

**Effects of cocaine.** The discrimination between 2.5 mg/kg and 10 mg/kg cocaine was acquired in all 39 animals that were trained (median sessions to final criterion, excluding sessions that were used to calculate criterion performance, 53 sessions; semi-interquartile range, 40–78 sessions). The average postcriterion accuracy after administration of the high training dose during training sessions was significantly greater (P < .0001; paired t test) than after administration of the low training dose (mean ± S.E. % correct lever selections = 96 ± 0.68 vs. 88 ± 1.2, 10 vs. 2.5 mg/kg training doses, respectively).

Administration of cocaine during test sessions engendered dose-related increases in responding on the lever associated with the 10 mg/kg cocaine dose (fig. 1), whereas saline engendered only low-dose-appropriate lever selection in dose-dose trained rats (n = 9). The estimated ED₅₀ value for cocaine was 3.7 mg/kg (95% confidence limits, 2.6–5.2 mg/kg). Administration of cocaine during test sessions produced dose-related decreases in the rate of responding expressed as a percentage of control training sessions (i.e., cocaine 2.5 mg/kg).

**Interactions with 5-HT/NE reuptake blockers.** Treatment with the relatively selective 5-HT reuptake blockers, paroxetine, citalopram, fluoxetine and alaproclate, 15 min before administration of the low training dose of cocaine, resulted in dose-related increases in HDL selection, with 71 to 100% of the animals selecting the HDL after administration of the highest doses of each compound (fig. 2). The cocaine-enhancing effects of 5-HT reuptake blockers occurred over a similar dose range (i.e., ED₅₀ values ranging from 0.74 to 4.0 mg/kg and the 95% confidence limits were overlapping, table 2).

Similar to that found after administration of selective 5-HT reuptake blockers, treatment with desipramine, talsupram, nortriptyline or imipramine 15 min before administration of the low training dose of cocaine engendered dose-related increases in HDL selection, with 89 to 100% of the animals selecting the HDL after administration of the highest doses of each compound. In contrast, the NE reuptake inhibitor nisoxetine produced only intermediate levels of HDL-appropriate responding (maximum HDL selection, 50%). With the exception of desipramine, the estimated ED₅₀ values were very similar (i.e., ranging from 3.6 to 5.6 mg/kg, table 2); desipramine (ED₅₀ = 0.60 mg/kg; 0.21–1.7 mg/kg) was apparently more potent, i.e., the 95% confidence limits did not include the ED₅₀ values of any of the remaining compounds from this group.

Maximal effects on HDL selection engendered by cotreatment with 5-HT and NE reuptake blockers were observed at doses that also produced apparent decreases in rate of responding (i.e., maximal decreases ranging from 22 ± 12 to 60 ± 9.1% of low-training-dose control sessions, table 2).

To determine whether NE/5-HT reuptake blockers produced HDL selection in the absence of the administration of cocaine, saline was administered in combination with the doses producing maximal %HDL selection. In contrast to the results obtained when 2.5 mg/kg cocaine was coadministered, HDL selection was not observed in any of the animals treated with paroxetine, citalopram, fluoxetine and alaproclate in combination with saline (fig. 1, filled symbols). When saline was administered in combination with the doses producing maximal %HDL selection, intermediate levels of HDL selection were observed after talsupram (50%) and nortriptyline (20%).

**Interactions with compounds having DA reuptake-blocking properties.** Similar to that found after administration of selective 5-HT and NE reuptake blockers, treatment with a variety of compounds that have DA reuptake-blocking properties 15 min before administration of the low training dose of cocaine engendered dose-related increases in HDL selection (fig 3, open symbols), with estimated ED₅₀ values ranging among high (0.32 mg/kg, mazindol), intermediate (5.8 mg/kg, cocaethylene and bupropion) and low potency (71 mg/kg, procaine; table 2).

