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# Monoamine Transporter and Sodium Channel Mechanisms in the Rapid Pressor Response to Cocaine

SRIHARI R. TELLA AND STEVEN R. GOLDBERG

*Department of Pharmacology, Georgetown University School of Medicine, 3900 Reservoir Road, Washington, DC 20007, and Behavioral Pharmacology and Genetics Section, Preclinical Pharmacology Laboratory, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health, P.O. Box 5180, Baltimore, MD 21224*

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TELLA, S. R. AND S. R. GOLDBERG. *Monoamine transporter and sodium channel mechanisms in the rapid pressor response to cocaine*. PHARMACOL BIOCHEM BEHAV **59**(2) 305–312, 1998.—Intravenous (IV) cocaine (0.03–3 mg/kg) produced dose-dependent, rapid, and brief increases in blood pressure (BP) in conscious rats pretreated with the dopamine receptor antagonist, SCH 23390. Monoamine uptake inhibitors structurally analogous to cocaine (cocaethylene, CFT, βCIT, CPT, (+)-cocaine, norcocaine, and benztropine) also produced this rapid pressor response, whereas structurally unrelated uptake inhibitors with diverse monoamine transporter selectivities (BTCP, indatraline, GBR 12935, mazindol, nomifensine, and zimeldine) either did not produce a rapid pressor response or produced only a small pressor response. At nonconvulsant doses, the sodium channel blockers acetylprocainamide, dibucaine, dyclonine, prilocaine, proparacaine, quinidine, and tetracaine produced a small pressor response or no increase in BP. In rats implanted with telemetric devices, cocaine and its analog, CFT, produced a biphasic pharmacological response that consisted of an initial brief and abrupt behavioral arousal associated with a rapid, large increase in BP followed by prolonged, parallel increases in BP and locomotor activity. Pretreatment with SCH 23390 prevented the prolonged but not the initial rapid and brief pressor and activity responses to both cocaine and CFT administration. The present data suggest that the inhibition of dopamine, norepinephrine, or serotonin transporter functions, either alone or in combination, does not mediate the rapid pressor response to cocaine. The sodium channel-blocking action of cocaine per se does not appear to be involved in the rapid pressor response to cocaine. Finally, the present results confirm previous findings that dopaminergic mechanisms mediate the prolonged increases in BP and locomotor activity produced by cocaine. © 1998 Elsevier Science Inc.

Behavior Blood pressure Cardiovascular Cocaine Dopamine Monoamine uptake Inhibition Sodium channel blockade

COCAINE consistently increases blood pressure (BP) and heart rate (HR) in humans (10,11,16,33) and in experimental animals (4,13,27,38,50,51,55). A large body of experimental evidence obtained from conscious animals suggests that the central nervous system plays an important role in the pressor and tachycardiac effects of cocaine (5,6,21,39,46,51–53,55). Thus, the actions of cocaine on the central nervous system are important not only for its reinforcing and behavioral effects but also for its cardiovascular effects. However, the precise central, neurobiological mechanisms underlying the cardiovascular effects of cocaine and their interrelationship with the mechanisms mediating the reinforcing and behavioral effects of cocaine remains to be determined.

Two prominent pharmacodynamic properties of cocaine are an inhibition of uptake of monoamines following binding to monoamine transporters and a local anesthetic action due

Requests for reprints should be addressed to Srihari Rao Tella, Department of Pharmacology, Georgetown University School of Medicine, 3900 Reservoir Road, NW, Washington DC 20007.

to its ability to block sodium channel (20,25,29,32,40). A preponderance of experimental evidence indicates that reinforcing and other behavioral actions of cocaine are due primarily to its ability to bind to dopamine transporters and thereby inhibit the uptake of dopamine. This leads to enhanced dopaminergic neurotransmission in the central nervous system, especially in the mesocorticolimbic system (9,17,19,23,34,35,57). We recently suggested that two distinct pharmacodynamic mechanisms may mediate different phases of the pharmacological response to cocaine (49). One is the dopamine-dependent action of cocaine described above, which mediates its prolonged excitatory effects on locomotor activity, BP and HR, while the other is a dopamine-independent action of cocaine and appears to mediate the initial rapid and brief effects, namely an abrupt and intense behavioral arousal that is accompanied by large increases in BP and HR. Because blockers that are selective for norepinephrine (nisoxetine) or serotonin (fluoxetine) transporters or for sodium channels (lidocaine) did not mimic the latter-mentioned rapid and brief effects of cocaine, it was inferred that neither selective inhibition of either norepinephrine or serotonin uptake nor blockade of sodium channels appears to mediate these rapid effects of cocaine.

A major goal of the present study was to extend the previous findings and explore the possibility that some combination of monoamine transporter inhibitory mechanisms, rather than any one alone, might underlie the initial rapid and brief cardiovascular responses to IV cocaine. The effects on BP of cocaine, various cocaine analogs, and several monoamine uptake inhibitors with diverse monoamine transporter selectivities were studied in conscious rats. Because sodium channel drugs differ in their rate kinetics of interaction (onset and recovery) with the channel (1,28,31), several sodium channel blockers were tested to further verify the lack of involvement of a sodium channel mechanism in the rapid pressor response to cocaine. The ability of these compounds to produce the initial rapid and brief pressor response was assessed using a cumulative, dose–response design. The dopamine $D_1$ receptor antagonist, SCH 23390, was administered prior to testing of each compound to prevent the possible complicating influence of dopamine-dependent effects on BP (49). Another goal of this study was to further verify our original hypothesis that the physiological response to cocaine is a biphasic phenomenon consisting of an initial dopamine-independent abrupt behavioral arousal associated with large, rapid, and brief increases in BP followed by dopamine-dependent prolonged increases in BP and locomotor activity. To achieve this objective, an additional group of rats implanted with telemetric devices were tested with CFT, an analog of cocaine, and cocaine both in the presence and the absence of dopamine receptor blockade.

## METHOD

### *Animals*

Male Sprague–Dawley rats (Charles River Laboratories, Wilmington, DE) weighing 400–500 g were used. Animals were housed individually in temperature- and humidity-controlled rooms with a 12 L:12 D (0700–1900 h; 1900–0700 h) cycle. Throughout the study, rats were fed their daily food requirement of 5 g/100 g body weight of standard rat chow as a single meal. This feeding schedule maintains a stable body weight. Our previous experience indicates that maintaining a stable body weight results in extended catheter life as opposed to catheter life in animals with unlimited access to food. Therefore, this feeding schedule was used throughout the study.

