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Possible Novel Pharmacodynamic Action of Cocaine: Cardiovascular and Behavioral Evidence

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TELLA, S. R. *Possible novel pharmacodynamic action of cocaine: Cardiovascular and behavioral evidence.* PHARMACOL BIOCHEM BEHAV **54**(2) 343–354, 1996.—Intravenous cocaine (0.03–3 mg/kg) produced two distinct and temporally separable effects in rats. One is an initial, large, and brief increase in blood pressure (BP) and heart rate (HR) of a rapid onset (abrupt hemodynamic stimulation). A rapid, brief, and intense behavioral arousal accompanied this abrupt hemodynamic stimulation. The other effect of cocaine is a prolonged locomotor activation of a relatively slower onset. Prolonged increases in BP and HR accompanied this locomotor effect. The threshold doses of cocaine to produce abrupt hemodynamic stimulation and locomotion are 0.03 and 0.3 mg/kg, respectively. Dopamine receptor antagonists, SCH 23390 or eticlopride, at a 0.03 mg/kg dose antagonized the locomotion and the parallel prolonged increases in BP and HR, but not the initial brief behavioral arousal and abrupt hemodynamic stimulation responses to cocaine. Peripheral dopamine receptor antagonist, domperidone, altered neither behavioral nor cardiovascular effects of cocaine. Chlorisondamine (1 mg/kg), an autonomic ganglionic blocker, did not alter either the initial brief behavioral arousal or the locomotor responses to cocaine, but it prevented the cardiovascular changes that accompanied both these behavioral responses. Norepinephrine, a direct adrenergic vasoconstrictor, although produced rapid and large increase in BP, did not cause abrupt behavioral arousal or locomotor activation. Unlike cocaine, monoamine reuptake inhibitors that are selective for norepinephrine (nisoxetine, 0.1–1 mg/kg) or serotonin (fluoxetine, 0.3–3 mg/kg) produced neither brief behavioral arousal and abrupt hemodynamic stimulation nor locomotor activation. Dopamine-selective reuptake inhibitor, GBR 12909, also did not elicit the initial brief behavioral arousal and abrupt hemodynamic stimulation. But, GBR 12909, like cocaine, produced a prolonged locomotor effect and parallel increases in BP and HR. These effects of GBR 12909 were prevented by SCH 23390 and eticlopride, but not by domperidone. Similar to cocaine, cardiovascular, but not the locomotor effects of GBR 12909 were prevented by chlorisondamine. Lidocaine (0.3–3 mg/kg), a sodium channel blocker and local anesthetic, produced neither behavioral nor physiological changes. Both cocaine (3 mg/kg) and GBR 12909 (1 mg/kg) increased plasma norepinephrine and epinephrine concentrations. These increases were antagonized by both eticlopride and SCH 23390. These results indicate that behavioral and cardiovascular effects of cocaine are intricately related with respect to the molecular mechanisms involved. Two pharmacodynamic actions of cocaine appear to mediate these effects. One is a dopamine-dependent while the other is a monoamine- and sodium channel-independent novel action. The former mediates cocaine's locomotor effect and the accompanying prolonged increases in BP and HR, while the latter mediates the initial brief behavioral arousal and the accompanying abrupt hemodynamic stimulation.

Cocaine Behavior Cardiovascular effects Monoamine reuptake Sodium channel Novel pharmacodynamic action

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THE pharmacodynamic actions of cocaine are the blockade of sodium channels resulting in local anesthetic effect and the binding to monoamine transporters leading to the inhibition of presynaptic reuptake of neurally released monoamines (34,44,51,62). There is a general consensus that the inhibition by cocaine of the neuronal reuptake of dopamine leading to an enhanced dopaminergic transmission, especially in the mesocorticolimbic system, plays a major role in its reinforcing and behavioral effects (30,33,38,49,91). However, various clinical efforts to develop effective pharmacotherapy using substances that alter dopaminergic functions have resulted in conflicting data (16,24,39,77,81). One reason for such conflicting clinical outcomes may be the complexity of cocaine's pharmacological actions. For example the roles of cocaine's nondopamine actions, namely, the inhibition of presynaptic reuptake of norepinephrine and serotonin and the local anesthetic effect in its behavioral and reinforcing effects, are less clearly understood (4,15,30,36,41,47,48,50,52,63,69,78,80). Another possibility may be that cocaine possesses an additional, as yet unknown, pharmacodynamic action and that such an action working in concert with dopamine may contribute to its abuse potential.

Cocaine also strongly influences the cardiovascular system. Cocaine consistently increases mean arterial blood pressure (BP) and heart rate (HR) in humans (20,22,29,53) and in experimental animals (8,25,46,60,73,74,83). Although experimental studies revealed a major involvement of central nervous system in the pressor and tachycardiac effects of cocaine (10,11,35,74–76,83), the nature of central neurotransmitter mechanisms involved in these effects remains to be elucidated. Further, it is also not known as to how these centrally initiated cardiovascular effects of cocaine are related to its behavioral effects with respect to the specific neurobiological mechanisms involved.

Previous cardiovascular studies have shown that the effects of cocaine on BP are biphasic, consisting of an initial rapid, large, and brief increase followed by a moderate and sustained increase (37,75). One goal of the present study, using conscious rats implanted with telemetric devices, is to determine whether these two temporally distinct phases in cardiovascular alterations by cocaine share a common neurobiological mechanism or are due to a two different and independent mechanisms in the brain. Another goal of the study is to determine whether there are also two distinct behavioral counterparts to the biphasic effects of cocaine on BP. To achieve these goals, cardiovascular and concurrent locomotor effects of IV cocaine were studied in parallel with that of various monoamine reuptake inhibitors that are selective for dopamine [GBR 12909; (1,79)], norepinephrine [nisoxetine; (70,90)], and serotonin [fluoxetine; (88,89)] or sodium channel blocker and local anesthetic, lidocaine (67). Animals were also visually observed immediately following the test drug injections for any behavioral manifestations so as to determine whether there is any unique and brief behavioral counterpart to the initial rapid phase of the biphasic effect of cocaine on BP. Because dopamine has been shown to be a major mediator of cocaine's behavioral effects (30,33,38,49,91), the effects of pharmacological interventions using dopamine receptor antagonists on cocaine's biphasic cardiovascular effects and the concurrent behavioral effects were also studied. In addition, autonomic ganglionic blocker, chlorisondamine, was also used as an intervention agent to determine the changes in centrally mediated autonomic nervous system function following the test drug injections.

METHOD

Subjects and Surgical Procedures

Male Sprague-Dawley rats weighing 350–450 g (Charles River Laboratories, Inc., Wilmington, DE) were used. The animals were housed individually in temperature- and humidity-controlled rooms with a 12-h light (0700–1900 h) and dark (1900–0700 h) cycle. Food and water were available ad lib.

Rats were surgically prepared with a small plastic pedestal on the skull under pentobarbital anesthesia (50–60 mg/kg IP). Four holes were made with #60 drill bit 3 to 5 mm apart from each other. Stainless steel mounting screws (1/16″) were pushed through the holes more than half the way. Cannula pedestal was placed in between those four screws and fixed with dental cement. This plastic pedestal served as a device to connect a swivel spring through which an external tubing was passed. External tubing was connected to animal's venous catheter during experimental sessions. Seven days following this head-mount surgery, animals were implanted with transmitters (TA11PA-C40, Data Sciences International, St. Paul, MN) for the chronic telemetric measurement of BP, HR, and motor activity and venous catheters for IV administration of drugs. Telemetric recording of cardiovascular parameters provide valid and precise data and has many advantages over the indwelling catheter technique (40,61). Further, transmitters provide a means of measuring both cardiovascular and locomotor effects of drugs simultaneously in the same animal (42,93). It has been reported that 86% and 78% telemetry implants are accurate within 5 mmHg at 8 and 12 weeks, respectively, after implantation (7). However, the changes from baseline values were used for the data analysis in the present study. Surgery for transmitter implantation was performed under halothane anesthesia (2–3% in medical grade oxygen). A midline incision of 4 to 5 cm long was made on the abdomen. The descending aorta was exposed below the renal arteries. A vascular clamp was placed immediately posterior to the renal arteries. A curved 21 gauge needle was used to puncture the descending aorta anterior to the bifurcation. The catheter (length, 8 cm) of the transmitter was inserted to a distance of about 2 cm into aorta and glued with a drop of tissue adhesive (Vetbond supplied by Minimitter Company Inc. Sunriver, OR). Transmitter body (length: 2.5 cm; diameter: 1.2 cm; weight: 10 gm) was sutured to the abdominal musculature. The incision and the skin were closed by suturing and autoclips. A 25,000 U/kg IM dual penicillin was injected to safeguard against infection. The IV cannula (tygone tubing) was placed into a femoral vein and passed subcutaneously to exit skin at midscapular region. Following 7 days of postoperative recovery period, animals were acclimatized to the testing environment 90 min daily for a period of 3 weeks so as to minimize the complicating influence of stress of testing environment on cocaine's effects.