In contrast to the effects of NE/5-HT reuptake blockers, almost all the compounds having DA reuptake-blocking properties, with the exception of GBR 12935, bupropion and procaine, engendered more than 50% HDL selection when administered in combination with saline (fig. 4, closed symbols); GBR 12935, bupropion and procaine did not produce HDL selection in more than 50% of the animals even when administered at doses that decreased the rate of responding to 14 to 60% of control rates. The ED₅₀ values when drugs were administered in combination with saline were approximately two to three times higher than when they were administered in combination with cocaine for all the compounds, with the exception of mazindol and bupropion, which were approximately 16 and 7 times higher, respectively. Doses of procaine larger than 80 mg/kg could not be examined because they produced lethality.

**Relationship between in vitro and in vivo potencies.** Table 1 shows the potencies (micromoles per kilogram) of the monoamine reuptake blockers for enhancing the DS effects of 2.5 mg/kg cocaine in dose-dose trained rats and in vitro relative potencies obtained from published biochemical studies (see “Methods”). Behavioral potencies relative to cocaine ranged from approximately five times more potent (mazin-
dol) to about five times less potent (e.g., bupropion), whereas
the in vitro biochemical potencies relative to cocaine varied
across a considerably wider range. For example, paroxetine is
reportedly about 800 times more potent than cocaine in in-
hibiting 5-HT reuptake, whereas bupropion and procaine are
73 and 1971 times less potent than cocaine, bupropion and
procaine, respectively. Similarly, reported biochemical poten-
cies for NE reuptake range from greater than 500 times more
potent (e.g., indatraline, mazindol, desipramine, talsupram)
to 145 to 136 less potent than cocaine (e.g., alaproclate and
procaine). Although a wide range of relative potencies in
blocking DA reuptake is seen, all the compounds referred to
in this study as 5-HT/NE reuptake blockers are about 12 to
132 times less potent than cocaine, whereas the remaining

\[
\begin{array}{llllllllllll}
\text{Drug} & \text{ED}_{50} & 95\% \text{ CL} & \text{Maximum Effect} & \text{Dose} & \text{ED}_{50} & 95\% \text{ CL} & \text{Maximum Effect} & \text{Dose} \\
\hline
5\text{-HT/NE} & & & & & & & & \\
Paroxetine & 5 & 0.74 & 0.14–3.7 & 100 & 24 ± 5.3 & 10 & 5 >10 & 0 & 95 ± 3.8 \\
Citalopram & 7 & 2.6 & 0.47–15 & 71 & 54 ± 7.7 & 10 & 5 >10 & 0 & 45 ± 12 \\
Fluoxetine & 5 & 3.4 & 1.3–9.1 & 100 & 22 ± 12 & 10 & 5 >10 & 0 & 82 ± 3.5 \\
Alaproclate & 7 & 3.7 & 1.4–9.6 & 100 & 32 ± 8.0 & 10 & 5 >10 & 0 & 53 ± 9.5 \\
Desipramine & 9 & 0.60 & 0.21–1.7 & 89 & 60 ± 9.1 & 2.5 & 7 >2.5 & 0 & 75 ± 10 \\
Talsupram & 7 & 3.6 & 1.5–8.5 & 100 & 33 ± 9.1 & 10 & 7 >10 & 50 & 23 ± 13 \\
Nortriptyline & 7 & 4.2 & 2.1–8.3 & 100 & 39 ± 4.4 & 10 & 7 >10 & 20 & 45 ± 14 \\
Imipramine & 7 & 5.6 & n.d. & 86 & 30 ± 6.7 & 10 & 7 >10 & 0 & 48 ± 7.8 \\
Nisoxetine & 9 & 10 & n.d. & 50 & 46 ± 10 & 10 & 5 >10 & 0 & 75 ± 7.7 \\
DA/5\text{-HT/NE} & & & & & & & & \\
Mazindol & 5 & 0.32 & 0.16–0.63 & 100 & 78 ± 23 & 10 & 5 & 5.0 & 2.6–9.5 & 100 & 51 ± 28 \\
Indatraline & 5 & 1.1 & 0.46–2.5 & 100 & 36 ± 12 & 2.5 & 5 & 1.7 & 0.70–4.1 & 100 & 28 ± 12 \\
Nomifensine & 5 & 1.3 & 0.65–2.5 & 100 & 59 ± 6.4 & 2.5 & 5 & 3.6 & 1.3–10 & 100 & 57 ± 32 \\
Cocaine & 5 & 1.7 & 0.62–4.9 & 100 & 46 ± 12 & 10 & 5 & 4.7 & 2.0–11 & 100 & 43 ± 9.8 \\
Methylphenidate & 5 & 1.8 & 0.69–4.8 & 100 & 54 ± 22 & 10 & 5 & 5.5 & n.d. & 100 & 36 ± 17 \\
GBR-12935 & 5 & 5.0 & n.d. & 100 & 22 ± 6.5 & 10 & 5 & 10 & n.d. & 0 & 12 ± 0.8 \\
Cocaethylene & 5 & 5.8 & n.d. & 80 & 56 ± 16 & 10 & 5 & 11 & 5.6–20 & 100 & 10 ± 9.0 \\
Bupropion & 7 & 5.8 & 2.7–12 & 100 & 14 ± 9.6 & 40 & 5 & 40 & n.d. & 0 & 0 \\
Procaine & 7 & 15 & 18–320 & 71 & 60 ± 2.2 & 80 & 7 & 80 & 43 & 75 ± 10 \\
\hline
\end{array}
\]