### *Surgical and Experimental Procedures for Recording BP Using a Catheter Technique*

The procedures used are the same as those described in our earlier publication (52). In brief, polyvinyl chloride catheters were inserted into the femoral artery and vein under halothane anesthesia for recording of BP and the infusion of drugs, respectively. The free ends of the catheters were passed subcutaneously and exited the skin at the midscapular region. Catheters were filled with heparinized saline (50 units of heparin sodium/ml of normal saline), closed with stainless steel obturators and protected with rodent jackets (Alice King Chatham Medical Arts, Hawthorne, CA). Rats were allowed a postoperative recovery period of 7 days before experiments began.

Daily experimental sessions were conducted in home cages Monday through Friday. The arterial catheter was connected to a pressure transducer (model T42-20, Coulbourn Instruments, Leigh Valley, PA). The pressure signal from transducer was processed by an amplifier (model S72-25, Coulbourn Instruments) and recorded on a Macintosh II computer using a MacLab (World Precision Instruments, Sarasota, FL) interface and software. The peak changes in mean arterial blood pressure (BP) within the first 30 s following administration of each dose of test drug was determined from the analog recording. The BP values at all other times were determined by averaging 5-s segments of the chart recording. Cumulative dose–response studies with several test drugs were done using a 20-min interdose interval. All rats were pretreated with 0.1 mg/kg of R-(+)-SCH 23390, a dopamine $D_1$ receptor antagonist, 10 min prior to the start of the cumulative dose–response testing. Pretreatment with SCH 23390 prevented the possible complicating influence of a dopamine-dependent prolonged BP response, which could be potentially produced by test drugs similar to cocaine (49). In view of the short duration of the effect of SCH 23390, two or three supplemental doses (0.05 mg/kg) were given at 45-min intervals during the dose–response testing. Drug testing was done twice a week with a minimum of 2 days of drug-free sessions. During drug-free sessions, animals did not receive SCH 23390 or test drugs. On any given test drug day, only one drug was studied. All doses of test drugs were given as rapid bolus IV injections over a period of about 2 s. Doses of monoamine uptake inhibitors were chosen based on the doses noted in the literature as pharmacologically active (2,45). Doses of sodium channel blockers tested were carefully selected as to avoid convulsant effects by testing the drugs in a separate group of control rats implanted with venous catheters alone. The effect of an appropriate volume of the vehicle for each test drug was also studied by administering it 20 min following the last dose of each test drug. For those drugs that produced rapid increases in BP, the effect of chlorisondamine (3 mg/kg) on the rapid pressor response was also evaluated. Chlorisondamine was administered 1 h following the completion of vehicle testing. At this time point, an additional dose of 0.1 mg/kg of SCH 23390 was also given. Ten minutes following chlorisondamine and SCH 23390 treatment, the effect of a single large dose of a given test drug on BP was studied. The dose was chosen to equal the maximum cumulative dose used in the dose–response study. All animals were visually monitored for possible occurrence of convulsions following administration of test drugs. All test drugs as well as SCH 23390 and chlorisondamine, were given IV.

*Surgical and Experimental Procedures for Recording of Cardiovascular and Locomotor Effects of Cocaine and Its Analog, CFT, Using Telemetric Devices*

Rats were surgically prepared with transmitters (TA11PA-C40, Data Sciences International, St. Paul, MN) and IV catheters using multiple surgical procedures as described in our previous publication (49). Transmitters provided a means of measuring both the cardiovascular and locomotor effects of drugs simultaneously in the same animal. After 7 days of postoperative recovery and 3 weeks of acclimatization to the testing environment, drug testing was conducted twice a week with a minimum of 2 days of drug-free sessions between test sessions. The effects of 1 mg/kg doses of CFT and cocaine were studied by administering them 10 min after a 0.03 mg/kg dose of SCH 23390 on test drug days 1 and 2, respectively. Similarly, the effects of 1 mg/kg dose of CFT and cocaine were reexamined 10 min after saline administration on test drug days 3 and 4, respectively. All drugs were administered IV. Cocaine and CFT were each given as a rapid bolus injection over a period of about 2 s. It has been reported that dopamine receptor antagonists are less effective in preventing the behavioral effects of cocaine challenge in animals that had previously received repeated daily injections of cocaine (48,54). In view of this, evaluation of the effects of SCH 23390 on cardiovascular and behavioral effects of CFT and cocaine was done first and then evaluation of the control responses (following saline administration) to CFT and cocaine were done in these rats. Although this introduced the possibility of order effects, the initial rapid pressor response to cocaine in this testing paradigm did not appear to differ from the rapid pressor response produced by cocaine in animals that had no prior drug history (49). The doses of SCH 23390 (0.03–0.1 mg/kg) used in the present study do not alter the cardiovascular responses to the adrenergic agonists norepinephrine and isoproterenol (49). A 1 mg/kg dose of CFT was chosen because this dose produced a significant increase in BP in cumulative dose–response studies.