Behavioral and Cardiovascular Measurements

Daily experimental sessions lasting 90 min were conducted Monday through Friday. During the sessions, rats were placed in test cages and venous catheters were connected to external tubing as described earlier. The radiofrequency signal from the transmitter passed to a receiver (RA1310, Data Sciences International) placed under the test cage. The receiver is connected to a BCM 100 consolidation matrix (Data Sciences International), which transmitted the information to the Dataquest IV acquisition system. The Dataquest IV system con-

verted the raw telemetered data into BP, HR, and locomotor activity. Animals were also visually observed for any behavioral manifestations.

Apparatus and Experimental Procedures

Following a prolonged acclimatization to experimental environment, drug testing was started. Drug testing was done once a day for 5 days a week. Only one test drug and one intervention drug was studied on each test day. Only a single dose of a given test drug or intervention drug was administered on any given test day. Test drugs were administered as a rapid bolus over a 2 s period at 30 min into the session unless otherwise stated. Catheter line (0.25 ml volume) was loaded with the test drug (0.1–0.2 ml). At the time of injection, this catheter line preloaded with the test drug was flushed with 0.3 ml of saline over 2 s period. Intervention drugs, when required, were given 10 min prior to the test drug. All drugs were given IV in a volume of 0.3 ml/kg unless otherwise specified. There were four groups of animals.

Group 1. This group (10 animals) was used for studying the effects of various pharmacological interventions such as dopamine receptor antagonists and autonomic ganglionic blocker, chlorisondamine, on the responses to equi-effective doses of cocaine (3 mg/kg) and GBR 12909 (1 mg/kg). The sequence of drug testings was as follows. First, the influence of various dopamine receptor antagonists namely 0.1, 0.03 mg/kg of SCH 23390, 0.1, 0.03 mg/kg of eticlopride, the combination of SCH 23390 and eticlopride (0.05 mg/kg each), 0.1, 0.03 mg/kg of SCH 39166, 0.3, 0.1 mg/kg of domperidone, and the ganglionic blocker, chlorisondamine (1 mg/kg) on cocaine's responses were tested in that order. This was followed by a cocaine control response (saline pretreatment) testing. Following this cocaine testing, the influence of dopamine receptor antagonists namely, 0.1, 0.03 mg/kg of SCH 23390, 0.1, 0.03 mg/kg of eticlopride, and 0.3 mg/kg domperidone and the ganglionic blocker, chlorisondamine (1 mg/kg) on GBR 12909's responses were studied in that order. This was followed by a GBR 12909 control response (saline pretreatment) testing. Following the completion of the above testing with GBR 12909, this group of rats was also used for the dose-response study of lidocaine (0.3–3 mg/kg), nisoxetine (0.1–1 mg/kg) followed by fluoxetine (0.3–3 mg/kg), in that order. Subsequently, the dose-response testing of nisoxetine (0.1–1 mg/kg) was repeated first in the presence of 0.1 mg/kg of SCH 23390 and then in the presence of 0.1 mg/kg of eticlopride. Following this, the dose-response testing of fluoxetine (0.3–3 mg/kg) was also repeated first in the presence of 0.1 mg/kg of SCH 23390 and then in the presence of 0.1 mg/kg of eticlopride. The doses of each test compound were randomly selected during the dose-response studies.

Group 2. This group (12 animals) was used for testing the dose-response of GBR 12909 (0.1–3 mg/kg) and cocaine (0.01–3 mg/kg) in the presence and in the absence of a 0.1 mg/kg dose of SCH 23390 or eticlopride. The sequence of drug testing for this group was the following. The GBR 12909 dose-response testings were done first in the presence of SCH 23390 followed by eticlopride. Following this GBR 12909 testing, the cocaine dose-response testings were done similarly first in the presence of SCH 23390 and then eticlopride. Following this, the dose-response testing in the presence of saline was done first with GBR 12909 followed by cocaine. The doses of each test compound were randomly selected during the dose-response studies.

Group 3. This group (10 animals) was used for testing the dose response of cocaine (0.01–3 mg/kg) in the presence of 0.03 mg/kg dose of SCH 23390, 0.03 mg/kg of eticlopride or 0.3 ml/kg of saline interventions in that order. The doses of cocaine were randomly tested in each intervention. 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 (71,82). In view of this, the evaluation of the effects of dopamine receptor antagonists on cardiovascular and locomotor effects of cocaine was done first and then the control responses (saline pretreatment) to cocaine were determined in all the above three groups of rats.

Group 4. This group (eight animals) was used for testing the dose–response of bolus injections of norepinephrine (0.01–1 μg/kg) and saline (0.3 ml/kg). The saline and various doses of norepinephrine were tested on a random basis. Only one dose was studied on any given test day. Following this testing with bolus injections, this group was also tested with a slow infusion (10 ml/kg/min) of saline administered for 20 s. On a subsequent day, this group was tested with 1 mg/kg of cocaine administered as a slow infusion (10 ml/kg/min) of its dilute solution (0.3 mg/ml) for 20 s.

Doses of cocaine and nisoxetine used in the present study effectively block the monoamine reuptake mechanism (74,75). Doses of GBR 12909 (3,27,66) and fluoxetine (8,15) used are in the same range that have been shown to produce behavioral effects. Because cocaine and lidocaine are equipotent as local anesthetics (23), the maximal dose of lidocaine tested is the same as that of cocaine. The doses of SCH 23390 and eticlopride used are in the same range that have been shown to block the behavioral effects of cocaine (6,28,71,86,87). As mentioned in results section, these doses of SCH 23390 and eticlopride also block the cardiovascular responses to dopamine D_1 and D_2 agonists.

Plasma Catecholamines

The effects of cocaine (3 mg/kg) and GBR 12909 (1 mg/kg) on plasma catecholamines and the influence of dopamine receptor antagonists on these changes were investigated in separate groups of rats. These animals were implanted with silastic catheters into the right carotid artery for withdrawal of blood and into the right jugular vein for IV administration of drugs. Following 7 days of postoperative recovery period, these rats were pretreated with saline (0.3 ml/kg), SCH 23390 (0.1 mg/kg) or eticlopride (0.1 mg/kg) 10 min prior to cocaine (3 mg/kg) or GBR 12909 (1 mg/kg) injection. Blood samples of 1.5 ml each were collected immediately before and 10 min after cocaine or GBR 12909 injection. The volume of blood withdrawn was immediately replaced by an equal volume of saline. All animals were used only once. Blood samples were collected in heparinized vacutainers and centrifuged to separate the plasma. Catecholamines assays were performed by American Medical Laboratories, Inc., Chantilly, VA, using HPLC and an electrochemical detection method as described in our previous publication (75).