\(a\) Mean ± S.E. rate of responding expressed as a percentage of preceding low-dose training sessions.
\(b\) n.d.: 95\% confidence limits not determined because of insufficient data.
\(c\) Estimated: lowest dose producing 50\% HDL selection.

With respect to the relative selectivity according to the
scheme of Koe (1976), few of the compounds (citalopram,
alaproclate and bupropion) were classified as “inactive” in
two of the three monoamines; procaine was “inactive” at all
the sites. Among the compounds typically classified as 5-HT
and/or NE reuptake blockers, only citalopram and alaproc-
cate were “inactive,” which indicates that the remaining
compounds in this group would be considered to have activity
as both 5-HT and NE reuptake blockers. Among the com-
ounds considered to have DA reuptake-blocking properties,
considerable variability in selectivity could be observed. Pro-

\[\text{Fig. 2. Serotonin/morepinephrine reuptake blockers}
\text{enhance the discriminative stimulus effects of a low}
dose of cocaine (2.5 mg/kg, open symbols) in rats
trained to discriminate a low dose of cocaine (2.5 mg/kg)
from a high dose of cocaine (10 mg/kg). Values
represent the percentage of animals (n = 5–9/dose)
selecting the high-dose lever during 15-min sessions
conducted in rats administered monoamine reuptake
blockers in combination with cocaine (open symbols) or
saline (closed symbols).}
Cocaine would be considered “inactive” at all three sites, whereas, in contrast, indatraline was classified as “potent” at 5-HT, NE and DA reuptake blockade.

To determine the relationship between the relative behavioral and biochemical potencies, a multiple linear regression was performed with log-transformation of the values shown in table 1. Analysis of results obtained from 14 of the 18 compounds, excluding the outliers, desipramine, GBR 12935, indatraline and nisoxetine, yielded a significant multiple $R$ (0.95, $P < .0001$) and in vitro potencies in blocking reuptake of DA (coefficient, 0.31; $P < .0005$) and 5-HT (coefficient, 0.25; $P < .0001$) were significant predictor variables. In contrast, in vitro potencies for NE reuptake blockade did not contribute significantly to the prediction of relative behavioral potency (coefficient, 0.056; $P > .25$).

As expected from the high coefficient of determination of the best-fitting equation, the residuals (i.e., differences between the potency values predicted from the multiple regression equation and the experimental potencies) are relatively small for most compounds examined in this study (see table 1 for predicted relative potencies). Predicted behavioral potencies relative to cocaine ($rbp_{pred}$) were obtained according to the following equation:

$$rbp_{pred} = 10^{0.31 \cdot \log(DA_{rip}) + 0.25 \cdot \log(5-HT_{rip}) + 0.056 \cdot \log(NE_{rip}) + 0.049}$$

where $DA_{rip}$, $5-HT_{rip}$ and $NE_{rip}$ are the in vitro potencies of the compounds for blocking reuptake of the different monoamines, relative to cocaine, as shown in table 1. Note, however, that the obtained potency of desipramine is smaller than that predicted from the relationship derived by use of the remaining compounds, whereas the reverse is true for nisoxetine, indatraline and GBR 12935. In contrast, the predicted potencies for talsupram and nortriptyline are relatively close to their obtained values, whereas their biochemical profiles closely resemble that of desipramine (see table 1).

