Effects of Proposed Treatments for Cocaine Addiction on Hemodynamic Responsiveness to Cocaine in Conscious Rats

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Accepted for publication July 11, 1997

ABSTRACT
Several agents may treat cocaine addiction and toxicity including bromocriptine, desipramine, GBR 12909 [1-(2-(bis(4-fluorphenyl)-methoxy)-ethyl)-4-(3-phenyl-propyl)piperazine], diazepam, buprenorphine and dizocilpine. In this study, we sought to determine whether these specific therapeutic agents alter cardiovascular responses to cocaine in conscious rats. Arterial pressure responses to cocaine (5 mg/kg, i.v.) were similar in all rats whereas cardiac output responses varied widely. In 26 of 33 rats (named vascular responders), cocaine induced a decrease in cardiac output of 8% or more. The remaining rats with little change or an increase in cardiac output were classified as mixed responders. Pretreatment with bromocriptine (0.1 mg/kg) or desipramine (1 mg/kg) increased cardiac output in mixed responders and increased systemic vascular resistance in vascular responders similar to the differential effects noted with cocaine. GBR 12909 (0.5–10 mg/kg) elicited a decrease in cardiac output at higher doses. Diazepam (0.1 and 0.5 mg/kg) had small, short-lasting effects on cardiovascular parameters. Buprenorphine (0.3 mg/kg) or the NMDA (N-methyl-D-aspartic acid) receptor antagonist, dizocilpine (0.05 mg/kg), increased arterial pressure, heart rate and cardiac output in vascular responders. Bromocriptine and desipramine prevented the difference in cardiac output responses in vascular and mixed responders by reducing the cocaine-induced decrease in cardiac output in vascular responders. Pretreatment with GBR 12909 (1 mg/kg) had little effect on cardiovascular responses to cocaine except to depress the increase in cardiac output noted in mixed responders. Buprenorphine selectively enhanced the increase in systemic vascular resistance whereas dizocilpine enhanced the pressor response. These data suggest that several treatment regimens for cocaine addiction alter the cardiovascular responses to cocaine and that dopamine D2 receptor activation may be necessary for the decrease in cardiac output noted in vascular responders.

Cocaine is a highly addictive agent that has been associated with myocardial ischemia, infarction and arrhythmias, sudden cardiac death and cardiomyopathies (for review see Minor et al., 1991). Several agents have been proposed as possible treatments for cocaine addiction and/or toxicity (Withkin, 1994). These include other reuptake blockers such as desipramine (Gawin and Kleber, 1984; Tennant and Rawson, 1983) and GBR 12909 (Rothman and Glowa, 1995; Rothman et al., 1989, 1991), dopamine agonists such as bromocriptine (Dackis and Gold, 1985; Hubner and Koob, 1990) and the mixed opiate agonist-antagonist, buprenorphine (Mello et al., 1989). In addition, several agents have been suggested to reduce toxicity to cocaine including the benzodiazepine, diazepam (Catravas and Waters, 1981; Derlet and Albertson, 1990), buprenorphine (Shukla et al., 1991; Withkin et al., 1991) and the NMDA receptor antagonist, MK-801 (Derlet and Albertson, 1990; Rockhold et al., 1991).

The mechanisms by which these agents act on the central nervous system and on behavior have been investigated by many laboratories. In contrast, the effects of these agents alone or in combination with cocaine on cardiovascular function are poorly understood. For example, bromocriptine and buprenorphine have been reported to produce modest decreases in arterial pressure in humans (Preston et al., 1992; Scott et al., 1980) whereas desipramine does not change arterial pressure in rabbits (Dorward et al., 1991). MK-801 has little effect in anesthetized dogs (Hageman and Simor, 1993) but increases arterial pressure and heart rate in conscious rats (Lewis et al., 1989). Because most data available are limited to studies of arterial pressure or heart rate, our study was conducted to better characterize the hemodynamic responses to these agents and their response profiles in combination with cocaine.

Understanding the interactions between cocaine and pro-

ABBREVIATIONS: ANOVA, analysis of variance; Brc, bromocriptine; Bup, buprenorphine; COC, cocaine hydrochloride; CHG, change; CO, cardiac output; Des, desipramine; Dzp, diazepam; GBR 12909 or GBR, 1-(2-(bis(4-fluorphenyl)-methoxy)-ethyl)-4-(3-phenyl-propyl)piperazine; HR, heart rate; INJ, injection; MAP, mean arterial pressure; MK-801 or MK8, dizocilpine; NMDA, N-methyl-D-aspartic acid; SV, stroke volume; SysVR, systemic vascular resistance.
posed treatments is important for several reasons. First, treatments for addiction should be examined for possible interactions with cocaine due to the high rate of recidivism among cocaine users. Noncompliant patients may experience additive or synergistic effects because many proposed treatments mimic the neurochemical effects of cocaine to reduce sensitivity to the cocaine-induced euphoria. This may result in enhanced predisposition to cardiovascular toxicity. Second, a better understanding of the actions of these agents on cocaine-induced responses may help to elucidate the mechanisms by which cocaine causes cardiovascular responses and toxicity. This may contribute to better design of treatments for addiction that may also reduce toxicity. Our experiment was designed to examine these interactions using doses of proposed treatments for addiction that were both clinically relevant and had minimal effects alone on hemodynamic variables.

It is known that individuals vary widely in their sensitivity to cocaine-induced coronary vasoconstriction (Lange et al., 1989), myocardial ischemia (Isner et al., 1986; Minor et al., 1991), cardiomyopathies (Minor et al., 1991) and mortality (Mittleman and Wetli, 1987; Smart and Anglin, 1987). These observations suggest that some individuals are at greater risk for severe cocaine-induced cardiovascular complications. We have proposed that the rat may provide a model to determine the causes of differential cardiovascular sensitivity and toxicity to cocaine (Branch and Knuepfer, 1993; Knuepfer et al., 1993a). We reported that in some but not all rats cocaine administration elicited a clear decrease in cardiac output and a substantial (>80%) increase in systemic vascular resistance whereas in the remaining rats cocaine elicited consistently little change or an increase in cardiac output and smaller increases in systemic vascular resistance (Branch and Knuepfer, 1993, 1994a; Knuepfer and Branch, 1992, 1993). During and after the daily 2-hr acclimation period, arterial pressure, heart rate and blood flows were monitored continuously. Rats were studied for up to 10 days.