Drugs

The following drugs were used. Chlorisondamine chloride (Ciba-Geigy Corp., Summit, NJ), fluoxetine hydrochloride, nisoxetine hydrochloride (Eli Lilly Co., Indianapolis, IN), (−)Cocaine hydrochloride (Mallinkrodt, St. Louis, MO), fenoldopam monomethane sulfonate (SmithKline Beecham, King

of Prussia, PA), GBR 12909 dihydrochloride (1-2-(bis(4-fluorophenyl)-methoxy)-ethyl-4-(3-phenylpropyl)piperazine), R(+)-SCH 23390 hydrochloride (*R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine), domperidone, S(−)-eticlopride hydrochloride, (−)-quinpirole hydrochloride (Research Biochemicals Inc., Natick, MA), SCH 39166 ((−)-trans-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-N-methyl-[^{3}H]-benzo(d)naphtho-(2,1-b)azepine) (Schering Corporation, Bloomfield, NJ), lidocaine hydrochloride, *l*-phenylephrine hydrochloride (Sigma Chemical Co., St. Louis, MO), *l*-norepinephrine bitartrate (Winthrop Pharmaceuticals, New York, NY), *dl*-isoproterenol hydrochloride (Sterling-Winthrop Research Institute, Rensselaer, NY). Fluoxetine and domperidone were dissolved in 0.85% lactic acid. GBR 12909 was dissolved (6.6 mg/ml) in sterile water with the aid of mild heating and sonification, and further dilutions were made in sterile water as appropriate. All other drugs were dissolved in sterile saline. GBR 12909 was given IV in a volume of 0.3 to 0.45 ml/kg. All drug solutions except cocaine were freshly prepared. A 30 mg/ml cocaine hydrochloride stock solution was prepared and daily dilutions were made as appropriate. Doses of domperidone, SCH 39166, and norepinephrine are expressed as bases, while all other drugs are expressed as salt.

Data Analysis

Locomotor activity (counts), BP (mmHg), and HR (beats/min) were analyzed by analysis of variance with follow up tests (C matrix) for determining individual effects (84). A paired *t*-test was also used where appropriate. Changes in plasma catecholamines (pg/ml) were analyzed by one-way analysis of variance followed by Tukey test for individual group comparisons. All the data are expressed as mean ± 1 SE.

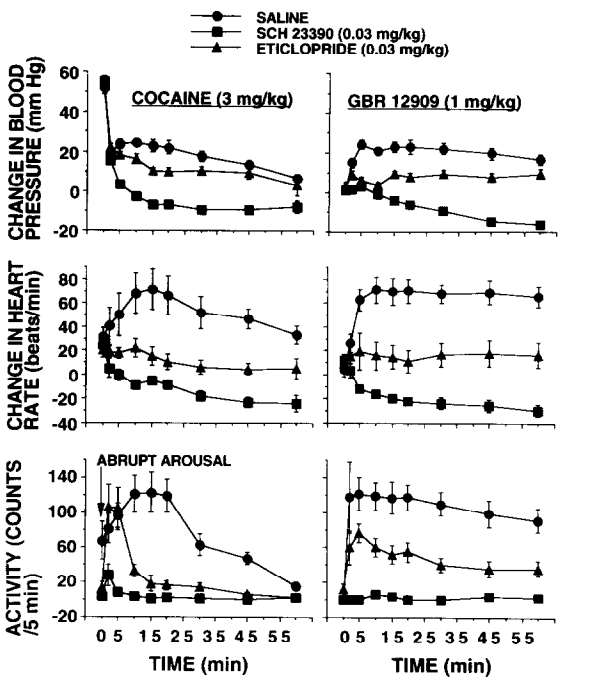

FIG. 1. The time course of blood pressure (top panels), heart rate (middle panels), and locomotor (bottom panels) responses to 3 mg/kg cocaine (left panels) and 1 mg/kg GBR 12909 (right panels) following saline (circles), SCH 23390 (0.03 mg/kg) (squares), or eticlopride (0.03 mg/kg) (triangles) pretreatments. Each point is mean of 10 rats. Besides producing prolonged locomotor activation, cocaine, unlike GBR 12909, also produced an initial, abrupt, brief, and intense behavioral arousal. See text for a detailed description of this initial arousal response to cocaine.

RESULTS

Cocaine (0.03–3 mg/kg) on IV administration produced rapid, brief, and large increases in BP and HR (abrupt hemodynamic stimulation) in rats (Figs. 1 and 2). A brief and intense behavioral arousal accompanied the abrupt hemodynamic stimulation. This behavioral arousal consisted of animals getting up abruptly on all four limbs from resting posture followed by rapid facial and head scratching and/or rapid running to the other end of the cage (at high doses of 0.3–3 mg/kg). Following the rapid running, there was a brief pause during which animals stood still for few seconds. These initial behavioral and physiological events are shown in Table 1. The rapid increases in BP during this abrupt hemodynamic stimulation phase peaked at 15 s following cocaine injections, and these were dose dependent (Figs. 1 and 2). In contrast to BP, the time of peak increase in HR was not monotonically dependent on the dose of cocaine. Indeed, the dose of cocaine vs. the increase in HR at 30 s following its injection revealed an inverted U-shaped dose response curve (Fig. 2). Although higher doses produced some increases in HR at 30 s after injection, maximal increases did not occur until later. The increase in HR produced by 3 mg/kg dose of cocaine at 30 s time point is not significantly different from that of saline. The 0.03 mg/kg was a threshold dose of cocaine that produced behavioral arousal and significant ($p < 0.01$) increases in BP and HR as compared to the corresponding responses to saline (5 ± 2 mmHg and 21 ± 5 beats/min) (Fig. 2).

Besides producing the initial abrupt hemodynamic stimulation and the accompanying brief behavioral arousal, cocaine at high doses (0.3–3 mg/kg) subsequently caused a gradual, prolonged, and dose-dependent locomotor activation (Table 1). Following the initial rapid increase, BP returned to baseline values within 1 min at low doses of cocaine (0.03–0.1), while at high doses (0.3–3 mg/kg) the recovery was partial and BP remained moderately elevated above baseline for a prolonged period in parallel with locomotion (Fig. 1; the data for low doses are not shown). Similarly, the high (0.3–3 mg/kg), but not the low (0.03–0.1 mg/kg), doses of cocaine produced prolonged increases in HR that remained elevated in parallel with its locomotor effects. In view of this biphasic nature of the behavioral and physiological responses to cocaine, the increases in BP and HR at a selected time point with in the time course of locomotor activation (10 min following cocaine injection) were also determined for further analysis. The magnitudes of these prolonged increases in BP and HR were dose dependent (Fig. 2).

Unlike cocaine, GBR 12909 (0.1–3 mg/kg) produced neither the initial abrupt hemodynamic stimulation (Figs. 1 and 3) nor the initial brief behavioral arousal. However, similar to cocaine, GBR 12909 produced a gradual (starting at 30 to 45 s after injection) and prolonged locomotion and parallel increases in BP and HR (Fig. 1). The high (3 mg/kg) dose of GBR 12909 produced an intense stereotypy and, thus, contributed to reduced activity counts as compared to its low (1 mg/kg) dose (Fig. 3). Dopamine D_1 receptor antagonist, SCH 23390 (0.03–0.1 mg/kg), or D_2 receptor antagonist, eticlopride (0.03–0.1 mg/kg), but not the peripheral dopamine D_2 recep-

tor antagonist, domperidone (0.3 mg/kg), antagonized the cardiovascular and the locomotor effects of 1 mg/kg dose of GBR 12909 (Table 2). In the presence of a fixed dose (0.1 mg/kg) of SCH 23390 or eticlopride, there were clear downward shifts in the GBR 12909 dose-response curves as compared to its corresponding control dose-response curves obtained in the presence of saline (Fig. 3). Chlorisondamine (1 mg/kg), an autonomic ganglionic blocker, antagonized the increases in BP and HR without altering the locomotor activity produced by 1 mg/kg dose of GBR 12909 (Table 2).