**Effects of prazosin on the cocaine-enhancing effects of desipramine and propranolol.** In rats treated with saline, both 60 and 30 min before the session, cocaine produced dose-related increases in HDL selection (fig. 4A, left panel). In control experiments in animals pretreated with saline 60 min before the session (fig. 4B, left panels), desipramine and the beta adrenergic antagonist propranolol ad...
ministered 15 min before the low training dose of cocaine, engendered dose-related increases in HDL selection, with maximal effects reaching 80 to 100%. Inasmuch as the 95% confidence limits overlapped, the potencies of cocaine (ED$_{50}$, 4.1 mg/kg; 95% confidence limits, 2.5–6.7) and desipramine (ED$_{50}$, 1.7 mg/kg; 95% confidence limits, 0.50–5.9 mg/kg) did not differ significantly from those observed under slightly different treatment conditions (i.e., single or double injections), although the ED$_{50}$ value for desipramine was apparently higher than that observed previously (0.60 mg/kg; table 2). The cocaine-enhancing potency of propranolol (ED$_{50}$, 3.5 mg/kg; 95% confidence limits, 1.3–9.0 mg/kg) was similar to that reported recently (Kleven and Koek, 1997).

Pretreatment with the alpha-1 adrenergic antagonist prazosin (0.16–2.5 mg/kg s.c.) 60 min before the session did not decrease HDL selection engendered by either cocaine (10 mg/kg i.p.) or the combination of desipramine (10 mg/kg i.p., 30-min presession) and the low training dose of cocaine (2.5 mg/kg i.p., 15-min presession) in more than 50% of the animals treated (fig. 4, right panels). Doses of prazosin higher that 10 mg/kg were not examined because of the high response-rate decreasing effects which were already evident in rats treated with this dose in combination with either cocaine (ED$_{50}$ 10 mg/kg, 15% ±4.8% of low-training-dose control sessions) or desipramine 10 mg/kg (6.6 ± 3.2%). In contrast to results obtained in combination with cocaine-enhancing doses of cocaine or desipramine, pretreatment with prazosin engendered dose-related decreases in the cocaine-enhancing effects of propranolol 10 mg/kg (ED$_{50}$ 0.81 mg/kg; 95% confidence limits, 0.31–2.1 mg/kg).

**Interactions with other compounds.** In addition to monoamine reuptake blockers, compounds from a variety of different pharmacological classes were tested in combination with the low dose of cocaine (table 3). The adenosine antagonist caffeine produced intermediate levels of HDL selection (i.e., maximal HDL selection of 60%) when administered in combination with the low dose of cocaine. The D$_{1}$ dopamine agonist SKF 81297 engendered dose-related increases in HDL selection when combined with the low dose of cocaine (ED$_{50}$ 0.27 mg/kg; 95% confidence limits, 0.074–0.98 mg/kg). Similar to the HDL selection observed with other cocaine-enhancing compounds, the highest doses of caffeine and SKF 81297 did not engender HDL selection when administered in combination with saline. In contrast to compounds that enhanced the DS effects of the low training dose, the weak DA reuptake blocker/muscarinic antagonist benzotropine, the benzodiazepine diazepam and the 5-HT$_{1A}$ agonist 8-OH-DPAT did not engender HDL selection in more than 25% of animals treated. All these latter compounds were tested at doses that decreased the rate of responding to less than 50% of that observed under low-training-dose sessions.