Materials and Methods

Animal preparation. Male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 300 to 420 g were surgically prepared under pentobarbital sodium (50 mg/kg, i.p.) anesthesia using aseptic technique as previously described (Branch and Knuepfer, 1993, 1994a; Knuepfer and Branch, 1992, 1993). Briefly, a thoracotomy was performed and a pulsed Doppler flow probe (2.4-mm cuff diameter, 20 MHz, Iowa Doppler Products, Iowa City, IA) filled with acoustic gel was sutured snugly on the ascending aorta. The thorax was closed and the lead wires brought subcutaneously to a socket on the skull. Rats were treated with cefazolin (10 mg/kg, i.m., once daily for 3 days) and allowed to recover for a minimum of 10 days. Rats with poor or varying velocity signals or that did not recover normal motor and feeding behavior within 24 hr were euthanized with pentobarbital. After recovery, rats were anesthetized with methoxyflurane for implantation of femoral arterial and venous cannulas filled with 15 mg/ml cefazolin. In a separate group of six rats, arterial and venous cannulas were implanted to examine the effects of higher doses of specific agents on arterial pressure and heart rate, only. One to two days later, each rat was acclimated in a Plexiglas cage for 6 hr. On the next day, rats were placed in the same cage for 2 hr before beginning experimentation.

Experimental procedure. The procedures employed in these experiments have been described in detail (Branch and Knuepfer, 1993, 1994a; Knuepfer and Branch, 1992, 1993). During and after the daily 2-hr acclimation period, arterial pressure, heart rate and blood flows were monitored continuously. Rats were studied for up to 10 days. Cocaine hydrochloride (5 mg/kg, i.v., infused over 45 sec) alone or after pretreatment with another agent was administered twice daily with a minimum cocaine dosing interval of 4 hr. In most cases, cocaine was delivered alone in the morning and was given 10 min after pretreatment in the afternoon. We have not observed significant tachyphylaxis of cardiovascular responses to cocaine when given alone in the morning and afternoon nor when given twice daily for up to 6 days (Branch and Knuepfer, 1994a). All experiments were conducted between the hours of 9 A.M. and 4 P.M. in a quiet room.

The contribution of several drugs used or proposed for treatment of cocaine addiction and/or toxicity was examined. Putative therapeutical agents were administered in random fashion before administration of cocaine (5 mg/kg, i.v.). Doses for each agent were selected either due to their potency in reducing cocaine-induced toxicity in animal models (usually rat or mouse), to evoke minimal changes in hemodynamic variables, particularly arterial pressure, or to avoid behavioral effects (e.g., sedation). The dopamine receptor agonist, bromocriptine (0.1–1 mg/kg, i.v.) was used. A dose of 1 mg/kg has been reported to produce a small depressor response in rats (Nagaha-ma et al., 1984). The catecholamine uptake inhibitor, desipramine (1–10 mg/kg), was used. The lower dose has relatively small effects on arterial pressure and heart rate but does potentiate the pressor and bradycardic responses to exogenous norepinephrine (Tellai et al., 1993).

Because little is known concerning the effects of GBR 12909 on cardiovascular function, this agent was administered (0.5–10 mg/kg, i.v., over 45 sec) alone in the same manner as cocaine. Only two rats were examined at the highest dose (10 mg/kg) because responses in these animals to subsequent administration of cocaine appeared to be altered for up to 5 days. After obtaining dose-response data, GBR 12909 (1 mg/kg, i.v.) or vehicle (3 mg/ml tartaric acid) was administered 5 min before cocaine administration (5 mg/kg). No more than two injections of cocaine or GBR12909 were given each day with a
minimum of 3 hr between drug administrations with the exception of experiments where cocaine was given 5 min after GBR 12909.

Diazepam (0.1, 0.5 and 1 mg/kg) was used in doses that had minimal cardiovascular effects. The lower doses did not evoke noticeable behavioral (sedative) effects that have been observed at 1 mg/kg. The mixed μ opioid receptor agonist/antagonist, buprenorphine (0.3 mg/kg) was used in a dose that protected mice from lethal doses of cocaine (Shukla et al., 1991). Finally, the NMDA receptor antagonist, MK-801 (0.05 mg/kg), was used. This dose is approximately at the threshold for preventing cocaine-induced seizures and death (Rockhold et al., 1991).

Bromocriptine and GBR 12909 were administered 5 min before cocaine administration. All other agents were administered 10 min before cocaine to insure distribution to the vasculature and nervous system. Rats were not retested after treatment with buprenorphine, diazepam and GBR 12909 for at least 3 days due to their prolonged half-lives.

Materials. Materials used included the methanesulfonate salt of 2-bromo-α-ergocryptine (bromocriptine) and desipramine hydrochloride from Sigma Chemical Company (St. Louis, MO). Cocaine hydrochloride was obtained from the National Institute on Drug Abuse. GBR 12909, provided by NOVO-Nordisk Pharmaceuticals, Malov, Denmark through the Medications Development Division of the National Institute on Drug Abuse (NIDA), was prepared in 3 mg/ml tartaric acid solution (Fischer Scientific Co., Fair Lawn, NJ). Buprenorphine was obtained in solution from Reckitt & Colman Pharmaceuticals, Inc. (Richmond, VA). MK-801 (α-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate) was purchased from Research Biochemicals, Inc. Diazepam was supplied by Hoffman-La Roche, Inc. (Nutley, NJ) in ampules containing a solution of 5 mg/ml. Drugs were dissolved in 0.9% sterile saline and were administered i.v. in a final volume of 1 ml/kg over a period of approximately 45 sec. Drug concentrations were calculated as the salt form. Cefazolin (Geneva Pharmaceuticals/Marsam Pharmaceuticals, Cherry Hill, NJ) was used postoperatively to reduce the risk of sepsis.

Data analysis. Data were analyzed at several time points. First, the peak arterial pressure response to cocaine, invariably occurring within the first minute, was recorded. A second set of values was obtained at the time of the peak change in cardiac output if it was not coincident with the peak change in arterial pressure. Using the data at the time of the maximum change in cardiac output, rats were classified as mixed or vascular responders. In addition, data were obtained during the sustained modest pressor response defined at 1, 3 and 5 min after initiating cocaine injection. Peak data points and sustained responses were examined separately using analysis of variance to avoid the occurrence of significant interactions. Two-way analysis of variance (for studies of vascular and mixed responders) included a post hoc simple main effects test to determine which groups were different. With one exception described below, these procedures have been used in previous reports (Branch and Knupefer, 1994a; Knupefer and Branch, 1992, 1993). In our study, instead of comparing hemodynamic responses to cocaine after drug pretreatment to the precocaine (postpretreatment) levels, cocaine-induced changes were determined from baseline levels before administration of the pretreatment. This change allows for consideration of the effects of altered baselines due to drug pretreatment on cocaine-induced responses. The figures of drug time courses reflect any differences in baselines that occurred with pretreatments.