*Drugs*

Acetylprocainamide hydrochloride (Sigma Chemical Co., St. Louis, MO), benztropine mesylate, BTCP hydrochloride, bupropion hydrochloride, CFT naphthalene sulfonate ((−)-2-β-carbomethoxy-3-β-(-fluorophenyl)tropane 1,5-naphthalenedisulfonate), β-CIT D-tartrate (2-β-carbomethoxy-3-β-(4-iodophenyl)tropane D-tartrate), cocaethylene (cocaine ethyl ester hydrochloride) (Research Biochemicals International, Natick, MA), (−)-cocaine hydrochloride (Mallinkrodt, St. Louis, MO), (+)-cocaine (NIDA, Rockville, MD), chlorisondamine chloride (Ciba-Geigy Corp., Summit, NJ), CPT tartrate ((−)-2β-carbomethoxy-3β-phenyltropane tartrate), dibucaine hydrochloride, dyclonine hydrochloride (Sigma Chemical Co.), GBR 12935 dihydrochloride, indatraline, mazindol, nomifensine maleate, norcocaine hydrochloride (Research Biochemicals International), prilocaine hydrochloride, proparacaine hydrochloride, quinidine hydrochloride (Sigma Chemical Co.), R(+)-SCH-23390 hydrochloride, tetracaine hydrochloride (Sigma Chemical Co.) and zimeldine dihydrochloride (Research Biochemicals International). Benztropine, BTCP, bupropion, cocaethylene, (−)-cocaine, norcocaine, zimeldine, prilocaine, quinidine, acetylprocainamide, proparacaine, dyclonine, dibucaine, and tetracaine were dissolved in sterile saline, while CFT, βCIT, CPT, GBR 12935, indatraline were dissolved in sterile water. Nomifensine (3 mg/ml) was dissolved in water following acidification with few drops of 1 N HCl and further dilutions were made in saline. Mazindol was prepared as a 10 mg/ml solution in 1 ml 1 N HCl and 9 ml saline, and further dilutions were made in saline. (+)-Cocaine was prepared as a 30 mg/ml solution in 3 ml 1 N HCl and 7 ml saline and further dilutions were made in saline.

*Data Analysis*

The maximal changes in BP within the first 30 s following injection of various doses of a given test drug were established by comparison with the corresponding preinjection baseline values. The change produced by a test drug was compared with the corresponding change produced by its vehicle using an analysis of variance for repeated measures followed by C matrix post hoc tests (56). The postchlorisondamine effects of the test drugs on BP were compared with their effects on BP prior to chlorisondamine administration by using repeated measures, paired *t*-tests. All values are expressed as mean ± SE.

## RESULTS

*Effects of Cocaine and Structurally Related Compounds*

The IV administration of (−)-cocaine (0.03–3 mg/kg) following treatment with the dopamine receptor antagonist, SCH 23390, produced dose-dependent and rapid increases in BP in conscious rats (Fig. 1). Similar to cocaine, all test drugs that are structurally related to cocaine also produced rapid pressor responses (Fig. 1). A maximal increase in BP occurred within the first 30 s following the administration of these test drugs and BP returned to baseline values within 3 min (data not shown). The threshold doses of the test drugs that produced a significant increase in BP ($p < 0.05$ to 0.001 compared to vehicle effects) were 0.03 mg/kg (−)-cocaine, 0.3 mg/kg (+)-cocaine, 0.1 mg/kg norcocaine, 0.03 mg/kg cocaethylene, 0.3 mg/

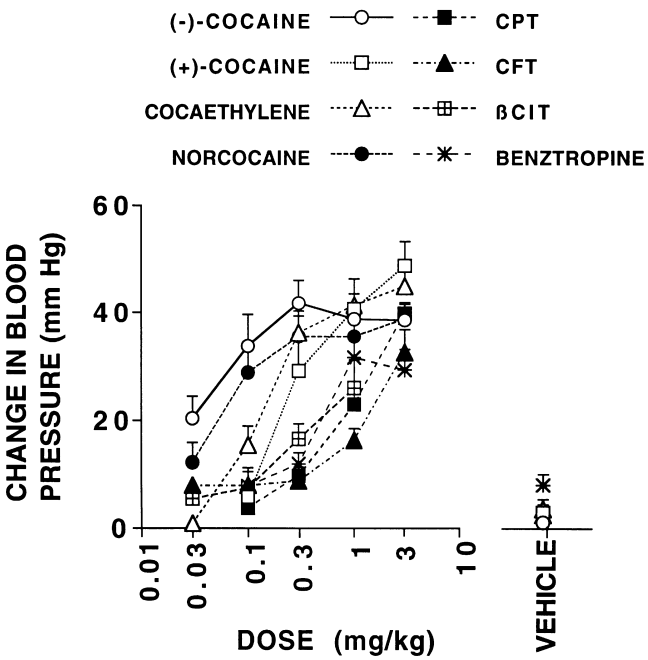


FIG. 1. Relationship between the dose (log scale) of cocaine and drugs that are structurally related to cocaine and the peak increases (within 30 s) in BP following their IV injections. Each point is the mean ± SE of results from six to nine rats.

TABLE 1

EFFECT OF CHLORISONDAMINE PRETREATMENT ON THE RAPID RESPONSE PRESSOR PRODUCED BY COCAINE AND RELATED DRUGS

| Test Drug | Dose (mg/kg) | *n* | BP (mmHg) | | | |
|---|---|---|---|---|---|---|
| | | | Before Chlorisondamine | | After Chlorisondamine | |
| | | | Basal | Change | Basal | Change |
| 1. (−) Cocaine | 3 | 5 | 94.4 ± 3.1 | 38.6 ± 2.2 | 61 ± 3.16 | 22 ± 3.5† |
| 2. (+) Cocaine | 3 | 6 | 90.2 ± 4.0 | 48.8 ± 4.6 | 57 ± 2.8 | −8.7 ± 1.5‡ |
| 3. Cocaethylene | 3 | 8 | 95 ± 3.2 | 45 ± 3.8 | 57.2 ± 1.5 | 21.4 ± 1.3‡ |
| 4. Norcocaine | 3 | 7 | 92.9 ± 2.6 | 38.9 ± 2.8 | 53.4 ± 0.9 | 4.1 ± 1.2‡ |
| 5. CPT | 3 | 5 | 91.8 ± 2.4 | 39.8 ± 2.1 | 60.2 ± 1.9 | 20.2 ± 4.5† |
| 6. CFT | 3 | 5 | 98.6 ± 4.2 | 32.6 ± 4.3 | 60 ± 1.7 | 14.6 ± 3.9* |
| 7. ßCIT | 1 | 6 | 93.7 ± 2.7 | 26 ± 5.2 | 61.7 ± 1.5 | 10 ± 2.4* |
| 8. Benztropine | 3 | 6 | 91.3 ± 2.5 | 29.8 ± 3.8 | 57 ± 2.0 | 2.3 ± 1.1‡ |
| 9. Bupropion | 3 | 6 | 90.8 ± 3.5 | 33.8 ± 4 | 54.9 ± 2.9 | −4.7 ± 1.8‡ |

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ compared to the corresponding changes in BP produced by test drugs prior to chlorisondamine administration.

kg CPT, 0.3 mg/kg CFT, 0.3 mg/kg βCIT, and 1.0 mg/kg benztropine. There were no significant differences in baseline BP prior to the administration of several doses of each test drug on any given test day. None of these test drugs produced convulsions in the dose range tested. Chlorisondamine (3 mg/kg) treatment lowered baseline BP and markedly attenuated the rapid pressor responses produced by either cocaine or the structurally related test drugs (Table 1).