The effects of dopamine receptor antagonists on the locomotor and the accompanying cardiovascular responses to equi-effective (as assessed by the increases in BP and HR at 10 min following drug injection and locomotor activity) doses of cocaine and GBR 12909 were similar (Figs. 1, 2, 3, and Table 2). The dopamine receptor antagonists, SCH 23390, SCH 39166, or eticlopride, at both low (0.03 mg/kg) and high (0.1 mg/kg) doses, and the combination of SCH 23390 (0.05 mg/kg) and eticlopride (0.05 mg/kg) antagonized the locomotor effect and the parallel increases in BP and HR produced by 3 mg/kg cocaine (Table 2). These antagonists at low dose (0.03 mg/kg) prevented neither the rapid running of the initial behavioral arousal response nor the accompanying rapid increase in BP of the abrupt hemodynamic stimulation response to 3 mg/kg cocaine. These antagonists at high (0.1 mg/kg) doses, though prevented rapid running, did not alter the rapid

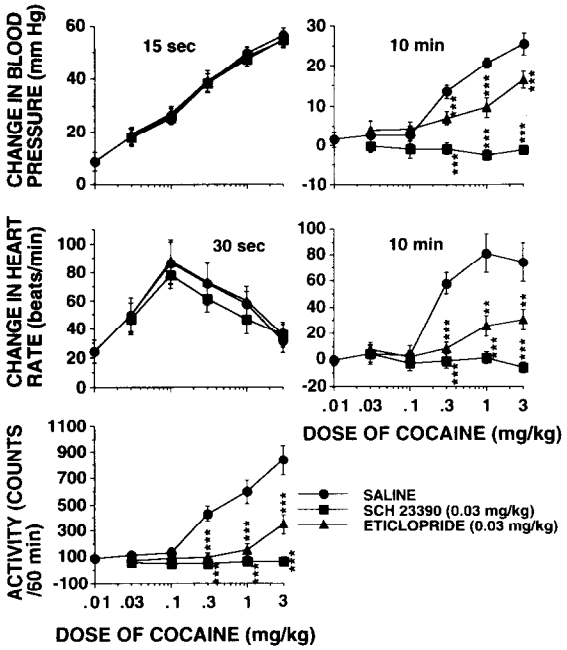

FIG. 2. Relationships of the log dose of cocaine vs. blood pressure (top panels), heart rate (middle panels), and locomotor (bottom panel) responses following saline (circles), SCH 23390 (0.03 mg/kg) (squares), or eticlopride (0.03 mg/kg) (triangles) pretreatments. Each point is mean of 10 rats and brackets show standard errors. $^{**}p < 0.01$, $^{***}p < 0.001$ as compared to the corresponding responses on saline pretreatment days. The blood pressure and heart rate responses shown in the top and middle left panels represent the changes that corresponded temporally to cocaine's abrupt hemodynamic stimulation effect, while the corresponding responses shown in the right panels represent changes that temporally corresponded to cocaine's locomotor effect.

increase in BP. An occasional animal produced a single, low-pitched vocalization following 3 mg/kg cocaine in the presence of these high doses (0.1 mg/kg) of dopamine receptor antagonists. Peripheral dopamine receptor antagonist, domperidone, failed to antagonize both behavioral and cardiovascular effects of 3 mg/kg cocaine (Table 2). Chlorisondamine altered neither the initial brief behavioral arousal nor the prolonged locomotor effects of 3 mg/kg cocaine. It did, however, prevent the cardiovascular changes that accompanied both these behavioral effects of cocaine (Table 2).

The low dose (0.03 mg/kg) of SCH 23390 or eticlopride did not prevent the initial brief behavioral arousal and the accompanying rapid increases in BP and HR (Fig. 2) of the abrupt hemodynamic stimulation produced by the entire dose range of cocaine tested. However, the high doses (0.1 mg/kg) of SCH 23390 or eticlopride did prevent the brief behavioral arousal, but not the rapid increases in BP and HR (data not shown) produced by the entire dose range of cocaine tested. None of the dopamine receptor antagonists altered baseline BP and HR (data not shown) as compared to saline tested (92 ± 2 mmHg; 277 ± 9 beats/min) days. Chlorisondamine significantly ($p < 0.001$) reduced the baseline BP (63 ± 2 mmHg). Cocaine (3 mg/kg) and GBR 12909 (1 mg/kg) increased plasma catecholamines. These increases were attenuated (cocaine) or prevented (GBR 12909) by SCH 23390 or eticlopride (Table 3). There were no significant differences in baseline plasma catecholamines among these groups.

Nisoxetine (0.1–1 mg/kg), fluoxetine (0.3–3 mg/kg), and lidocaine (0.3–3 mg/kg) produced neither behavioral arousal and abrupt hemodynamic stimulation nor the locomotor activation. Fluoxetine (3 mg/kg) significantly ($p < 0.01$) increased BP (21 ± 2 mmHg), but not HR, as compared to its lactic acid (0.85%) vehicle (10 ± 2 mmHg). The 0.1, 0.3, and 1 mg/kg doses of nisoxetine also produced significant ($p < 0.05$) increases in BP of 11.3 ± 1, 17 ± 2, and 24 ± 3 mmHg, respectively, as compared to saline responses (6.8 ± 2 mmHg). Nisoxetine at 1 mg/kg dose produced a brief (3 ± 1 min) reduction ($p < 0.01$) in HR of 27 ± 5 beats/min. Unlike cocaine, the increases in BP were gradual with maximal responses occurring at 40 ± 11 and 44 ± 8 s following the injections of nisoxetine (1 mg/kg) and fluoxetine (3 mg/kg), respectively. The corresponding mean durations were 5 ± 1 and 12 ± 2 min. These cardiovascular responses to nisoxetine (1 mg/kg) and fluoxetine (3 mg/kg) were prevented by neither SCH 23390 (0.1 mg/kg) nor eticlopride (0.1 mg/kg) (data not shown). Lidocaine (0.3–3 mg/kg), unlike cocaine, produced no change in BP, HR, and behavior (data not shown).

Norepinephrine (0.01–1 μg/kg) produced a rapid and dose-dependent increase in BP. The peak effects occurred between 5 to 7 s following norepinephrine injections and lasted between 30 s to 4 min, depending on the dose. The peak increases in BP produced by 0.01, 0.03, 0.1, 0.3, and 1 μg/kg doses of norepinephrine were 5.6 ± 2.2, 15.5 ± 2.1, 30 ± 2.3, 46.8 ± 2.7, and 59.4 ± 3.3 mmHg, respectively. The corresponding control response to saline was 3.6 ± 1.8 mmHg. The changes in HR produced by 0.01, 0.03, 0.1, 0.3, and 1 μg/kg doses of norepinephrine were 13.4 ± 5.3, −5.8 ± 5.5, −14.4 ± 12, −54.9 ± 7.8, and −101 ± 11.8 beats/min, respectively. The corresponding control response to saline was 11 ± 6.1 beats/min. Norepinephrine, unlike cocaine, elicited neither the rapid and abrupt facial and head scratching nor abrupt running to the other end of the cage. The locomotor activity counts for 60 min following 0.01, 0.03, 0.1, 0.3, and 1 μg/kg doses of norepinephrine were 183 ± 40, 183 ± 41, 150 ± 45, 223 ± 48, and 288 ± 58, respectively. These activity

TABLE 1

BEHAVIORAL AND CARDIOVASCULAR EFFECTS OF IV COCAINE IN CONSCIOUS RATS

Cocaine Dose (mg/kg)	Cardiovascular and the Salient Behavioral Characterstics of Abrupt Hemodynamic Stimulation and Behavioral Arousal§	Locomotor activity†*		
		Magnitude (Counts/60 min)	Onset (sec)	Duration (min)
Saline	None	95 ± 37	–	–
0.03	Getting up abruptly‡ and rapid facial scratching Rapid increase in BP and HR	71 ± 17	–	–
0.1	Getting up abruptly‡ and rapid facial and head scratching Rapid increase in BP and HR	188 ± 31	–	–
0.3	Getting up abruptly‡ and rapid running to the other end of the cage and rapid facial and head scratching Rapid increase in BP and HR	367 ± 63**	46 ± 6	14.4 ± 2
1	Getting up abruptly‡ and rapid running to the other end of the cage and rapid facial and head scratching Rapid increase in BP and HR	563 ± 70***	38 ± 4	31 ± 3
3§	Getting up abruptly‡ and extremely rapid running to the other end of the cage with 1 or 2 jumps Rapid increase in BP	855 ± 72***	25 ± 2	56 ± 2.4

†Values are expressed as mean ± SE. $p < 0.01$; $p < 0.001$ as compared to the response to saline. ‡Getting up abruptly on all four limbs from resting posture. The resting postures consisted of lateral fetal position and prone position. §There was no siginifcant increase in HR within 30 s following 3 mg/kg cocaine injection. *The onset of behavioral changes was 6–8 s and lasted between 5 to 30 s. The onset of increase in BP and HR was 10 s. At low doses (0.03–1 mg/kg) of cocaine BP and HR returned to baseline within a minute, while at high doses (0.3–3 mg/kg) the recovery of BP to basal levels was partial and a moderate elevation in BP and a large increase in HR continued to persist in parallel with locomotor activation.

counts were not significantly different from the saline (184 ± 44) response.