All analyses were performed using CRUNCH (CRUNCH Software, Oakland, CA). Significant differences were noted if P < .05. Data are expressed as mean ± S.E.M.

Results

Conscious rats instrumented for cardiac output determination (n = 33) had a mean arterial pressure of 117.1 ± 1.7 mmHg, a heart rate of 388 ± 4 bpm and an ascending aortic velocity signal of 9.7 ± 0.3 kHz shift. Cocaine administration (5 mg/kg, i.v.) elicited pressor responses and variable changes in cardiac output and systemic vascular resistance. Each rat received cocaine alone several times (3–12 trials, mean = 7.8 ± 0.5 trials) to determine hemodynamic responsivity. Individual rats (n = 26) were designated vascular responders if the mean maximum decrease in cardiac output was more than 8% (mean = -15.4 ± 1%). The remaining rats, classified as mixed responders, had smaller decreases or increases in cardiac output (mean = 8.2 ± 3.8%). The resting arterial pressures and heart rates were not different between groups. In contrast, the mean ascending aortic flow signals were significantly different in vascular and mixed responders (10.0 ± 0.3 and 8.45 ± 0.5 kHz shift, respectively). Figure 1 depicts the mean responses to cocaine alone in all rats. Five rats were tested with two pretreatment drugs (on different days), five were tested with three drugs and two were examined in four different experimental protocols. In all cases, control responses to cocaine were repeated before each pretreatment regimen to verify consistency of responses.

In a separate group of rats instrumented for arterial pressure and heart rate determination only (n = 7), mean arterial pressure was 116.8 ± 2.2 mmHg and heart rate was 404 ± 9 bpm. These rats were used to determine appropriate doses of some pretreatment drugs.

Effects of bromocriptine. Resting hemodynamic values between vascular and mixed responders were similar (table 1). The D2 receptor agonist, bromocriptine (0.1 mg/kg, i.v.), elicited a biphasic arterial pressure response; a brief pressor response within 30 to 90 sec after injection (fig. 2) followed by a small depressor response (table 2). The pressor response was caused by an increase in cardiac output in mixed responders (P = .02) and by an increase in systemic vascular resistance in vascular responders (P = .045, table 2; fig. 2). Five minutes later, arterial pressure was lower in vascular responders only due to a decrease in systemic vascular resis-

Fig. 1. Mean hemodynamic responses to intravenous cocaine (5 mg/kg, i.v., injected over 45 sec as depicted by the bar labeled COC) in vascular responders (open squares, n = 24) and mixed responders (filled squares, n = 7). Specific responses shown include mean arterial pressure (MAP, mmHg), heart rate (HR, bpm), cardiac output (CO, % change) and systemic vascular resistance (SysVR, % change). Control values are given in the first sentence of “Results.” Data were analyzed with an unpaired Students’ t test at the time of the peak pressor response and with a two-way ANOVA and simple main effects test during the sustained response (1, 3 and 5 min after cocaine administration). Asterisks denote significant (P < .05) differences between groups (vascular and mixed responders) at specific time points.
Bromocriptine pretreatment reduced the pressor response elicited by cocaine primarily by reducing the increase in systemic vascular resistance (fig. 3) although, in individual groups, this decrease was only significant in vascular responders. These changes were due, in part, to reduced baseline values (table 2). There was a significant reduction in the decrease in cardiac output in vascular responders at the 1 min time point. Bradycardic responses to cocaine were also reduced by bromocriptine pretreatment (fig. 3) but stroke volume was unaffected (data not shown). A greater dose of bromocriptine (1 mg/kg) also reduced the peak pressor response to cocaine (table 3).

Desipramine was studied in 14 rats (table 1). The monoamine uptake inhibitor, desipramine (1 mg/kg, i.v.), increased arterial pressure in all rats (fig. 2) within 1 to 2 min after administration. As seen with bromocriptine, the pressor response was caused by an increase in cardiac output in mixed responders and with an increase in systemic vascular resistance in vascular responders (fig. 2). Furthermore, heart rate fell in vascular responders only. Stroke volume was not altered in either group. A larger dose of desipramine (10 mg/kg, i.v.) elicited an equivalent peak increase in arterial pressure in five conscious rats without cardiac output instrumentation (table 3). Ten minutes later, arterial pressure remained elevated in all rats but vascular responders had a significantly higher resting arterial pressure than mixed responders. The increase in arterial pressure was due to an increase in systemic vascular resistance (table 2, time 0 in fig. 5) because heart rate and cardiac output remained depressed in vascular responders only (table 2).

Desipramine pretreatment (1 mg/kg) did not alter the peak pressor responses to cocaine despite higher baseline values (fig. 5) but did produce several changes at the 1-min time period. These included a significant reduction in the cocaine-induced bradycardia in mixed responders and a smaller decrease in cardiac output and increase in systemic vascular resistance in vascular responders. When measured at the time of the peak change in cardiac output, desipramine pretreatment selectively prevented the cocaine-induced decrease in cardiac output and heart rate in vascular responders without affecting significantly the responses in mixed responders (fig. 4). Stroke volume was not altered by desipramine (data not shown). At a higher dose of desipramine (10 mg/kg), the pressor responses to cocaine were significantly reduced (table 3).

Responses recorded at the time of the peak change in cardiac output were also measured (fig. 4). Again the pressor response was reduced due to a decrease in the cocaine-induced increase in systemic vascular resistance. The bradycardia was reduced in vascular responders and there was a significant difference between heart rate responses in the two groups (fig. 4). After bromocriptine, there was no longer a difference between the cardiac output responses in vascular and mixed responders (figs. 3 and 4).

Effects of desipramine. Desipramine was studied in 14 rats (table 1). The monoamine uptake inhibitor, desipramine (1 mg/kg, i.v.), increased arterial pressure in all rats (fig. 2) within 1 to 2 min after administration. As seen with bromocriptine, the pressor response was caused by an increase in cardiac output in mixed responders and with an increase in systemic vascular resistance in vascular responders (fig. 2). Furthermore, heart rate fell in vascular responders only. Stroke volume was not altered in either group. A larger dose of desipramine (10 mg/kg, i.v.) elicited an equivalent peak increase in arterial pressure in five conscious rats without cardiac output instrumentation (table 3). Ten minutes later, arterial pressure remained elevated in all rats but vascular responders had a significantly higher resting arterial pressure than mixed responders. The increase in arterial pressure was due to an increase in systemic vascular resistance (table 2, time 0 in fig. 5) because heart rate and cardiac output remained depressed in vascular responders only (table 2).