*Effects of Monoamine Uptake Inhibitors Structurally Unrelated to Cocaine*

With the exception of bupropion, the IV administration of several test drugs that are structurally unrelated to cocaine, following treatment with SCH 23390, produced a small (mazindol) or no increases in BP in conscious rats (Fig. 2). Some of these test compounds, namely GBR 12935 ($p < 0.001$) and indatraline ($p < 0.05$) at 3 mg/kg doses, produced rapid (10 s), transient (<30 s), and small but significant reductions in BP. Although mazindol did produce a pressor response, the mean increase was small (<20 mmHg) and only occurred at the highest dose (3 mg/kg) tested. Bupropion (0.1–3 mg/kg), like (−)-cocaine, produced large, rapid, and dose-dependent increases in BP. The minimal dose of bupropion that produced a significant increase in BP was 0.3 mg/kg. Chlorisondamine (3 mg/kg) antagonized the rapid pressor response to bupropion (Table 1). The serotonin-selective uptake inhibitor, zimeldine, did not increase BP and, instead, at a high dose (10 mg/kg) significantly ($p < 0.01$) reduced BP (Fig. 2). This reduction in BP was brief, lasting less than 1 min. There were no significant differences in baseline BP prior to the administration of different doses of each test drug on any given test day (data not shown). None of these test drugs produced convulsions in the dose ranges tested.

*Effects of Sodium Channel Blockers*

Unlike cocaine, the IV administration of several sodium channel blockers, following treatment with SCH 23390, produced small or no increases in BP in conscious rats (Fig. 3). The maximally tolerated (nonconvulsant) doses of prilocaine (0.1–3 mg/kg), quinidine (0.3–10), acetylprocainamide (0.1–10 mg/kg), or proparacaine (0.01–0.3 mg/kg) did not significantly alter BP. The effects of higher doses of these four drugs were not tested since on pilot testing they produced convulsions. In a dose range of 0.03–0.3 mg/kg, the test drugs dyclonine, dibucaine, and tetracaine also did not increase BP, but 1 mg/kg dose, produced small but significant increases in BP ($p < 0.01$). A 3 mg/kg dose of these three drugs was not tested because pilot testing had convulsant effects. There were no significant differences in baseline BP prior to the administration of different doses of each test drug on any given test day (data not shown).

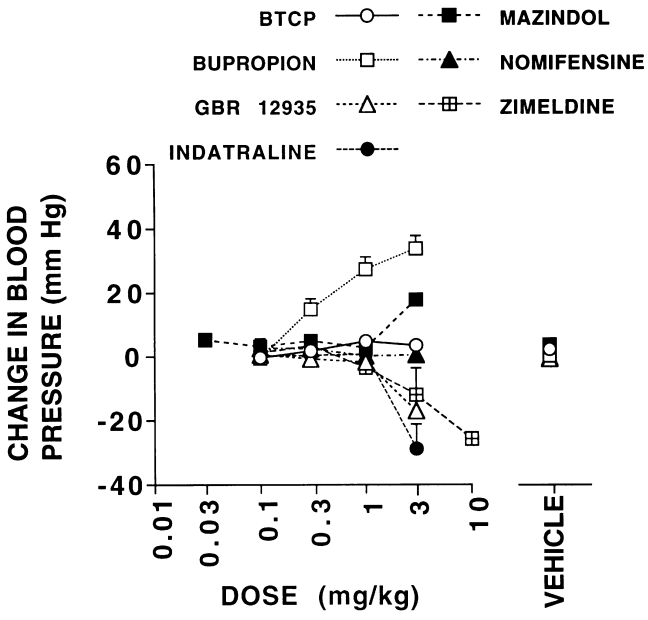


FIG. 2. Relationship between the dose (log scale) of monoamine uptake inhibitors that are structurally unrelated to cocaine and the peak changes (within 30 s) in BP following their IV injections. Each point is the mean ± SE of results from six to nine rats.

*Telemetric Recording of BP and Locomotor Activity Following IV Cocaine and CFT*

Both cocaine and CFT at a dose of 1 mg/kg produced rapid and brief increases in BP with peak effects occurring 15 s after drug injection. The increase in BP produced by cocaine was significantly ($p < 0.01$) larger than that of CFT (Fig. 4). Cocaine produced a rapid onset (within 6–8 s), brief (<30 s), and intense behavioral arousal immediately prior to and during this rapid pressor response. This arousal consisted of animals rising abruptly on all four limbs from a resting posture, followed by rapid running to the other end of the cage and intense facial and head scratching. Following CFT, animals got up on all four limbs from a resting posture. Unlike cocaine, CFT produced neither rapid running nor facial and head scratching. Following initial increases in BP, it rapidly, but only partially, returned towards baseline. Thereafter, BP remained moderatively elevated for a relatively prolonged period following both cocaine and CFT. Both cocaine and CFT also produced prolonged increases in locomotor activity. Intervention with SCH 23390 (0.03 mg/kg), antagonized the prolonged increases in locomotor activity and BP, but not the initial rapid pressor, and abrupt arousal responses produced by both cocaine and CFT (Fig. 4).

## DISCUSSION

Endogenous dopaminergic systems play an important role in the behavioral and reinforcing effects of cocaine (2,3,8, 14,15,17,42,43,45,57). In a recent study using monoamine-selective uptake inhibitors (GBR-12909, nisoxetine, and fluoxetine), we reported that the central dopaminergic systems also play a major role in mediating cocaine-induced prolonged increases in BP and HR. These prolonged increases in BP and HR produced by cocaine temporally paralleled its prolonged locomotor effects (49). We further suggested that the initial brief and abrupt behavioral arousal and the accompanying brief but large increases in BP and HR that rapidly occur following IV bolus cocaine may be independent of monoamine uptake inhibition or sodium channel blockade. In the present study the maximal increase in BP that occurred within 30 s following IV injection of test drugs in the presence of dopamine receptor blockade was used as a quantitative measure of these rapid effects. A number of test drugs with a wide range of selectivities for monoamine transporters and a number of sodium channel blockers were evaluated for their ability to produce the rapid pressor response. As reported in our previous study (49), cocaine produced an initial, rapid, and brief increase in BP in the presence of dopamine receptor blockade in the present study.