Similar to the 2 s bolus injection, the 1 mg/kg dose of cocaine when given as a slow infusion over 20 s from a dilute solution (0.3 mg/ml) continues to produce the initial intense and brief behavioral arousal and the abrupt hemodynamic stimulation (Fig. 4). The behavioral arousal consisted of rapid facial and head scratching and rapid running to the other end of the cage. The initial, rapid increases in BP and HR corresponding to the abrupt hemodynamic stimulation were 48.8 ± 4.2 mmHg and 45.4 ± 7.8 beats/min, respectively. These increases by cocaine were significantly ($p < 0.05$) different from the corresponding responses to saline, which were 0.6 ± 2.8 mmHg and 20.9 ± 5.6 beats/min. The behavioral arousal occurred between 6 to 8 s, while the maximal increases in BP occurred between 15 to 18 s following the commencement of cocaine infusion. The slow infusion of cocaine, similar to its bolus injection, besides producing the initial abrupt hemodynamic stimulation also elicited sustained increases in BP and HR (Fig. 4). For example, at 10 min following cocaine infusion, there were increases in BP of 17.9 ± 2.7 mmHg and in HR of 41 ± 11 beats/min over its preinfusion baseline values. These increases following cocaine infusion were significantly ($p < 0.05$) different from the corresponding responses of −1 ± 1.7 mmHg and 0.5 ± 5 beats/min following saline control infusion. Similarly, following the initial intense and brief behavioral arousal, cocaine infusion also produced a significant ($p < 0.01$) and prolonged locomotor activation (543 ± 97 counts/60 min) as compared to saline control infusion (121 ± 42 counts/60 min) (Fig. 4).

Effectiveness of the present doses of antagonists in blocking their respective receptors was verified in a separate group of 10 rats using standard receptor agonists. These animals were implanted with arterial and venous catheters, as described in our previous publication (74). Chlorisondamine (1 mg/kg) reversed the phenylephrine-induced (30 μg/kg) reflex bradycardia (−109 ± 8.3 beats/min) to a tachycardia (50.1 ± 6.1 beats/min). Eticlopride (0.1 mg/kg) prevented the pressor response to dopamine D_2 receptor agonist, quinpirole (30 μg/kg/min for 10 min), from a control value of 17.8 ± 1.9 to −5 ± 2.6 mmHg and antagonized its tachycardiac response from 75 ± 12.7 to −11 ± 10.9 beats/min. SCH 23390 (0.1 mg/kg) antagonized the depressor response to dopamine D_1 receptor agonist, fenoldopam (3 μg/kg/min for 10 min) in ganglionic blocked (by pretreatment with 1 mg/kg of chlorisondamine) animals from a control value of −20.7 ± 1.5 to −2.5 ± 2.3 mmHg. Doses of domperidone used are within the ranges of doses that have been shown to block the peripheral dopamine D_2 receptors (9,17). Pressor response to 0.2 μg/kg dose of norepinephrine (36.7 ± 3.7 mmHg) and the depressor response to 1 μg/kg dose of isoproterenol (−33 ± 1 mmHg) were altered by neither 0.1 mg/kg of SCH 23390 (38.5 ± 3.5; −36 ± 2.2 mmHg), 0.1 mg/kg of eticlopride (39 ± 3.1; −34.8 ± 1.1 mmHg), nor 0.3 mg/kg of domperidone (35.1 ± 4.2; −32.1 ± 2.1 mmHg). These data with norepinephrine and isoproterenol indicate that the doses of dopamine receptor antagonists used in the present study do not alter the adrenoceptor mediated cardiovascular responses.

DISCUSSION

The present behavioral and cardiovascular data indicate that cocaine elicits two distinct and temporally separable effects in conscious rats: 1) one is a monoamine- and sodium channel-independent effect of a rapid onset. This is comprised of a brief and intense behavioral arousal associated with rapid and large increases in BP and HR (abrupt hemodynamic stimulation). The behavioral arousal consisted of animals getting

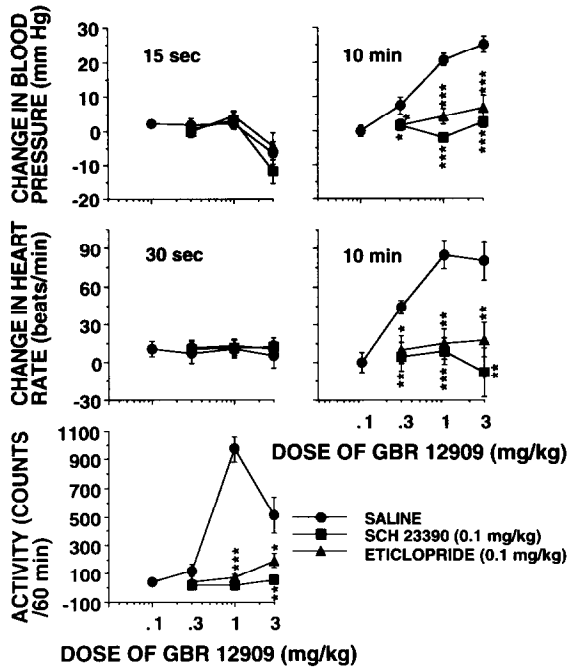

FIG. 3. Relationships of the log dose of GBR 12909 vs. blood pressure (top panels), heart rate (middle panels), and locomotor (bottom panel) responses following saline (circles), SCH 23390 (0.1 mg/kg) (squares), or eticlopride (0.1 mg/kg) (triangles) pretreatments. Each point is mean of 12 rats and brackets show standard errors. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ as compared to the corresponding responses on saline pretreatment days. The blood pressure and heart rate responses shown in the top and middle left panels represent the changes that corresponded temporally to cocaine's abrupt hemodynamic stimulation effect, while the corresponding responses shown in the right panels represent changes that temporally corresponded to GBR 12909's locomotor effect.

up abruptly from resting posture, rapid facial and head scratching, and/or rapid running to the other end of the cage. This behavioral arousal could not be quantified for the following reasons. Firstly, the low doses of cocaine (0.03–0.1 mg/kg) elicited strong behavior involving intense and rapid facial and head scratching with no running activity. The transmitters used in the present study do not measure head movements. A change in the distance between the animal position with respect to the receiver is needed for the recording of activity counts. Secondly, the intensities of abrupt and rapid running produced by high doses of cocaine (0.3–3 mg/kg) varied by the rapidity with which the animal ran rather than the total length (usually one cage length) covered. Transmitters do not measure the rate of change in motion. Finally, the rapid running activity is very brief (about a second) in duration to make any meaningful quantification. 2) The other effect of cocaine is a dopamine-mediated response of a slower onset. This consisted of prolonged and parallel increases in BP, HR and locomotion.

Monoamine- and Sodium Channel-Independent Behavioral and Cardiovascular Effects of Cocaine

GBR 12909, a dopamine-selective reuptake inhibitor, shares cocaine's prolonged effect on BP, HR, and locomotion, but not its brief abrupt hemodynamic stimulation and the accompanying abrupt behavioral arousal response. Dopamine D_1 receptor antagonist, SCH 23390, or D_2 receptor antagonist, eticlopride, at 0.03 mg/kg dose markedly antagonized cocaine's prolonged locomotor effect and the parallel prolonged increases in BP and HR, but did not alter the initial brief behavioral arousal and the accompanying abrupt hemodynamic stimulation. These antagonists at high dose (0.1 mg/kg), although prevented the initial behavioral arousal response, but did not alter the rapid increases in BP and HR of the abrupt hemodynamic stimulation phase. These findings suggest that the initial abrupt hemodynamic stimulation and the accompanying brief behavioral arousal produced by cocaine is a dopamine-independent action. The prevention produced by high doses of dopamine receptor antagonists of cocaine's brief behavioral arousal response may be due to cataleptic effects of these drugs. Unlike cocaine, nisoxetine, a norepinephrine-selective reuptake inhibitor, fluoxetine, a serotonin-selective reuptake inhibitor and lidocaine, a sodium channel blocker, failed to produce abrupt hemodynamic stimulation and behavioral arousal responses. Desipramine, another norepinephrine-selective reuptake inhibitor, also does not alter BP and HR (75). Similarly, zimeldine, another serotonin-selective reuptake inhibitor, and indatraline, which inhibits dopamine, serotonin, as well as norepinephrine transporters, failed to increase BP and HR (Tella, in preparation). Further, (+)-cocaine is only about six times less potent than (−)-cocaine in producing abrupt hemodynamic stimulation (Tella, in preparation), while it has about 150 to 500 times less affinity to monoamine transporters than that of (−)-cocaine (44,54). These findings collectively suggest that the cocaine's abrupt hemodynamic stimulation and the accompanying intense behavioral arousal responses are not due to its known actions on either norepinephrine, serotonin, and dopamine transporters or sodium channels. These initial effects of cocaine appear to be due to as yet undefined novel pharmacodynamic action of cocaine.