Desipramine pretreatment (1 mg/kg) did not alter the peak pressor responses to cocaine despite higher baseline values (fig. 5) but did produce several changes at the 1-min time period. These included a significant reduction in the cocaine-induced bradycardia in mixed responders and a smaller decrease in cardiac output and increase in systemic vascular resistance in vascular responders. When measured at the time of the peak change in cardiac output, desipramine pretreatment selectively prevented the cocaine-induced decrease in cardiac output and heart rate in vascular responders without affecting significantly the responses in mixed responders (fig. 4). Stroke volume was not altered by desipramine (data not shown). At a higher dose of desipramine (10 mg/kg), the pressor responses to cocaine were significantly reduced (table 3).

### Table 1: Baseline values for different experiments

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>Arterial Pressure (mm Hg)</th>
<th>Heart Rate (beats/min)</th>
<th>Cardiac Output (kHz Shift)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>MR</td>
<td>6</td>
<td>100 ± 2</td>
<td>362 ± 4</td>
<td>9.3 ± 0.3</td>
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<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>109 ± 5</td>
<td>376 ± 8</td>
<td>10.2 ± 0.6</td>
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<tr>
<td>Desipramine</td>
<td>MR</td>
<td>7</td>
<td>111 ± 2</td>
<td>396 ± 4</td>
<td>8.8 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>117 ± 6</td>
<td>372 ± 13</td>
<td>10.0 ± 0.9</td>
</tr>
<tr>
<td>GBR12909</td>
<td>MR</td>
<td>5</td>
<td>121 ± 2</td>
<td>366 ± 8</td>
<td>8.3 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>10</td>
<td>123 ± 5</td>
<td>383 ± 8</td>
<td>9.6 ± 0.6</td>
</tr>
<tr>
<td>Diazepam</td>
<td>MR</td>
<td>5</td>
<td>113 ± 3</td>
<td>369 ± 11</td>
<td>8.1 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>13</td>
<td>110 ± 4</td>
<td>403 ± 5*</td>
<td>9.4 ± 0.6</td>
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<tr>
<td>Buprenorphine</td>
<td>VR</td>
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<td>110 ± 4</td>
<td>389 ± 4</td>
<td>11.2 ± 0.6</td>
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<tr>
<td>MK-801</td>
<td>VR</td>
<td>9</td>
<td>120 ± 3</td>
<td>385 ± 9</td>
<td>10.3 ± 0.6</td>
</tr>
</tbody>
</table>

* Denotes significant difference from mixed responders (P < .05). Group names refer to mixed responders (MR) and vascular responders (VR).
Effects of GBR 12909. The effects of administration of the vehicle for GBR 12909 (3 mg/ml tartaric acid) were examined in 10 conscious rats. Vehicle injections elicited increases in arterial pressure and heart rate that were not unlike those elicited by low doses of GBR 12909 (table 3; fig. 6). There were no differences in hemodynamic parameters 5 min after vehicle injection (fig. 6).

The resting values of arterial pressure, heart rate and ascending aortic flow were not different between rats (table 1). GBR 12909 (0.5–10 mg/kg, i.v.) evoked smaller hemodynamic responses compared to cocaine (figs. 1 and 6). Lower doses (0.5–1 mg/kg) produced small pressor responses and tachycardia that were not different from vehicle-induced effects. Lower doses produced decreases in systemic vascular resistance and increases in cardiac output whereas higher doses (5 and 10 mg/kg) elicited biphasic cardiovascular changes (fig. 6, responses to 10 mg/kg are not shown). There was a significant dose-response relationship for arterial pressure, heart rate, cardiac output and systemic vascular resistance (fig. 6) but not for stroke volume (data not shown). There were no differences in the hemodynamic effects noted in vascular and mixed responders except that the initial peak pressor response was significantly greater in mixed responders compared to vascular responders at the 1- and 5-mg/kg doses of GBR 12909 (data not shown). Arterial pressure and cardiac output were elevated 5 min after GBR 12909 (1 mg/kg, i.v.) administration (data not shown). Although the increase in cardiac output was noted only in mixed responders (table 2).

Administration of cocaine (5 mg/kg, i.v.) resulted in peak pressor responses that were significantly greater in mixed responders compared to vascular responders (fig. 7). GBR 12909 pretreatment did not alter this difference. GBR 12909 had little effect on the time course of cocaine-induced responses in vascular responders but, at the 1-min time point, the increase in systemic vascular resistance was greater in mixed responders and the increase in cardiac output was changed to a decrease despite the elevated baseline value (fig. 7). Cocaine elicited an increase in stroke volume in mixed responders that was blocked by GBR 12909 (data not shown).

At the time of the maximum change in cardiac output, GBR 12909 reduced the pressor response to cocaine in mixed responders by reducing cardiac output responses (fig. 4). After GBR 12909 pretreatment, cardiac output responses in mixed responders were similar to those in vascular responders (fig. 4).

Effects of diazepam. There was a difference in pretreatment baseline values for heart rate between mixed and vascular responders in rats studied using diazepam (table 1). Two doses of diazepam (0.1 and 0.5 mg/kg) were administered to rats instrumented for cardiac output determination (n = 12 and 6, respectively). Dose-related differences in arterial pressure, heart rate and cardiac output baseline values or cocaine-induced responses were not observed using analysis of variance. Therefore, these data were combined in figures 2, 4 and 8. Diazepam pretreatment elicited an initial increase in arterial pressure in all rats within 60 to 90 sec due to an increase in cardiac output (fig. 2). Mixed responders, but not vascular responders, demonstrated an increase in arterial pressure and heart rate that was not unlike that observed in vascular responders in rats studied using diazepam (table 1). Further, the increase in cardiac output was greater in mixed responders than in vascular responders. After diazepam pretreatment, the increase in cardiac output was greater in mixed responders than in vascular responders.