One important finding of the present study is that inhibition of dopamine, norepinephrine, or serotonin transporter

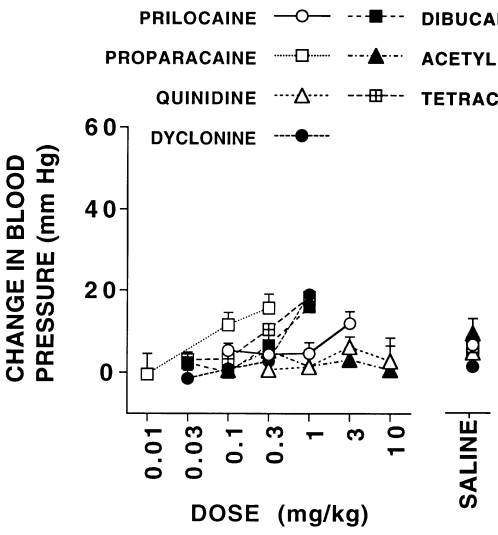


FIG. 3. Relationship between the dose (log scale) of sodium channel blockers and the peak changes (within 30 s) in BP following their IV injections. Each point is the mean ± SE of results from six to nine rats.

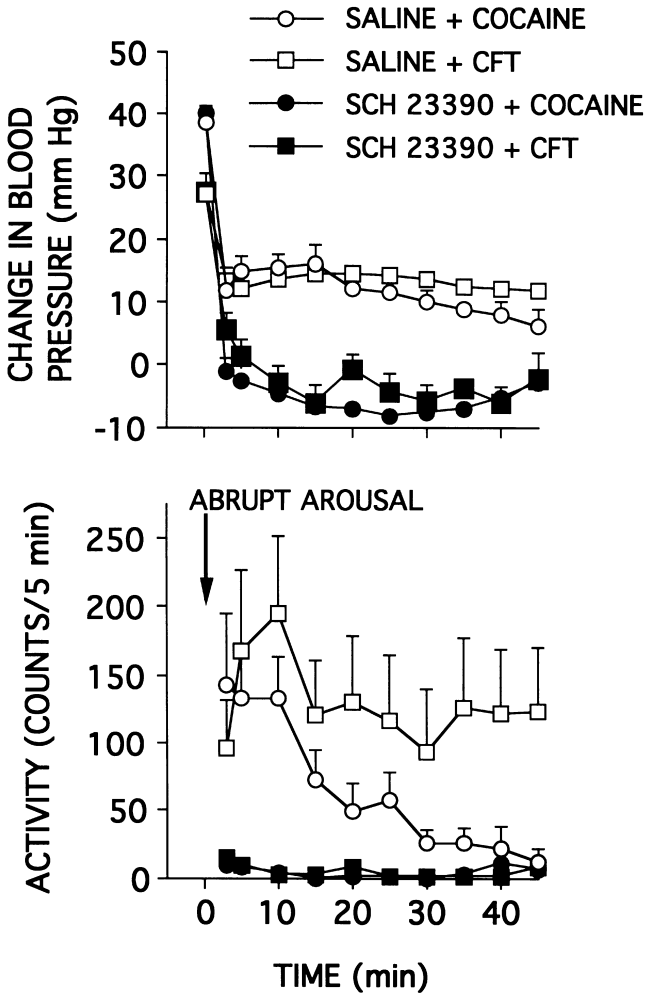


FIG. 4. The time course of BP (top panel) and locomotor (bottom panel) responses to cocaine (1 mg/kg) and CFT (1 mg/kg) following saline or SCH 23390 (0.03 mg/kg) pretreatments. Each point is the mean ± SE of results from eight rats. Besides producing prolonged locomotor activation, both cocaine and CFT produced an initial, abrupt, and brief behavioral arousal. The abrupt arousal produced by cocaine was of greater intensity than that produced by CFT. See text for detailed description of this initial arousal response. The baseline BP prior to the injection of cocaine were 93.5 ± 3.7 and 97.8 ± 2.7 mmHg on saline and SCH23390 pretreatment days. The corresponding values prior to CFT administration were 96 ± 2.8 and 95.5 ± 4.0 mmHg.

function either alone or in combination does not appear to mediate the initial, rapid, and brief pressor response to cocaine. This interpretation is based on the following observations. First, dopamine- and serotonin-selective uptake inhibitors, namely GBR-12935 and zimeldine, did not cause a rapid pressor response. These results are consistent with our previous data (49) obtained with different dopamine- and serotonin-selective uptake inhibitors, namely GBR 12909 and fluoxetine, respectively. Similarly, the norepinephrine-selective uptake inhibitors, desipramine and nisoxetine, did not produce a rapid pressor response (49,52). Second, the binding affinities of cocaine analogs, namely, CPT, CFT, and βCIT to monoamine transporters are higher than that of cocaine, while these drugs were considerably less potent than cocaine in eliciting rapid pressor responses (Fig. 1). Third, the affinities of (+) cocaine to monoamine transporters is about 150- to 500-fold less than that of (−) cocaine (34) and has been shown to be inactive in behavioral testing paradigms (44). In contrast, (+) cocaine, like (−) cocaine, clearly produced a dose-dependent rapid pressor response. Fourth, nomifensine and mazindol inhibit both dopamine and norepinephrine transporters, but they did not produce a rapid pressor effects. βCIT, an analog of cocaine, binds to both dopamine and serotonin transporters with very high affinity, but it was considerably less potent than cocaine. Finally, indatraline, which is similar to cocaine in inhibiting nonselectively all three monoamine transporter systems, did not produce a rapid pressor response in the present study. The fact that CPT, βCIT, and CFT, the long-acting analogs with slow kinetics (7,36,37), produce rapid pressor responses suggests that these initial effects to cocaine are not due to its rapid pharmacokinetics. Further, the fact that cocaine, when administered as a slow IV infusion, also produces these rapid pressor responses (49).