Lidocaine, unlike cocaine, did not increase BP and HR in the present study. This is consistent with a number of previous studies reporting that lidocaine at subconvulsive doses produces either minimal or no effects on BP and HR in conscious rats (43,92), dogs (19,45), rabbits (2), sheep (56), and humans (21). In contrast to these findings, there are also reports in the literature that lidocaine increases BP in humans (5,31) and dogs (32). One possible factor for these contrasting reports may be due to the dose of lidocaine tested. In fact, it has been shown recently that lidocaine at subconvlusive dose produces minimal cardiovascular effects in conscious sheep, while at convulsive doses, it increases BP in the same species (56). Similar dose-dependent qualitative changes in BP were reported in conscious dogs (19,26) and humans (85). However, more importantly, Fischman and colleagues (21), using equal doses of cocaine and lidocaine, have reported that the behavioral or cardiovascular profile of action of cocaine was significantly different from that produced by lidocaine and placebo injection, whereas the corresponding effects of lidocaine were indistinguishable from those of placebo in normal human volunteers.

It may be argued that the initial abrupt hemodynamic stimulation and the accompanying behavioral arousal produced by cocaine is also a dopamine-mediated response, and the lack of these rapid behavioral and hemodynamic responses to GBR 12909 may be due to its slower penetration into brain as compared to cocaine. However, it is unlikely that such is the case

TABLE 2

EFFECTS OF VARIOUS PHARMACOLOGICAL INTERVENTIONS ON CARDIOVASCULAR AND LOCOMOTOR EFFECTS PRODUCED BY COCAINE AND GBR 12909 IN CONSCIOUS RATS

	Cocaine (3 mg/kg)				GBR 12909 (1 mg/kg)			
	Change in BP (mmHg)		Peak Change in HR (Beats/min) at 10–15 min After Cocaine Injection	Activity (Counts/60 min)	Change in BP (mmHg)		Peak Change in HR (Beats/min) at 10–15 min After GBR 12909 Injection	Activity (Counts/60 min)
Intervention Drug (mg/kg)	At 15 s After Cocaine Injection	At 10 min After Cocaine Injection			At 15 s After GBR 12909 Injection	At 10 min After GBR 12909 Injection		
Saline*	55 ± 3	23 ± 3	77 ± 18	815 ± 101	2 ± 2	24 ± 2	86 ± 11	1102 ± 141
SCH 23390 (0.03)	55 ± 3	−3 ± 1†	7 ± 11†	23 ± 5†	6 ± 3	−3 ± 2†	9 ± 11†	14 ± 8†
SCH 23390 (0.1)	56 ± 4	1 ± 2†	−13 ± 10†	5 ± 2†	5 ± 3	−1 ± 1†	12 ± 11†	5 ± 4†
Eticlopride (0.03)	54 ± 2	14 ± 2‡	36 ± 9	228 ± 46†	5 ± 2	8 ± 4‡	41 ± 16	283 ± 79†
Eticlopride (0.1)	56 ± 3	7 ± 2§	22 ± 10*	18 ± 6†	5 ± 2	4 ± 3†	19 ± 17‡	62 ± 27†
SCH 23390 (0.05) + eticlopride (0.05)	53 ± 2	−6 ± 2†	−22 ± 10†	3 ± 1†	–	–	–	–
SCH 39166 (0.03)	52 ± 4	10 ± 1‡	29 ± 16	289 ± 37†	–	–	–	–
SCH 39166 (0.1)	55 ± 3	7 ± 3‡	15 ± 16§	100 ± 42†	–	–	–	–
Domperidone (0.1)	51 ± 3	24 ± 2	87 ± 11	736 ± 187	–	–	–	–
Domperidone (0.3)	52 ± 3	22 ± 2	80 ± 11	727 ± 106	0 ± 1	21 ± 3	98 ± 9	1111 ± 170
Chlorisondamine (1)	2 ± 3†	−2 ± 3†	14 ± 15‡	679 ± 88	−21 ± 2†	0 ± 2†	−1 ± 18‡	902 ± 201

*The volume of saline injected was 0.3 ml/kg. The number of animals tested with each drug ranged from 7 to 10. Values are expressed as mean ± SEM. Values in parentheses indicate the doses of drugs used. †$p < 0.01$; ‡$p < 0.05$; §$p < 0.001$ as compared to corresponding responses after saline intervention.

for the following reasons. First, dopamine receptor antagonists did not alter the rapid increases in BP and HR of abrupt hemodynamic stimulation produced by the entire dose range of cocaine tested. Secondly, recent cumulative dose-response studies revealed that the drugs that are structurally related to cocaine (cocaethylene, norcocaine, (+)-cocaine, CPT, β-CIT, and CFT) produce abrupt hemodynamic stimulation, while the dopamine reuptake inhibitors that are structurally unrelated to cocaine (BTCP, indatraline, GBR 12935, nomifensine) do not elicit this response in rats pretreated with dopamine receptor antagonist, SCH 23390 (Tella, in preparation). The fact that the CPT, β-CIT, and CFT, the long-acting analogs of cocaine with slower kinetics (12,57,58), also produce abrupt hemodynamic stimulation suggests that these initial effects to cocaine are not due to its rapid pharmacokinetics.

The results obtained using slow infusion of cocaine indicate that the abrupt hemodynamic stimulation is not unique to the rapid injection of cocaine administered as a bolus over 2-s period. For example, the 1 mg/kg of cocaine administered over 20 s as a slow infusion of its dilute solution (0.3 mg/ml) continued to elicit rapid and abrupt increases in BP and behavioral arousal. This data also rules out the possibility that the abrupt effect is due to the use of concentrated cocaine solution. It may be argued that the rapid increase in BP produced by cocaine may be causing a startle response and, thus, causing the initial abrupt behavioral arousal of the animal. However,

TABLE 3

EFFECTS OF COCAINE AND GBR 12909 ON PLASMA CATECHOLAMINES (pg/ml) AND THEIR ALTERATION BY PRETREATMENT WITH DOPAMINE RECEPTOR ANTAGONISTS

	Cocaine (3 mg/kg)		GBR 12909 (1 mg/kg)	
Intervention Drug (mg/kg)	Basal	Change	Basal	Change
Norepinephrine:				
Saline	347 ± 26	271 ± 44	371 ± 19	125 ± 30
SCH 23390 (0.1)	349 ± 37	48 ± 44*	413 ± 34	−130 ± 49*
Eticlopride (0.1)	323 ± 33	100 ± 58†	382 ± 34	−85 ± 76†
Epinephrine:				
Saline	310 ± 38	467 ± 75	242 ± 32	275 ± 60
SCH 23390 (0.1)	295 ± 41	160 ± 69†	329 ± 52	−61 ± 57‡
Eticlopride (0.1)	241 ± 35	207 ± 71†	303 ± 66	36 ± 42†

*$p < 0.01$; †$p < 0.05$; ‡$p < 0.001$ as compared to the corresponding values in saline (0.3 ml/kg) control group. There were 6 to 10 animals in each group. Values are expressed as mean ± SEM.