### Table 2: Change in baseline values

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>n</th>
<th>Dose (mg/kg)</th>
<th>Arterial Pressure (mm Hg)</th>
<th>Heart Rate (Beats/Min)</th>
<th>Cardiac Output (% Change)</th>
<th>Systemic Vascular Resistance (% Change)</th>
<th>Stroke Volume (% Change)</th>
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</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>MR</td>
<td>6</td>
<td>0.1</td>
<td>-4.2 ± 2.9</td>
<td>5.7 ± 6.4</td>
<td>-1.5 ± 2.0</td>
<td>-43 ± 4.6</td>
<td>-0.3 ± 1.4</td>
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<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>0.1</td>
<td>-11.7 ± 5.3</td>
<td>0.3 ± 15.4</td>
<td>-1.5 ± 1.2</td>
<td>-9.4 ± 4.1*</td>
<td>-1.1 ± 3.6</td>
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<tr>
<td>Desipramine</td>
<td>MR</td>
<td>7</td>
<td>1</td>
<td>6.0 ± 1.3</td>
<td>-12.7 ± 3.4</td>
<td>-2.9 ± 2.3</td>
<td>9.3 ± 3.1*</td>
<td>0.5 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>6</td>
<td>1</td>
<td>12.2 ± 2.0*</td>
<td>-31.7 ± 11.3*</td>
<td>-6.6 ± 2.4*</td>
<td>18.7 ± 3.1*</td>
<td>1.4 ± 1.6</td>
</tr>
<tr>
<td>GBR 12909</td>
<td>MR</td>
<td>5</td>
<td>1</td>
<td>9.2 ± 3.8*</td>
<td>-1.0 ± 12.4</td>
<td>8.3 ± 4.3*</td>
<td>0.1 ± 3.3</td>
<td>9.9 ± 8.4</td>
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<tr>
<td></td>
<td>VR</td>
<td>10</td>
<td>1</td>
<td>6.6 ± 1.6*</td>
<td>12.9 ± 8.1</td>
<td>2.1 ± 1.6</td>
<td>3.5 ± 1.2</td>
<td>-1.5 ± 1.4</td>
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<tr>
<td>Diazepam</td>
<td>MR</td>
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<td>0.1–0.5</td>
<td>-4.2 ± 2.5</td>
<td>6.8 ± 8.9</td>
<td>5.7 ± 5.9</td>
<td>-7.4 ± 5.2</td>
<td>4.2 ± 6.1</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>13</td>
<td>0.1–0.5</td>
<td>-4.6 ± 1.6*</td>
<td>1.8 ± 4.6</td>
<td>0.1 ± 0.7</td>
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<td>-0.2 ± 1.5</td>
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<tr>
<td>Buprenorphine</td>
<td>MR</td>
<td>7</td>
<td>0.1</td>
<td>21.4 ± 3.8*</td>
<td>48.1 ± 13.3*</td>
<td>5.0 ± 1.9*</td>
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<tr>
<td></td>
<td>VR</td>
<td>9</td>
<td>0.05</td>
<td>20.1 ± 2.8*</td>
<td>49.4 ± 6.2*</td>
<td>5.8 ± 1.2*</td>
<td>10.2 ± 1.8*</td>
<td>-6.3 ± 1.3</td>
</tr>
</tbody>
</table>

*Denotes significant drug-induced change from baseline as determined by two-way ANOVA.

Data were measured 5 min (bromocriptine and GBR 12909) or 10 min (all other drug treatments) after drug administration (immediately before cocaine administration) and compared to pre-drug control values. Group names refer to mixed responders (MR) and vascular responders (VR).
TABLE 3
Changes in arterial pressure and heart rate elicited by drug pretreatments and cocaine

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Dose (mg/kg)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>12</td>
<td>0.1</td>
<td>20.4 ± 3.7^b</td>
<td>5 ± 9</td>
<td>17.7 ± 3.1^c</td>
<td>25 ± 11</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.0</td>
<td>12.8 ± 2.8^b</td>
<td>-25 ± 17</td>
<td>7.3 ± 4.4^c</td>
<td>11 ± 13</td>
</tr>
<tr>
<td>Desipramine</td>
<td>13</td>
<td>1.0</td>
<td>20.7 ± 2.1^b</td>
<td>-16 ± 6^b</td>
<td>44.7 ± 4.1</td>
<td>12 ± 13</td>
</tr>
<tr>
<td>GBR12909</td>
<td>10</td>
<td>0.5</td>
<td>10.2 ± 2.5^b</td>
<td>27 ± 5^b</td>
<td>26 ± 3.3^c</td>
<td>-53 ± 8</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.0</td>
<td>6.8 ± 2.8^b</td>
<td>31 ± 4^b</td>
<td>49.4 ± 3.3</td>
<td>5 ± 13</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>-4.2 ± 4.0</td>
<td>40 ± 7^b</td>
<td>47.7 ± 2.9</td>
<td>29 ± 9</td>
</tr>
<tr>
<td>Diazepam</td>
<td>12</td>
<td>0.1</td>
<td>10.8 ± 1.7^b</td>
<td>11 ± 7</td>
<td>42.7 ± 5.1^c</td>
<td>25 ± 9</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.5</td>
<td>6.5 ± 1.0^b</td>
<td>33 ± 9^b</td>
<td>46.8 ± 3.7</td>
<td>16 ± 8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.0</td>
<td>17.5 ± 2.4^b</td>
<td>56 ± 8^b</td>
<td>46.8 ± 2.5</td>
<td>6 ± 19</td>
</tr>
</tbody>
</table>

^a Peak cocaine effect after drug pretreatment as compared to values before pretreatment.
^b Denotes significant change from control value (P < .05).
^c Denotes significant change from cocaine alone (P < .05).
^d nt, Not tested.

Fig. 4. Arterial pressure and cardiac output responses to cocaine at the time of the peak change in cardiac output (0.5–3 min after cocaine). Responses to cocaine alone (5 mg/kg, i.v., Coc) are depicted for all control values combined. In addition, responses to cocaine after pretreatment with bromocriptine (0.1 mg/kg, Brc), desipramine (1 mg/kg, Des), GBR 12909 (1 mg/kg, GBR), diazepam (0.1 and 0.5 mg/kg, Dzp), buprenorphine (0.3 mg/kg, Bup) and MK-801 (0.05 mg/kg, MK) are shown. Data were analyzed by one-way (all other drugs) ANOVA. There was a significant interaction for the maximum cardiac output response noted after GBR 12909 pretreatment because the mixed responders had a negative change and the vascular responders had a positive change. Asterisks denote a significant change (P < .05) in comparison to cocaine alone for control values obtained in each experiment. The control values for cocaine administration are a mean obtained from each animal used and are not necessarily represented by the combined control value shown for cocaine alone. Significant differences between vascular and mixed responders are designated with a #. Other abbreviations are described in figure 1.

in heart rate also (fig. 2). After 10 min, arterial pressure was significantly lower compared to baseline values in all rats although the differences were only significant in vascular responders (table 2). No apparent sedative effects were noted but rats were relatively quiescent before and after all drugs administered except cocaine. In contrast, a higher dose of diazepam (1 mg/kg, i.v.) elicited an initial behavioral excitation in some rats (as noted by increased motor activity) followed by an apparent lethargy (lying on cage bottom for several minutes) in all six rats tested. These responses were associated with an initial increase in arterial pressure (table 3) that was no longer apparent 10 min later. Heart rate was elevated for the entire 10-min period before cocaine administration.