Another finding of the present study is that the sodium channel blocking action of cocaine per se is also not involved in triggering the rapid pressor response. This interpretation is based on the following. Several sodium channel blockers, at doses that do not evoke clinical seizures, produced either small or no increases in BP. Both rapid (lidocaine) as well as slow (quinidine) acting sodium channel blockers lacked the rapid pressor response. The sodium channel blockers that produced small, but significant, increases in BP did so at doses only two to three times less than the convulsant threshold doses. In contrast to these drugs, the threshold dose of cocaine that produces a significant rapid pressor response in conscious Sprague–Dawley rats was about 0.03 mg/kg, while a 100-fold (3 mg/kg) increase in the dose of cocaine did not produce convulsions. It is, therefore, likely that the small increases in BP produced by high doses of several sodium channel blockers is due to their nonclinical proconvulsant effects on the brain. Further, lidocaine, at doses up to 100 times greater than the threshold dose of cocaine, does not elicit a rapid pressor response (49), although it is equipotent to cocaine as a sodium channel blocker (12). Moreover, cocaethylene and norcocaine are more potent than cocaine in blocking sodium channels (18,26,58), yet these compounds were either less (cocaethylene) or equipotent (norcocaine) to cocaine in producing rapid pressor responses in the present study. There is one recent study in conscious rabbits, suggesting that the pressor response to cocaine is partly due to its sodium channel blocking property (47). But the pressor response to cocaine was observed at a 5 mg/kg dose, which also produced convulsions. In this study cocaine at nonconvulsant doses (0.2 and 1 mg/kg) did not increase BP, but instead decreased BP. It is important to note that the BP effects of cocaine in conscious rabbits appear to be qualitatively different from the reported consistent pressor responses to nonconvulsant doses of cocaine in conscious rats (21,22,51,52), dogs (46,55), squirrel monkeys (13,38,39,50), rhesus monkeys (4) and humans (10,11,16,33).

In the present study, test drugs with chemical structures similar to cocaine also produced a rapid pressor response, while several monoamine uptake inhibitors not structurally related to cocaine, with the exception of bupropion, did not produce a rapid pressor response. This suggests that cocaine and its structural analogs may share a common pharmacodynamic action mediating the rapid pressor response. The fact that bupropion, which is not structurally similar to cocaine, also elicited a rapid and brief pressor response suggests that this drug may be similar to cocaine in this regard. Alternatively, bupropion may be producing a rapid pressor response through a mechanism different from that of cocaine and its analogs. The rapid pressor responses produced by cocaine analogs and bupropion were antagonized by chlorisondamine administration. This is in agreement with several previous reports that ganglionic blockers can antagonize the pressor response to cocaine in a number of species. (5,21,22,46,51–53,55). The mechanism underlying the rapid pressor response to cocaine remains unclear. One possible mechanism that needs to be studied is an unknown complex interplay between monoamine transporter and sodium channel mechanisms. Alternatively, this action may be due to an undefined novel pharmacodynamic action of cocaine.

The data obtained from rats implanted with telemetric devices indicate that cocaine produces biphasic effects on BP and behavior. These consist of an initial, abrupt, and brief arousal associated with a rapid, large increase in BP followed by prolonged and parallel increases in BP and locomotor activity. These biphasic effects of cocaine are similar to those reported in our previous report with regard to their time course and the susceptibility of the prolonged, but not the initial effects, to blockade by a dopamine receptor antagonist (49). This hypothesis of biphasic effects of cocaine is further extended to CFT, a cocaine analog. Similar to cocaine, CFT produced biphasic effects on BP and behavior and the dopamine receptor antagonist, SCH 23390, clearly prevented the prolonged increases in BP and locomotion produced by CFT.

It is important to note certain methodological limitations of the present study. First, a cumulative dose–response study was performed by administering doses of each test drug at 20-min intervals. It is not clear as to the extent of possible contribution of within-session acute tolerance to pressor responses of the test drugs. Tolerance to the pressor effects of repeated IV doses of 1 mg/kg cocaine has been reported in rats, when cocaine is given at 5 min, but not at 2-h interdose intervals (41). Cocaine in doses less than 0.8 mg/kg IV, when administered repeatedly at 1-h intervals, does not appear to produce tolerance in conscious dogs (30). Kumor et al. (24) have reported that tolerance to cocaine's pressor actions does not develop in humans. It is likely that the occurrence of tolerance may be dependent on the dose of cocaine studied and the interdose interval, with small doses and high interdose intervals not likely producing tolerance. It is not clear whether the 20-min interdose interval in the present study was adequate to avert the manifestation of acute tolerance. Further, it is also not known whether tolerance could occur with the cocaine analogs used in the present study.

In summary, the present study suggests that inhibition of dopamine, norepinephrine, or serotonin transporter function neither alone nor in combination mediates the rapid pressor effects of cocaine. The sodium channel blocking action of co-

caine per se also does not mediate its rapid pressor effects. Prolonged increases in BP occurring after IV cocaine administration, unlike the rapid increases, are mediated by dopaminergic mechanisms.