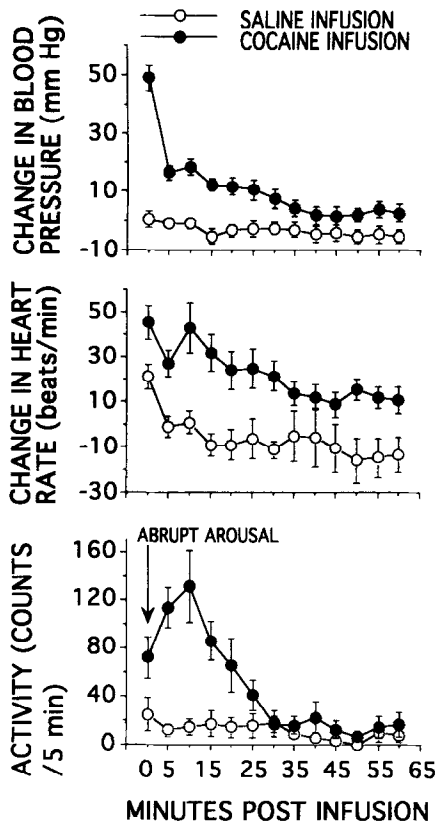

FIG. 4. The time course of blood pressure (top panel), heart rate (middle panel), and locomotor (bottom panel) responses to slow infusions (over 20 s) of 1 mg/kg cocaine (closed circles) or saline (open circles). Each point is mean of eight rats, and brackets show standard errors. Besides producing a prolonged locomotor activation, cocaine also produced an initial, abrupt, brief, and intense behavioral arousal. See text for a detailed description of this initial arousal response to cocaine.

this is unlikely due to the following reasons. First, the time course of events suggests that the onset of abrupt behavioral arousal precedes the onset and the time of peak increase in BP. Second, chlorisondamine, although it blocked the initial rapid increase in BP, did not prevent the rapid facial and head scratching and abrupt running of the abrupt behavioral arousal phase. Third, norepinephrine produces large increase in BP with a onset that is faster than that of cocaine. The maximal increase produced by norepinephrine is comparable to that produced by cocaine. Yet norepinephrine did not elicit the initial intense and abrupt behavioral arousal as seen with cocaine. These results clearly indicate that the abrupt behavioral arousal is not secondary to the rapid increase in BP produced by cocaine. Rather, the intense abrupt behavioral arousal is causing the initial rapid increase in BP.

A large body of evidence indicates that the central nervous system plays an important role in cocaine's pressor and tachycardiac effects. For example, general anesthetics (73,83) and ganglionic blockers (35,74–76,83) markedly attenuate the pressor and tachycardiac effects of cocaine. The IV administration of cocaine methiodide, a quaternary derivative of cocaine, has very little effect on cardiovascular function in conscious rats (72) and squirrel monkeys (59). Although cocaine has an inhibitory effect on the norepinephrine reuptake at peripheral sympathetic nerve terminals, for a variety of reasons that follow, it is unlikely that this peripheral action is important in triggering the pressor and tachycardiac effects. First, desipramine markedly inhibits the uptake of norepinephrine, yet the same doses of desipramine were ineffective in producing the increase in BP and HR (75). Nisoxetine, another norepinephrine-selective reuptake inhibitor, at doses that produced marked inhibition of norepinephrine uptake (as assessed by the potentiation of norepinephrine's pressor response), clearly does not produce the initial rapid and marked increase in BP as seen with cocaine (75). Secondly, cocaine increases plasma catecholamines (11,75) and thereby increases blood pressure and heart rate (35), while desipramine (11,14,18,68) and nisoxetine (75) do not increase plasma catecholamines. The fact that chlorisondamine antagonized the cardiovascular changes of the abrupt hemodynamic stimulation phase suggests that these initial cardiovascular changes are of central nervous system origin. This is consistent with the previous reports (10,11,35,74–76,83). Prazosin, an alpha1 adrenoceptor blocker, also attenuates the initial rapid increase in BP of the abrupt hemodynamic stimulation phase (75). It is likely that these initial rapid increases in BP and HR are the physiological consequences of the intense, brief, and abrupt behavioral arousal of animals leading to sudden sympathetic excitation. It is to be noted that unlike BP, the dose-response relationships of cocaine on HR increases corresponding to the initial abrupt hemodynamic stimulation phase is an inverted U-shaped function. It is likely that the reflex reduction in HR secondary to the increase in BP and the direct depressant action of cocaine on cardiac pacemaker due to its sodium channel blocking property (67) at high doses may be counteracting its rapid tachycardiac response.

Dopamine-Dependent Behavioral and Cardiovascular Effects of Cocaine

Dopamine D_1 receptor antagonists, SCH 23390 and SCH 39166, or D_2 receptor antagonist, eticlopride, but not the peripheral dopamine D_2 receptor antagonist, domperidone, blocked cocaine's prolonged locomotor effects and the accompanying prolonged increases in BP and HR. GBR 12909, a dopamine-selective reuptake inhibitor, like cocaine, produced locomotor effect and the parallel increases in BP and HR. These effects of GBR 12909 were similar to that of cocaine with respect to the time course, their susceptibility for blockade by dopamine receptor antagonists, SCH 23390 and eticlopride, and their resistance for antagonism by domperidone. These findings collectively suggest that the inhibition of dopamine reuptake in the brain mediates cocaine's locomotor effects and the accompanying prolonged cardiovascular changes. These data on locomotor effects is consistent with a number of previous studies implicating dopamine in self-administration, discriminative stimulus properties, and behavioral effects of cocaine (3,6,13,27,28,30,64–66,91). Although this dopamine hypothesis of cocaine's behavioral effects is now generally accepted, there are some findings in the literature that remains to be reconciled. For example, it has been reported that D_1 or D_2 dopamine receptor selective agonists, given either singly or in combination, do not fully substitute for cocaine on drug discrimination testing (65,87). Cocaine and the dopamine selective reuptake inhibitor, GBR 12909, produce equivalent locomotor responses at different degrees

of occupancy of the dopamine transporters (55). It also has been reported that GBR 12909 does not completely displace [^{3}H]cocaine binding to caudate-putamen membranes of monkeys (44). It remains to be seen whether the above findings that are not in full agreement with dopamine hypothesis can be attributed to the novel pharmacodynamic action of cocaine described in the present study.

Chlorisondamine, like on the initial abrupt hemodynamic stimulation response of cocaine, also antagonized cocaine's prolonged effects in BP and HR. This is consistent with a number of studies suggesting that the central stimulation of sympathoadrenal activity leading to increases in plasma norepinephrine and epinephrine play a main role in cocaine's pressor and tachycardiac effects (10,11,35,74–76,83). Further, cocaine and the dopamine-selective reuptake inhibitor, GBR 12909, increased plasma catecholamines (assayed at 10 min following their injections) and these increases were attenuated by either SCH 23390 or eticlopride. These findings collectively suggest that the central stimulation of sympathoadrenal neural axis activity produced by cocaine is due in part to its inhibitory effect on dopamine reuptake in the brain. The failure of earlier studies (35,60) to demonstrate the involvement of dopamine in cocaine's cardiovascular effects may be due to the experimental conditions such as the treatment of animals with repeated daily injections of cocaine prior to testing with dopamine receptor antagonists (71,82), the centrally mediated dopamine-independent cardiovascular effects of cocaine complicating its central dopamine-mediated cardiovascular effects or the use of peak BP change as the parameter (present study).

It is important to note that there are potential methodological limitations in the present study. First, a number of drugs were studied in each group. Thus, the drug history might have influenced the results of the present study. Second, the time course and cumulative actions of drugs were not known. Although, only one dose of a given test drug was studied on any given test day, the present study does not provide evidence that this dosing interval is sufficient to prevent the cumulative actions of drugs. Third, the effects of antagonists were studied first. This indicates the possibility of order effects. Although these are important considerations, it is unlikely that the initial abrupt responses to cocaine are due to these methodological limitations. For example, the increases in BP at 15 s following cocaine injection as reported in our previous reports are comparable to the present abrupt hemodynamic stimulation data with respect to the peak effects and dose-response relationships (74,75). In these earlier studies, the control responses to cocaine were determined in animals that had no prior drug history.