**Discussion**

In this study, the discriminative stimulus effects of a relatively low dose of cocaine (2.5 mg/kg) were enhanced dose-dependently by pretreatment with compounds having varying in vitro potencies for blocking reuptake of DA, NE and/or 5-HT. Multiple regression analysis of the relationship between behavioral and in vitro potencies indicated that DA and 5-HT reuptake-blocking properties explain the cocaine-enhancing effects of most of the compounds we examined in this study. In contrast, evidence for the involvement of NE reuptake-blocking properties was not as convincing, despite the paradoxical finding that relatively selective NE reuptake inhibitors (nortriptyline, talsupram and desipramine) effectively enhanced the DS effects of cocaine. However, pretreatment with the alpha-1 adrenergic antagonist prazosin did not decrease completely the cocaine-enhancing effects of desipramine, which suggested that NE reuptake blockade does not play a unique role in its ability to enhance the DS effects of cocaine. The pharmacological specificity of the observed enhancement of the DS effects of cocaine was demonstrated by findings that pretreatment with a variety of compounds from other pharmacological classes (caffeine, benzotropine, 8-OH-DPAT and diazepam) did not produce effects similar to.

**TABLE 3**

Results of tests of compounds in combination with saline or the low training dose of cocaine (2.5 mg/kg i.p.) in rats trained to discriminate a low dose from a high dose (10 mg/kg) of cocaine

<table>
<thead>
<tr>
<th>Drug + Cocaine$^a$</th>
<th>Dose (mg/kg)</th>
<th>N</th>
<th>% HDL Selection</th>
<th>% Low-Dose Response Rate (mean ± S.E.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztropine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
<td>1/5</td>
<td>20</td>
<td>29 ± 5.5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0/0</td>
<td>–</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
<td>1/5</td>
<td>20</td>
<td>85 ± 14</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>3/5</td>
<td>60</td>
<td>80 ± 24</td>
</tr>
<tr>
<td>40</td>
<td>5</td>
<td>2/5</td>
<td>40</td>
<td>42 ± 7.6</td>
</tr>
<tr>
<td>(caffeine + saline)</td>
<td>40</td>
<td>5</td>
<td>0/5</td>
<td>0</td>
</tr>
<tr>
<td>SKF 81297</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.04</td>
<td>7</td>
<td>1/7</td>
<td>14</td>
<td>84 ± 15</td>
</tr>
<tr>
<td>0.16</td>
<td>7</td>
<td>2/6</td>
<td>33</td>
<td>64 ± 16</td>
</tr>
<tr>
<td>0.63</td>
<td>7</td>
<td>5/7</td>
<td>71</td>
<td>45 ± 10</td>
</tr>
<tr>
<td>(SKF 81297 + saline)</td>
<td>0.63</td>
<td>7</td>
<td>1/7</td>
<td>14</td>
</tr>
<tr>
<td>Diazepam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
<td>1/5</td>
<td>20</td>
<td>74 ± 10</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>2/2</td>
<td>–</td>
<td>5.6 ± 3.5</td>
</tr>
<tr>
<td>8-OH-DPAT</td>
<td>0.16</td>
<td>5</td>
<td>1/4</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.63</td>
<td>5</td>
<td>1/4</td>
<td>25</td>
</tr>
</tbody>
</table>

$^a$ Parentheses refer to data obtained when saline was administered instead of cocaine (2.5 mg/kg).

$^b$ Percentage HDL not calculated when less than 50% of animals selected a lever.
those found after coadministration of monoamine reuptake blockers. Altogether these findings establish the pharmacological basis for reported interactions between cocaine and monoamine reuptake blockers (Cunningham and Callahan, 1991; Spealman, 1993; Callahan and Cunningham, 1995a) and confirm the idea that 5-HT may be an important modulator of behavioral effects of cocaine in the rat.