Most cardiovascular responses to subsequent administration of cocaine were not altered by diazepam pretreatment (0.1 and 0.5 mg/kg) with the exception of an enhanced tachycardia and reduced systemic vasoconstriction at the time of the initial peak pressor response (fig. 8). Vascular responders had a significant decrease in the peak pressor response due to a decrease in the cocaine-induced increase in systemic vascular resistance. Stroke volume was unchanged (data not shown). At the time of the peak change in cardiac output, arterial pressure and heart rate responses to cocaine alone differed in vascular and mixed responders (data not shown) but after diazepam pretreatment no differences were observed (fig. 4). Administration of cocaine after pretreatment with 1 mg/kg diazepam elicited similar arterial pressure and heart rate responses. There was a small but significant reduction in the pressor response after the lowest dose of diazepam (0.1 mg/kg) only (table 3).
Effects of buprenorphine. Buprenorphine (0.3 mg/kg) alone produced a delayed (6–7 min) increase in arterial pressure due to increases in heart rate, cardiac output and systemic vascular resistance in seven vascular responders (fig. 2, mixed responders were not tested). No differences were noted between the effects of GBR 12909 on vascular responders compared to mixed responders so the combined data are presented. Other abbreviations are described in figure 1.

Effects of MK-801 (dizocilpine). Administration of MK-801 (50 µg/kg) evoked an increase in arterial pressure mediated by increases in systemic vascular resistance, heart rate, and cardiac output in nine vascular responders (mixed responders were not tested) that reached peak values approximately 7 to 9 min after administration (fig. 2). These values remained elevated 10 min after administration when cocaine was injected. The arterial pressure and heart rate responses to cocaine administration were greater (fig. 10) due to higher baseline values (table 2). The pressor response appeared to be due to an increase in baseline cardiac output possibly due to inhibition of the bradycardia. At the time of the peak maximum cocaine-induced decrease in cardiac output were not changed significantly by buprenorphine pretreatment (fig. 4).

Effects of MK-801 (dizocilpine). Administration of MK-801 (50 µg/kg) evoked an increase in arterial pressure mediated by increases in systemic vascular resistance, heart rate, and cardiac output in nine vascular responders (mixed responders were not tested) that reached peak values approximately 7 to 9 min after administration (fig. 2). These values remained elevated 10 min after administration when cocaine was injected. The arterial pressure and heart rate responses to cocaine administration were greater (fig. 10) due to higher baseline values (table 2). The pressor response appeared to be due to an increase in baseline cardiac output possibly due to inhibition of the bradycardia. At the time of the peak
cardiac output response, the cardiovascular responses were unaltered (fig. 4). Stroke volume responses were not altered (data not shown).

Discussion

These data provide the first detailed description of cardiac output and systemic vascular resistance responses to a variety of agents proposed for the treatment of cocaine addiction and/or toxicity. The responses to proposed treatments and to the combination of the treatments and cocaine were described in two subsets of a population. Our laboratory has reported that the cardiac output responsiveness to cocaine is highly variable and is correlated with their predisposition to the development of cocaine-induced hypertension and cardiomyopathies (Branch and Knuepfer, 1994a; Knuepfer et al., 1993a). We divided rats into vascular responders (with a decrease in cardiac output) and mixed responders (no change or an increase in cardiac output) to facilitate analysis of the differences in responsivity. In our study, resting ascending aortic flow values were significantly higher in vascular responders compared to mixed responders. It may be argued that this difference may predispose these rats to a decrease in cardiac output in response to cocaine. This is unlikely because we have published several reports using relatively large numbers of rats classified in this manner (Branch and Knuepfer, 1993, 1994a; Knuepfer et al., 1993a, b). We have not noted such differences in these studies. Therefore, this difference may contribute to the differential responsiveness but is not likely to be the sole cause.

Amphetamine administration (1 mg/kg), ethanol administration (0.475 or 0.95 mg/kg) or a brief air jet stress evoke differential cardiovascular responsiveness that is directly related to the differential hemodynamic responses elicited by cocaine in vascular and mixed responders (Branch and Knuepfer, 1994a; Gan and Knuepfer, 1994; Knuepfer et al., 1993b). In our study, bromocriptine (0.1 mg/kg, i.v.) or desipramine (1 mg/kg, i.v.) evoked an acute increase in arterial pressure in all rats. The pressor response was a result of increasing cardiac output in mixed responders and of increasing systemic vascular resistance in vascular responders. These data suggest that rats exhibit differential hemodynamic responses to dopamine (D2 receptor) agonists or reuptake blockers in addition to acute stress, ethanol and amphetamine. These data provide further support for a differential sensitivity to a range of drug treatments whether these are agents that mimic cocaine’s pharmacologic effects (e.g., desipramine, bromocriptine) or not. We propose that individual rats are predisposed to specific hemodynamic response patterns evoked by behavioral stress that, in most examples cited here, occurs after administration of psychoactive agents.

Bromocriptine. Dopamine agonists, such as bromocriptine, are the most common class of agents used to treat cocaine addiction and toxicity (Halikas et al., 1993). Bromocriptine has been shown to reduce cocaine craving in humans (Daeks and Gold, 1985), and self-administration behavior and motor responses in rats (Campbell et al., 1989; Hubner and Koob, 1990) presumably by desensitizing dopamine receptors responsible for cocaine-induced euphoria. With regard to the autonomic nervous system, bromocriptine alone increased heart rate and pupillary diameter but lowered arterial pressure in human subjects (Preston et al., 1992). We noted a biphasic response (increase followed by a decrease) in arterial pressure after bromocriptine administration (0.1 and 1 mg/kg, i.v.) in conscious rats (fig. 2; table 2).

After bromocriptine pretreatment, pressor responses to cocaine were reduced but heart rate responses were enhanced in humans (Kumor et al., 1989; Preston et al., 1992). Our results in conscious rats also suggest that pressor responses are reduced and heart rate responses are greater. Furthermore, we noted that cardiac output and systemic vascular resistance responses in both groups were smaller (figs. 3 and 4) thereby eliminating differences in cocaine-induced cardiovascular reactivity between vascular and mixed responders. This may be due, in part, to a difference in baseline values because reductions in arterial pressure and systemic vascular resistance were noted 5 min after bromocriptine administration (table 2). Alternatively, if cocaine alters hemodynamic responses by enhancing dopamine receptor activation, bromocriptine might reduce the response by desensitizing the receptors. Although others have suggested that the combination of bromocriptine and cocaine does not appear to enhance potential cardiovascular toxicity (Kumor et al., 1989; Preston et al., 1992), our data suggest that the combined effects of these two agents may ameliorate cardiotoxicity.