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## REFERENCES

1. Bajaj, A. K.; Kopelman, H. A.; Wikswo, J. P., Jr.; Cassidy, F.; Woosley, R. L.; Roden, D. M.: Frequency- and orientation-dependent effects of mexiletine and quinidine on conduction in the intact dog heart. Circulation 75:1065–1073; 1987.
2. Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D.: Effects of cocaine and related drugs in nonhuman primates. III Self-administration by squirrel monkeys. J. Pharmacol. Exp. Ther. 251:150–155; 1989.
3. Britton, D. R.; Curzon, P.; Mackenzie, R. G.; Kebabian, J. W.; Williams, J. E. G.; Kerkman, D.: Evidence for involvement of both $D_1$ and $D_2$ receptors in maintaining cocaine self-administration. Pharmacol. Biochem. Behav. 39:911–915; 1991.
4. Carroll, M. E.; Krattiger, K. L.; Gieske, D.; Sadoff, D. A.: Cocaine-base smoking in rhesus monkeys: Reinforcing and physiological effects. Psychopharmacology (Berlin) 102:443–450; 1990.
5. Chen, B. X.; Wilkerson, R. D.: Role of sympathetic neurons and adrenal medulla in the cardiovascular response to cocaine in conscious, unrestrained rats. FASEB J. 6:A1177; 1992.
6. Chiueh, C. C.; Kopin, I. J.: Centrally mediated release by cocaine of endogenous epinephrine and norepinephrine from the sympathoadrenal medullary system of unanesthetized rats. J. Pharmacol. Exp. Ther. 205:148–154; 1978.
7. Cline, E. J.; Scheffel, U.; Boja, J. W.; Mitchell, W. M.; Carroll, F. I.; Abraham, P.; Lewin, A. H.; Kuhar, M. J.: In vivo binding of [$^{1}$25I]RTI-55 to dopamine transporters: Pharmacology and regional distribution with autoradiography. Synapse 12:37–46; 1992.
8. Corrigall, W. A.; Coen, K. M.: Cocaine self-administration is increased by both $D_1$ and $D_2$ dopamine antagonists. Pharmacol. Biochem. Behav. 39:799–802; 1991.
9. De Wit, H.; Wise, R. A.: Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with noradrenergic blockers phentolamine and phenoxybenzamine. Can. J. Psychol. 31:195–203; 1977.
10. Fischman, M. W.; Schuster, C. R.; Resnekov, L.; Shick, J. F. E.; Krasnegor, N. A.; Fennell, W.; Freedman, D. X.: Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch. Gen. Psychiatry 33:983–989; 1976.
11. Foltin, R. W.; Fischman, M. W.; Levin, F. R.: Cardiovascular effects of cocaine in humans: Laboratory studies. Drug Alcohol Depend. 37:193–210; 1995.
12. Garfield, J. M.; Gugino, L.: Central effects of local anesthetic agents. In: Strichartz, G. R., ed. Local anesthetics. New York: Springer Verlag; 1987:253–284.
13. Gonzalez, F. A.; Byrd, L. D.: Physiological effects of cocaine in the squirrel monkey. Life Sci. 21:1417–1424; 1977.
14. Howell, L. L.; Byrd, L. D.: Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. J. Pharmacol. Exp. Ther. 258:178–185; 1991.
15. Hubner, C. B.; Moreton, J. E.: Effects of selective $D_1$ and $D_2$ dopamine antagonists on cocaine self-administration in the rat. Psychopharmacology (Berlin) 105:151–156; 1991.
16. Javaid, J. I.; Fischman, M. W.; Schuster, C. R.; Dekirmenjian, H.; David, J. M.: Cocaine plasma concentration: Relation to physiological and subjective effects in humans. Science 202:227–228; 1978.
17. Johanson, C. E.; Fischman, M. W.: The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3–52; 1989.
18. Just, W. W.; Hoyer, J.: The local anesthetic potency of norcocaine, a metabolite of cocaine. Experientia 33:70–71; 1977.
19. Kelly, P.; Iversen, S. D.: Selective 6OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activities in rats. Eur. J. Pharmacol. 40:45–56; 1976.
20. Kennedy, L. T.; Hanbauer, I.: Sodium-sensitive cocaine binding to striatal membranes: Possible relationship to dopamine uptake sites. J. Neurochem. 41:172–178; 1983.
21. Kiritsy-Roy, J. A.; Halter, J. B.; Gordon, S. M.; Smith, M. J.; Terry, L. C.: Role of the nervous system in hemodynamic and sympathoadrenal responses to cocaine in rats. J. Pharmacol. Exp. Ther. 255:154–160; 1990.
22. Knuepfer, M. M.; Branch, C. A.: Cardiovascular responses to cocaine are initially mediated by the central nervous system in rats. J. Pharmacol. Exp. Ther. 263:734–741; 1992.
23. Koob, G. F.; Vaccarino, F. J.; Amalric, M.; Bloom, F. E.: Positive reinforcement properties of drugs: Search for neural substrates. In: Engel, J.; Oreland, L., eds. Brain reward systems and abuse. New York: Raven Press; 1987:35–50.
24. Kumor, K. M.; Shere, M. A.; Thompson, L.; Cone, E.; Mahafey, J.; Jaffe, J.: Lack of cardiovascular tolerance during intravenous cocaine infusions in human volunteers. Life Sci. 42: 2063–2071; 1988.
25. Madras, B. K.; Fahey, M. A.; Bergman, J.; Cafield, D. R.; Spealman, R. D.: Effects of cocaine and related drugs in nonhuman primates. I. [$^{3}$H]cocaine binding sites in caudate-putamen. J. Pharmacol. Exp. Ther. 251:131–141; 1989.
26. Mathews, J. C.; Collins, A.: Interactions of cocaine and cocaine congeners with sodium channels. Biochem. Pharmacol. 32:455–460; 1983.
27. Matsuzaki, M.; Spingler, P. J.; Whitlock, E. G.; Misra, A. L.; Mule, S. J.: Comparative effects of cocaine and pseudococaine on EEG activities, cardiorespiratory functions, and self-administration behavior in the rhesus monkey. Psychopharmacology (Berlin) 57:13–20; 1978.
28. Morady, F.; Dicarlo, L. A.; Baerman, J. M.; Krol, R. B.: Rate-dependent effects of intravenous lidocaine, procainamide and amiodorone on intraventricular conduction. J. Am. Coll. Cardiol. 6:179–185; 1985.
29. Muscholl, E.: Effects of cocaine and related drugs on the uptake of noradrenaline by heart and spleen. Br. J. Pharmacol. 16:352–359; 1961.
30. Pagel, P. S., Tessmer, J. P.; Warltier, D. C.: Systemic and coronary hemodynamic effects of repetitive cocaine administration in conscious dogs. J. Cardiovas. Pharmacol. 24:443–453; 1994.
31. Ranger, S.; Talajic, M.; Lemery, R.; Roy, D.; Villemaire, C.; Nattel, S.: Kinetics of use-dependent ventricular conduction slowing by antiarrhythmic drugs in humans. Circulation 83:1987–1994; 1991.
32. Reith, M. E. A.; Kim, S. S.; Lajtha, A.: Structural requirements for cocaine congeners to interact with [$^{3}$H]batrachotoxin A 20-a-benzoate binding sites on sodium channels in mouse brain synaptosomes. J. Biol. Chem. 261:7300–7305; 1986.
33. Resnick, R. B.; Kestenbaum, R. S.; Schwartz, L. K.: Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. Science 195:696–698; 1977.
34. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J.: Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
35. Roberts, D. C. S.: Neural substrates mediating cocaine reinforcement: The role of monoamine systems. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine: Pharmacology, physiology and clinical strategies. Boca Raton, FL: CRC Press; FL; 1992:73–90.
36. Scheffel, U.; Dannals, R. F.; Cline, E. J.; Ricaurte, G. A.; Carroll, F. I.; Abraham, P.; Lewin, A. H.; Kuhar, M. J.: [$^{123}$/$^{125}$I]RTI-55,