The pharmacological specificity of the enhancement of the DS effects of cocaine is supported by the finding that a variety of compounds from different pharmacological classes do not engender HDL selection when combined with the low dose of cocaine. Compounds that do not have cocaine-like DS properties (the 5-HT\(_{1A}\) agonist 8-OH-DPAT (Callahan and Cunningham, 1995b), the benzodiazepine agonist diazepam (Emmett-Oglesby et al., 1983) and the weak DA reuptake blocker/muscarinic antagonist benzotropine (Acri et al., 1996) did not produce more than 25% HDL selection when combined with the low training dose of cocaine. Further, we reported recently (Kleven and Koek, 1997) that neither the \(\alpha_1\) adrenergic agonist cirazoline nor the \(\alpha_2\)-adrenergic ligands (\(\pm\))-efaroxan and UK-14304 enhanced the DS effects of a low dose of cocaine. In contrast to compounds that were completely ineffective, several drugs from other classes produced a limited enhancement of the DS effects of cocaine. For example, caffeine engendered HDL selection along an inverted U-shaped dose-response function, but it also enhanced the DS effects of cocaine in cocaine-saline-trained rats (Gauvin et al., 1989,1990; Harland et al., 1989). Similarly, the D\(_1\) dopamine agonist SKF 81297 engendered intermediate levels of drug-appropriate responding in cocaine-saline-trained rats (Witkin et al., 1991) and, in the present study, produced dose-related increases in HDL selection when combined with cocaine. This latter finding agrees with recently reported results wherein intermediate efficacy D\(_1\) dopamine agonists, including SKF 81297, enhanced the DS effects of cocaine in monkeys (Spealman et al., 1997). Because compounds from a variety of different pharmacological classes do not engender HDL-appropriate responding, the results suggested that specific pharmacological mechanisms are involved in the enhancement of the DS effects of cocaine by monoamine reuptake blockers.

In addition to evidence supporting the involvement of DA reuptake blockade in the DS of cocaine (Broadbent et al., 1991; Baker et al., 1993), the multiple regression analysis indicated that 5-HT reuptake blockade properties contribute significantly to the ability of monoamine reuptake blockers to enhance the DS effects of cocaine. These findings agree with previous results demonstrating that fluoxetine and citalopram enhanced the DS effects of cocaine in cocaine-saline-trained rats (Cunningham and Callahan, 1991; Callahan and Cunningham, 1995a) and strongly suggest that in vivo blockade of 5-HT reuptake is responsible for this phenomenon. As noted above, however, citalopram did not enhance the DS effects of cocaine in squirrel monkeys. Although it is conceivable that species differences account for this, squirrel monkeys are sensitive to cocaine-enhancing effects of fluoxetine when a lower training dose is used (Schama et al., 1997). Therefore, with respect to drug discrimination studies, it is possible that differences in effective training doses may explain the discrepancies between data obtained in rats and squirrel monkeys. Alternatively, methodological differences such as route of administration, differences in onset of action, session length and cumulative dosing procedure may be responsible. Irrespective of these differences, it is clear not only from our study, but also from previous studies in rats (Cunningham and Callahan, 1991; Callahan and Cunningham, 1997) that 5-HT reuptake inhibition effectively enhances the DS effects of cocaine in this species.

Because cocaine can be considered a strong inhibitor of 5-HT reuptake (Koe, 1976; Hyttel, 1982), it is conceivable that this monoamine could be involved in its DS effects. In favor of this idea is the recent finding that systemic injection of cocaine (10 mg/kg i.p.) significantly increased extracellular levels of 5-HT in the nucleus accumbens, an effect that also can be mimicked by local perfusion of cocaine in the nucleus accumbens (Teneud et al., 1996). But, 5-HT receptor antagonists do not block the DS effects of cocaine (Meert and Janssen, 1992; Peltier et al., 1994), and moreover, the selective 5-HT reuptake blockers examined in this study were generally less potent than cocaine, despite their considerably higher in vitro potencies. In this context, the in vivo 5-HT reuptake-blocking properties of cocaine may contribute little to its DS effects. Even so, it is clear that combined administration of cocaine and 5-HT reuptake blockers influences its behavioral effects (Walsh and Cunningham, 1997), which suggests that 5-HT could play a modulatory role.