Desipramine. Tricyclic antidepressants have been shown to be effective in treating craving for cocaine (Tennant and Rawson, 1983) and cocaine toxicity (Antelman et al., 1981). For example, desipramine is widely used for treatment of addiction to cocaine (Halikas et al., 1993). Desipramine may reduce the stimulant properties of cocaine in some patients and enhance it in others (Fischman et al., 1990) suggesting that individual differences may alter the effectiveness of desipramine in treating cocaine addiction. The autonomic responses to both agents may also vary because both cocaine and desipramine produce an initial brief excitation of sympathetic activity in some conscious animals followed by a sustained inhibition of sympathetic activity in all subjects (Branch and Knuepfer, 1994b; Dorward et al., 1991; Knuepfer and Branch, 1992). As noted with cocaine, arterial
pressure was elevated for at least 10 min after desipramine administration (1 or 10 mg/kg) despite the reported sympathetic inhibition caused by both agents. Others have not observed a change in arterial pressure with desipramine administration in conscious rats (Tella et al., 1993), rabbits (Dorward et al., 1991) and humans (Kosten et al., 1992) although Fischman et al. (1990) reported an increase in arterial pressure in human subjects after chronic desipramine maintenance therapy. Therefore, the decrease in central sympathetic drive may not offset the enhanced catecholamine levels due to reuptake blockade.

It has been suggested that desipramine attenuates the tachycardic responses to cocaine (Kosten et al., 1992). Some investigators have suggested that the potential for toxicity after desipramine may be greater (Fischman et al., 1990; Misra et al., 1986). This has been suggested to be a result of the ability of acute desipramine administration to enhance plasma levels of cocaine (Misra et al., 1986; Tella and Goldberg, 1993) although others have not noted a change in cocaine levels during desipramine maintenance therapy (Kosten et al., 1992). In our study, acute desipramine treatment prevented the decrease in cardiac output in vascular responders. Although the smaller cardiac output responses may be a result of lower baseline values of cardiac output (table 2), attenuating the decrease in cardiac output (fig. 5) suggests a beneficial effect of desipramine. Although these changes were small, the results with 10 mg/kg desipramine (table 3) demonstrate that the peak pressor response to cocaine, at least, would be attenuated at higher doses. In fact, Tella and coworkers (1993) did not observe significant changes in arterial pressure or heart rate 5 min after a similar dose of desipramine in conscious rats. The possible significance regarding reuptake blockade will be discussed below.

**GBR 12909.** GBR 12909 is more selective and more potent in its ability to bind to the dopamine transporter compared to cocaine (Andersen, 1989; Izenwasser et al., 1990; Rothman et al., 1989) and inhibits cocaine-induced increases in extracellular dopamine (Rothman et al., 1991). It has been shown to produce similar behavioral responses to those elicited by cocaine in animal studies (Cunningham and Callahan, 1991; Heikkila and Manzino, 1984; Howell and Byrd, 1991). GBR 12909 substitutes for cocaine at least in some animals in drug discrimination studies (Johanson and Barrett, 1993). Because of its selectivity for the dopamine transporter and the known involvement of dopamine in eliciting cocaine-induced euphoria, GBR 12909 has been proposed as a treatment for cocaine addiction (Rothman and Glowa, 1995; Rothman et al., 1989, 1991).

The cardiovascular responses to GBR 12909 were, in general, smaller than those elicited by equivalent doses of cocaine but were otherwise similar. We noted increases in cardiac output and heart rate after lower doses of cocaine that changed to decreases at higher doses (Branch and Knuepfer, 1993; 1994a) as noted with GBR 12909. Because GBR 12909 is more selective than cocaine in inhibiting dopamine uptake (Andersen, 1989), the responses to GBR 12909 more specifically reflect the contribution of dopamine in mediating the autonomic responses to cocaine. These data do not differentiate between possible actions in the CNS and/or in the peripheral tissue. These data suggest that GBR 12909 evokes hemodynamic responses that are qualitatively similar to those elicited by cocaine. Therefore, it is likely that the mechanisms these two agents have in common may be responsible for the hemodynamic responses.

Pretreatment with GBR 12909 had some effects on the hemodynamic responses to cocaine (fig. 7). Specifically, mixed responders had a relatively selective conversion of an increase in cardiac output to a decrease such that they were no longer different from vascular responders. Some agents (e.g., propranolol, phystostigmine, ethanol) appear to shift the cardiovascular output responses of both groups of rats in a negative direction whereas others (e.g., methyl atropine) shift the cardiac output responses to more positive values (Branch and Knuepfer, 1994a; Gan and Knuepfer, 1993; Knuepfer et al., 1995; Mueller et al., 1995). Tella and Goldberg (1993) reported that GBR 12909 pretreatment produced a substantial increase in cocaine levels 30 sec after cocaine administration suggesting toxicity might be enhanced. This is unlikely to explain the selective effects on mixed responders because earlier dose-response studies do not suggest that higher doses produce a decrease in cardiac output in mixed responders unless seizure activity ensues (Branch and Knuepfer, 1993, 1994a). The effects of higher doses of GBR 12909 (5–10 mg/kg) on cardiovascular responses are more profound and apparently long-lasting. This suggests that there is a greater chance of possible toxicity with cocaine although we did not investigate this. It is not known at present whether these effects are mediated by actions on central or peripheral monoamine uptake systems but the selectivity of GBR 12909 for the dopamine transporter and the high density of these transporters in the CNS suggests these effects may be centrally mediated. It is apparent, at least, that GBR 12909 alone (0.5–5 mg/kg) is not likely to produce untoward cardiovascular effects.

**Dopamine hypothesis.** The actions of bromocriptine, desipramine and GBR 12909 give insight into the causes of hemodynamic responses to cocaine. Both bromocriptine and desipramine will enhance dopamine receptor activation by different mechanisms. Because these agents selectively reduce the decrease in cardiac output elicited by cocaine, it is possible that dopamine receptor activation alleviates the cardiodepression noted in some rats. Interestingly, GBR 12909 would be expected to have similar results but did not. It is possible that the dose of GBR 12909 was insufficient to attenuate the responses to cocaine, but, due to the prolonged effects of GBR 12909 higher doses were not used. Schindler et al. (1991) reported that the cocaine-induced pressor response was not antagonized by D1 or D2 receptor antagonists or mimicked by a D2 agonist in conscious squirrel monkeys. In our study, the agonists or uptake inhibitors could mimic the effects of cocaine to some extent (figs. 2 and 6) but only bromocriptine was effective in reducing the pressor response to cocaine. In contrast, all three agents were capable of preventing differential cardiac output and systemic vascular resistance responses in the two groups of animals. These data suggest that dopamine receptors may be responsible for the differences in hemodynamic response patterns noted in vascular and mixed responders.