an in vivo label for the serotonin transporter. Synapse 11:134–139; 1992.
37. Scheffel, U.; Pogun, S.; Stathis, M.; Boja, J. W.; Kuhar, M. J.: In vivo labeling of cocaine binding sites on dopamine transporters with [$^3$H]WIN 35,428. J. Pharmacol. Exp. Ther. 257:954–958; 1991.
38. Schindler, C. W.; Tella, S. R.; Witkin, J. M.; Goldberg, S. R.: Effects of cocaine alone and in combination with haloperidol and SCH 23390 on cardiovascular function in squirrel monkeys. Life Sci. 48:1547–1554; 1991.
39. Schindler, C. W.; Tella, S. R.; Katz, J. L.; Goldberg, S. R.: Effects of cocaine and its quaternary derivative cocaine methiodide on cardiovascular function in squirrel monkeys. Eur. J. Pharmacol. 213:99–105; 1992.
40. Schoemaker, H.; Pimoule, C.; Arbilla, S.; Scatton, B.; Jayoy-Agid, F.; Langer, S. Z.: Sodium dependent [$^3$H]cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinson disease. Naunyn Schmiedebergs Arch. Pharmacol. 329:227–235; 1985.
41. Smith, T. L.; Callahan, M.; Williams, D.; Dworkin, S. I.: Tachyphylaxis in cardiovascular responses to cocaine in conscious rats. J. Cardiovasc. Pharmacol. 21:272–278; 1993.
42. Spealman, R. D.: Antagonism of behavioral effects of cocaine by selective dopamine receptor blockers. Psychopharmacology (Berlin) 101:142–145; 1990.
43. Spealman, R. D.; Bergman, J.; Madras, B. K.; Melia, K. F.: Discriminative stimulus effects of dopamine receptor subtypes. J. Pharmacol. Exp. Ther. 258:945–953; 1991.
44. Spealman, R. D.; Kelleher, R. T.; Goldberg, S. R.: Stereoselective behavioral effects of cocaine and a phenyltropane analog. J. Pharmacol. Exp. Ther. 225:509–514; 1983.
45. Spealman, R. D.; Madras, B. K.; Bergman, J.: Effects of cocaine and related drugs in nonhuman primates. II. Stimulant effects on schedule-controlled behavior. J. Pharmacol. Exp. Ther. 251:142–149; 1989.
46. Stambler, B. S.; Komamura, K.; Ihara, T.; Shannon, R. P.: Acute intravenous cocaine causes transient depression followed by enhanced left ventricular function in conscious dogs. Circulation 87:1687–1697; 1993.
47. Szabo, B.; Obergfell, A.; Starke, K.: Involvement of monoamine uptake inhibition and local anesthesia in the cardiovascular response to cocaine in conscious rabbits. J. Pharmacol. Exp. Ther. 273:128–137; 1995.
48. Tella, S. R.: Differential blockade of chronic vs. acute effects of intravenous cocaine by dopamine receptor antagonists. Pharmacol. Biochem. Behav. 48:151–159; 1994.
49. Tella, S. R.: Possible novel pharmacodynamic action of cocaine: Cardiovascular and behavioral evidence. Pharmacol. Biochem. Behav. 54:343–354; 1996.
50. Tella, S. R.; Schindler, C. W.; Goldberg, S. R.: The role of central and autonomic neural mechanisms in the cardiovascular effects of cocaine in conscious squirrel monkeys. J. Pharmacol. Exp. Ther. 252:491–499; 1990.
51. Tella, S. R.; Schindler, C. W.; Goldberg, S. R.: Cardiovascular effects of cocaine in conscious rats: Relative significance of central sympathetic stimulation and peripheral neuronal monoamine uptake and release mechanisms. J. Pharmacol. Exp. Ther. 262:602–610; 1992.
52. Tella, S. R.; Schindler, C. W.; Goldberg, S. R.: Cocaine: Cardiovascular effects in relation to inhibition of peripheral neuronal monoamine uptake and central stimulation of the sympathoadrenal system. J. Pharmacol. Exp. Ther. 267:153–162; 1993.
53. Tella, S. R.; Schindler, C. W.; Goldberg, S. R.: Chlorisondamine, a noncompetitive ganglionic blocker, antagonizes the cardiovascular effects of cocaine in conscious squirrel monkeys. Pharmacol. Res. 27:233–239; 1993.
54. Weiss, S. R. B.; Post, R. M.; Pert, A.; Woodward, R.; Murman, D.: Context-dependent cocaine sensitization: Differential effect of haloperidol on development vs. expression. Pharmacol. Biochem. Behav. 34:655–661; 1989.
55. Wilkerson, R. D.: Cardiovascular effects of cocaine in conscious dogs: Importance of fully functional autonomic and central nervous systems. J. Pharmacol. Exp. Ther. 246:466–471; 1988.
56. Wilkinson, L.: SYSTAT: The system for statistics. Evanston, IL: SYSTAT, Inc.; 1989.
57. Woolverton, W. L.; Kleven, M. S.: Multiple dopamine receptors and the behavioral effects of cocaine. Natl. Inst. Drug Abuse Res. Monogr. 88:160–184; 1988.
58. Xu, Y.-Q.; Crumb, W. J., Jr.; Clarkson, C. W.: A metabolite of cocaine and ethanol, is a potent blocker of cardiac sodium channels. J. Pharmacol. Exp. Ther. 271:319–325; 1994.