The model that accounts for the cocaine-enhancing effects of the majority of the compounds examined in this study fails to predict accurately the potencies of GBR 12935, indatraline, nisoxetine and desipramine. With respect to indatraline and members of the 1,4-dialklypiperazine series of DA reuptake inhibitors (e.g. GBR 12783 and GBR 12909), previous studies indicate that their in vivo potencies are not consistent with their ability to block reuptake of DA in vitro. GBR 12935 is less potent behaviorally than cocaine, whereas indatraline is only slightly more potent than cocaine; however, both of these compounds are more than 100 times more potent than cocaine in blocking DA reuptake. For indatraline, pharmacokinetic factors may be largely responsible for this dissociation: it has a slow onset of action and its effects can last for several days (Rosenzweig-Lipson et al., 1992). But, the unexpectedly low in vivo potency of GBR-related compounds (Heikkila and Manzino, 1984) remains enigmatic, although it has been suggested (Rosenzweig-Lipson et al., 1992) that dispositional factors might explain the low in vivo potency of GBR 12909. Additionally, it has been proposed that multiple binding sites or different binding kinetics (Matecka et al., 1996) can explain the unexpectedly low in vivo potency of related GBR-related compounds.

The results obtained with nisoxetine and desipramine are more problematic; however, desipramine was somewhat less potent in the replication experiment when saline was administered subcutaneously 30 min before desipramine (fig. 4B). Moreover, as with indatraline, it may be unreasonable to expect that all the compounds examined in this study should exhibit their peak effects 30 min after administration. In contrast to the effects of nisoxetine and desipramine, the selective reuptake inhibitors talsupram and nortriptyline did enhance the DS effects of cocaine, although their in vivo potencies are closely predicted by a model which does not rely on in vitro NE reuptake-blocking potency. Note that talsupram and nortriptyline could be considered “moderate” inhibitors of 5-HT reuptake (table 1) according to the classification scheme of Koe (1976). Moreover, findings that
prazosin did not inhibit completely the cocaine-enhancing effects of desipramine support the idea that NE reuptake may not be the only mechanism involved in this phenomenon. Because the model that explains the cocaine-enhancing effects of most of the compounds examined in this study, including many that have strong NE reuptake-blocking properties, does not contain a significant NE component, it is likely that NE reuptake blockade plays a relatively weak role in modulating the DS effects of cocaine.

Although the absence of cocaine-enhancing effects of some compounds, such as the NE reuptake blocker nisoxetine (Hyttel, 1982), may be related to differences in onset of action or peak effects, the finding that prazosin did not fully antagonize the cocaine-enhancing effects of desipramine suggests that factors other than NE reuptake blockade play a role. Whereas these results are consistent with the model, in that the NE component failed to reach significance, they contradict the idea that alpha-1 adrenergic stimulation plays a significant role in the stimulant effects of cocaine (Snoddy and Tessel, 1985; Tessel and Barrett, 1986). In further contradiction, prazosin failed to antagonize the ability of cocaine (10 mg/kg) to engender HDL selection. However, findings that prazosin reverses the behavioral effects of psychomotor stimulants have almost invariably been reported in species other than the rat (Snoddy and Tessel, 1985; Tessel and Barrett, 1986; Johanson and Barrett, 1993; Spealman, 1995), again raising the possibility that species or methodological differences are important factors in this phenomenon. In contrast, in the present study, neither the regression model nor the findings obtained with prazosin support the idea that NE reuptake blockade is solely responsible for the cocaine-enhancing effects of compounds such as desipramine.

Thus, mechanisms other than NE reuptake blockade may also account for the cocaine-enhancing effects of nortriptyline, desipramine and talsupram in the rat. One such possible mechanism may be that monoamine reuptake blockers increase brain levels of cocaine (Tella and Goldberg, 1993). This effect is reportedly short-lived, but it could contribute to the enhancement of the DS effects of cocaine. A more likely explanation for the discrepancy between in vitro and in vivo potencies of NE reuptake inhibitors is that they enhance cocaine by blocking reuptake of DA by noradrenergic neurons (Kelly et al., 1985; Izenwasser et al., 1990). This has been demonstrated in microdialysis studies in prefrontal cortex (Carboni et al., 1990) and the VTA and nucleus accumbens (Chen and Reith, 1997) areas that receive noradrenergic neurons from the locus ceruleus. However, the density of NE uptake sites in the nucleus accumbens, the region that is most highly implicated in the DS effects of cocaine, is quite low relative to DA uptake sites (Li et al., 1996), which suggests that this mechanism may be less important than in other regions. Nonetheless, the association between nucleus accumbens DA and NE output after administration of various monoamine reuptake blockers was significantly correlated, although the relationship was reportedly weaker than in the VTA (Chen and Reith, 1994, 1997). Indeed, desipramine showed the weakest relationship between DA and NE output (Chen and Reith, 1997), consistent with the report that acute administration of a dose of desipramine similar to that used in this study (5 mg/kg i.p.) did not alter extracellular levels of DA in the nucleus accumbens (Nomikos et al., 1991). Although the effects of selective NE compounds, with the exception of beta adrenergic antagonists (Kleven and Koek, 1997) may not be as robust as DA and/or 5-HT compounds, the finding that the alpha-1 adrenergic antagonist prazosin reverses the cocaine-enhancing effects of the beta adrenergic antagonist (-)-propranolol, suggests that NE mechanisms may indeed modulate the DS effects of cocaine (Spealman, 1995). That beta adrenergic receptors play a role in the DS effects of cocaine is supported not only by previous findings that propranolol substitutes in rats trained to discriminate cocaine from saline (Colpaert et al., 1979), but also by recent studies showing that propranolol augments unconditioned and conditioned behavioral effects of cocaine and cocaine-induced increases in extracellular dopamine in the nucleus accumbens (Harris et al., 1996).