It is unclear at this time whether the hemodynamic responses are dependent on the direct actions of dopamine or whether the affective component of the psychoactive agents, mediated in part by dopamine, indirectly triggers the cardiovascular responses. In this regard, the data are consistent...
because bromocriptine and desipramine both elicited differential cardiac output responses and attenuated the cocaine-induced decrease in cardiac output. In contrast, GBR 12909 did not elicit differential responsiveness alone at the 1-mg/kg dose and did not prevent the decrease in cardiac output. Again, it is possible that a higher dose of GBR 12909 would have such effects.

**Diazepam.** Diazepam is effective in ameliorating stress-induced hormonal and neurochemical responses (Lahti and Barsuhn, 1975) that are similar to effects observed after cocaine administration (Levy et al., 1992; Moldow and Fishman, 1987, Rivier and Vale, 1987). Larger doses of diazepam are reported to reduce cocaine toxicity (Catravas and Waters, 1981; Derlet and Albertson, 1989; Guinn et al., 1980) although others have reported no significant protection (Trouvé and Nahas, 1990). The effectiveness of diazepam in reducing toxicity may only be manifest at greater doses (>1 mg/kg) when anticonvulsant effects are manifest whereas lower doses, such as those used in our study, may not be effective in protecting rats from lethal doses of cocaine (Smith et al., 1991). Diazepam is effective for treating toxicity in patients experiencing cocaine-induced seizures (Jonsson et al., 1983; Resnick and Resnick, 1984). In humans, sedative and antianxiety effects are noted at doses of 30 to 300 µg/kg (Rall, 1990). Although doses in humans cannot be directly compared to those in rats, the substantial difference (100-fold) between doses in rats and those in humans suggests that greater sedation is necessary to prevent toxicity in rats. Diazepam (0.1 or 0.5 mg/kg) produced biphasic arterial pressure responses (fig. 2; table 2). A small depressor response remaining noted only in vascular responders was not likely to substantially alter responses to cocaine administration. Therefore, these data suggest that diazepam may not alter cocaine-induced cardiovascular toxicity.

**Buprenorphine.** Buprenorphine is a mixed agonist/antagonist at the μ opioid receptor with potent analgesic effects and little or no potential for dependence (Cowan et al., 1977; Mello et al., 1989). Buprenorphine has been suggested as a treatment for cocaine addiction because it suppresses cocaine-induced responding in self-administration studies (Mello et al., 1989; Mendelson et al., 1990; Winger et al., 1992) and blocks cocaine-induced place preference (Suzuki et al., 1992). Little is known concerning the possible cardiovascular interactions between buprenorphine and cocaine. It was reported that arterial pressure and heart rate responses to cocaine and plasma cocaine levels were not altered by buprenorphine maintenance therapy in human subjects (Teoh et al., 1993). Buprenorphine, even at a low dose (0.3 mg/kg), reduced toxicity to lethal injections of cocaine in mice (Shukla et al., 1991; Witkin et al., 1991). At this dose, we noted net increases in arterial pressure, heart rate and cardiac output in vascular responders that were still present after 10 min (fig. 2; table 2). Despite these changes in hemodynamic variables, buprenorphine had little effect on the cardiovascular responses to cocaine with the exception of a possible increase in the systemic vascular resistance response. If the shift in baseline is not considered, buprenorphine pretreatment would blunt the initial pressor response and enhance both the decrease in cardiac output and heart rate (data not shown). Therefore, if buprenorphine-induced cardiovascular effects were allowed to resolve, it is possible that cocaine-induced cardiodepression might be greater.

**MK-801.** It has been reported that MK-801 (dizocilpine) and other NMDA receptor antagonists reduce toxicity to lethal doses of cocaine (Derlet and Albertson, 1990; Rockhold et al., 1991; Witkin and Tortella, 1991) although the precise mechanism by which this occurs remains to be determined. MK-801 also reduces the untoward proarrhythmic effects of cocaine on the myocardium (Hageman and Simor, 1993). Interestingly, MK-801 did not alter heart rate, arterial pressure or sympathetic nerve activity substantially in pentobarbital-anesthetized dogs (Hageman and Simor, 1993). In contrast, we and others (Lewis et al., 1989) noted that this dose of MK-801 elicited increases in arterial pressure and heart rate in conscious rats (fig. 2; table 2). Because higher doses produce more profound changes in cardiovascular parameters in conscious animals making interpretation more difficult, these were not used in our study. Although the changes evoked by MK-801 were reduced somewhat 10 min after pretreatment (table 2), it is possible that the shift in baseline heart rate may have contributed to the enhanced tachycardia followed by a reduced bradycardia after cocaine administration. In addition, an increase in aortic flow and in systemic vascular resistance was noted 10 min after MK-801 administration. Taking into account the higher arterial pressure, heart rate and cardiac output, the cocaine-induced responses were shifted upward in vascular responders. We suggest that the difference in baseline may be largely responsible for changes in hemodynamic responses to cocaine because no differences in the pressor or cardiac output responses are noted if the baseline shift is not taken into consideration (data not shown). It appears as though the increase in the cocaine-induced pressor response is due entirely to an increase in the cardiac output response with the likely contribution of heart rate to this response. These data suggest that this dose of MK-801 may exacerbate pressor and heart rate responses to cocaine possibly due to the change in baseline. These data also demonstrate that the pressor responses can be dissociated from the cardiac output responses. Interestingly, propranolol has the opposite effect; ameliorating the pressor response and enhancing the decrease in cardiac output (Branch and Knuepfer, 1994a).

In conclusion, our data describe, for the first time in most cases, detailed cardiovascular responses to cocaine after pretreatment with a variety of proposed and currently used treatment regimens for cocaine addiction and toxicity. Our previous studies suggest that arterial pressure and heart rate responses alone are not sufficient to predict potential cocaine-induced myocardial toxicity (Knuepfer et al., 1993a). Although it is clear that humans also vary in their susceptibility to cocaine-induced cardiotoxicity, related studies are necessary to demonstrate whether or not hemodynamic variables can predict those individuals at risk. These results also implicate potential neurotransmitters that may mediate specific hemodynamic responses to cocaine.

**Acknowledgments**

The authors acknowledge the technical assistance of Mr. David De Ornellas and the editorial assistance of Dr. Patrick J. Mueller. We are indebted to NOVO-Nordisk Pharmaceuticals and Drs. David N. Johnson and James Terrill from the NIDA, Medications Development Division for providing the GBR 12909. Portions of this work were presented in abstract form (Gan, Q. and Knuepfer, M.M., 1997).


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