It has been hypothesized that the ability of NE compounds to modulate or mimic the DS effects of cocaine is mediated by stimulation of postsynaptic alpha-1 adrenergic receptors in the VTA (Spealman, 1995). However, several findings are inconsistent with this hypothesis: 1) the presynaptic alpha-2 adrenergic antagonist efavoxan, which via autoreceptor inhibition (Grenhoff and Svensson, 1989) should augment post synaptic NE tone effectively, does not enhance the DS effects of cocaine, either in squirrel monkeys (Spealman, 1995) or rats (Kleven and Koek, 1997); 2) the alpha-1 adrenergic agonist cirazoline did not enhance the effects of the low dose of cocaine (Kleven and Koek, 1997); and 3) neurochemically lesions of noradrenergic fibers innervating the VTA decreases DA utilization in the prefrontal cortex, but not in the nucleus accumbens (Herve et al., 1982). Because the DS effects of cocaine are mediated predominantly by the nucleus accumbens (Wood and Emmett-Oglesby, 1989; Callahan et al., 1994), it is likely that noradrenergic control of DA neurons projecting from the VTA to the nucleus accumbens cannot explain interactions between noradrenergic compounds and the DS effects of cocaine. However, 6-hydroxydopamine lesions of the locus ceruleus reportedly decrease DA levels in the nucleus accumbens (Lategan et al., 1990), thus other pathways or mechanisms may be responsible for the interactions between, for example, beta adrenergic agents and cocaine. Nonetheless, the many inconsistencies indicate that further studies are needed to explain this phenomenon.

In conclusion, in this study 5-HT and DA reuptake-blocking properties explain the ability of monoamine reuptake blockers to enhance the DS effects of cocaine. Because complete drug-appropriate responding generally is not obtained after administration of direct serotonergic agonists in cocaine-saline-trained rats (Callahan and Cunningham, 1995b) and 5-HT antagonists do not block cocaine-appropriate responding (Peltier et al., 1994; Callahan and Cunningham, 1995b), 5-HT is neither necessary nor sufficient to evoke cocaine-like DS effects. However, 5-HT reuptake blockers reliably enhance the DS effects of cocaine when combined with cocaine. That 5-HT reuptake blockade plays a modulatory role in the DS effects of cocaine agrees with previous studies (see Cunningham et al., 1995; Walsh and Cunningham, 1997). In contrast to interactions between DA and 5-HT, the involvement of NE reuptake inhibition in the DS effects of cocaine may be relatively limited. A neuronal mechanism for the interaction between cocaine and catecholaminergic drugs remains to be elucidated, although several independent groups have reported that NE reuptake blockers...
enhance cocaine (Cunningham and Callahan, 1991; Speal- man, 1995) and there are clearly other conditions (i.e., spe- cies and training dose) where NE has been demonstrated to play a role in the DS effects of cocaine. The generality or mechanism of these findings remains to be established, whereas 5-HT may play a modulatory role in the effects of cocaine under a larger variety of conditions.

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