In summary, the present data suggest that the cardiovascular and the behavioral effects of cocaine are intricately linked with respect to their mechanisms of origination. Both these effects appear to be due to at least two pharmacodynamic actions. The locomotor effects and the accompanying prolonged increases in BP and HR are due to cocaine's inhibitory effect on dopamine reuptake in the brain. The initial brief behavioral arousal and the accompanying abrupt hemodynamic stimulation appear to be due to a monoamine- and sodium channel-independent and as yet undefined pharmacodynamic action of cocaine. Comparison of the threshold dose of cocaine that produced significant locomotion vs. its dose to elicit abrupt hemodynamic stimulation suggests that cocaine has about a 10-fold selectivity to the molecular mechanism underlying abrupt hemodynamic stimulation as opposed to the inhibition of dopamine reuptake. This conclusion is also consistent with the earlier finding that cocaine has a 10-fold selectivity to produce the initial rapid increase in BP as compared to its ability to inhibit the reuptake of norepinephrine (74,75). Future studies addressing the nature of this novel pharmacodynamic action of cocaine may enhance our understanding of the addictive properties of cocaine. This may also facilitate the development of effective pharmacotherapy for the treatment of cocaine abuse.

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REFERENCES

1. Anderson, P. H. The dopamine uptake inhibitor GBR 12909: Selectivity and molecular mechanism of action. Eur. J. Pharmacol. 166:493–504; 1989.
2. Beltrame, J.; Aylward, P. E.; McRitchie, R. J.; Chalmers, J. P. Comparative hemodynamic effects of lidocaine, mexiletine, and disopyramide. J. Cardiovasc. Pharmacol. 6:483–490; 1984.
3. 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.
4. Berthold, C. W., III; Gonzales, R. A.; Moerschbaecher, J. M. Prazosin attenuates the effects of cocaine on motor activity but not on schedule-controlled behavior in the rat. Pharmacol. Biochem. Behav. 43:111–115; 1992.
5. Blair, M. R. Cardiovascular pharmacology of local anesthetics. Br. J. Anesth. 47:247–252; 1975.
6. 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.
7. Brockway, B. P.; Mills, P. A.; Azar, S. H. A new method for continuous chronic measurement and recording of blood pressure, heart rate, and activity in the rat via radio-telemetry. Clin. Exp. Hypertens. Theory Practice A13:885–895; 1991.
8. 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.
9. Cavero, I.; Lefevre-Borg, F.; Gomeni, R. Heart rate lowering effects of *N,N*-di-*n*-propyl-dopamine in rats: Evidence for stimulation of central dopamine receptors leading to inhibition of sympathetic tone and enhancement of parasympathetic outflow. J. Pharmacol. Exp. Ther. 219:510–519; 1981.
10. Chen, B. X.; Wilkerson, R. D. Role of sympathetic neurons and adrenal medulla in the cardiovascular response to cocaine in conscious, unrestrained rats. (Abstract). FASEB J. 6:A1177; 1992.
11. 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.
12. 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 [^{125}I]RTI-55 to dopamine transporters: Pharmacology and regional distribution with autoradiography. Synapse 12:37–46; 1992.
13. 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.
14. Cousineau, D.; Goresky, C. A.; Rose, C. P. Decreased basal

cardiac interstitial norepinephrine release after neuronal uptake inhibition in dogs. Circ. Res. 58:859-866; 1986.
15. Cunningham, K. A.; Callahan, P. M. Monoamine reuptake inhibitors enhance the discriminative state induced by cocaine in the rat. Psychopharmacology (Berlin) 104:177-180; 1991.
16. Dackis, C. A.; Gold, M. S.; Davies, R. K.; Sweeney, D. R. Bromocriptine treatment for cocaine abuse: The dopamine depletion hypothesis. Int. J. Psychiatr. Med. 15:125-135; 1985.
17. Damase-Michel, C.; Montastruc, J. L.; Gharib, C.; Geelen, G.; De Saint-Blanquat, G.; Tran, M. A. Effect of quinpirole, a specific dopamine DA_2 receptor agonist on the sympathoadrenal system in dogs. J. Pharmacol. Exp. Ther. 252:770-777; 1990.
18. Dorward, P. K.; Saigusa, T.; Eisenhofer, G. Differential effects of central and peripheral desipramine on sympathoadrenal function and HR in conscious rabbits. J. Cardiovasc. Pharmacol. 17: 519-531; 1991.
19. Edouard, A.; Berdeaux, A.; Langloys, J.; Samii, K.; Giudicelli, J. F.; Noviant, Y. Effects of lidocaine on myocardial contractility and baroreflex control of heart rate in conscious dogs. Anesthesiology 64:316-321; 1986.
20. Fischman, M. W.; Schuster, C. R. Cocaine self-administration in humans. Fed. Proc. 41:241-246; 1982.
21. Fischman, M. W.; Schuster, C. R.; Hatano, Y. A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans. Pharmacol. Biochem. Behav. 18:123-127; 1983.
22. 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.
23. 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.
24. Gawin, F. H.; Kleber, H. D.; Byck, R.; Rounsaville, M. D.; Kosen, R. R.; Jatlow, P. I.; Morgan, C. Desipramine facilitation of initial cocaine abstinence. Arch. Gen. Psychiatry 46:117-121; 1989.
25. Gonzalez, F. A.; Byrd, L. D. Physiological effects of cocaine in the squirrel monkey. Life Sci. 21:1417-1424; 1977.
26. Hofman, W. F.; Jerram, D. C.; Gangarosa, L. P. Cardiorespiratory and behavioral reactions to the lidocaine-induced convulsion in the dog. Res. Commun. Chem. Pathol. Pharmacol. 16:581-591; 1977.
27. 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.
28. 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.
29. 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.
30. Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3-52; 1989.
31. Jorfeldt, L.; Lofstrom, B.; Pernow, B.; Wahren, J. The effect of mepivacaine and lidocaine on forearm resistance and capacitance vessels in man. Acta Anesth. Scand. 14:183-201; 1970.
32. Kao, F. F.; Jalar, U. H. The central action of lignocaine and its effect on cardiac output. Br. J. Pharmacol. 14:522-526; 1959.
33. Kelly, P. H.; Iversen, S. D. Selective 6-OHDA induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. 40: 45-56; 1976.
34. Kennedy, L. T.; Hanbauer, I. Sodium-sensitive cocaine binding to striatal membranes: Possible relationship to dopamine uptake sites. J. Neurochem. 41:172-178; 1983.
35. 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.
36. Kleven, M. S.; Woolverton, W. L. Effects of bromocriptine and desipramine on behavior maintained by cocaine or food presentation in rhesus monkeys. Psychopharmacology (Berlin) 101:208-213; 1990.
37. 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.
38. Koob, G. F.; Stinus, L.; Le Moal, M. Hyperactivity and hypoactivity produced by lesions to the mesolimbic dopamine system. Behav. Brain Res. 3:341-359; 1981.
39. Kosten, T. R.; Morgan, C. M.; Falcione, J.; Schottenfeld, R. S. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. Arch. Gen. Psychiatry 49:894-898; 1992.
40. Krulan, C.; Bazil, M. K.; Webb, R. L. Comparison of cardiovascular parameters measured with telemetry and directly via indwelling catheters (INC) in conscious spontaneously hypertensive rats (SHR). FASEB J. 6:A1174; 1992.
41. Lacosta, S.; Roberts, D. C. S. MDL 72222, ketanserin, and methysergide pretreatments fail to alter breaking points on a progressive ratio schedule reinforced by intravenous cocaine. Pharmacol. Biochem. Behav. 44:161-165; 1993.
42. Lange, J.; Brockway, B.; Azan, S. Telemetric monitoring of laboratory animals: An advanced technique that has come of age. Lab. Anim. 20:28-34; 1991.
43. Lescanic, M. L.; Miller, E. D.; DiFazio, C. A. The effects of lidocaine on the whole body distribution of radioactively labeled microspheres in the conscious rat. Anesthesiology 55:269-272; 1981.
44. 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.
45. Mandel, W. J.; Laks, M. M.; Arieff, A. I.; Obayashi, K.; Hayakawa, H.; McCullen, A. Cardiorenal effects of lidocaine and procaine in the conscious dog. Am. J. Physiology. 228:1440-1445; 1975.
46. 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.
47. Meert, T. F.; Janssen, P. A. J. Ritanserin, a new therapeutic approach for drug abuse. Part 2: Effects on cocaine. Drug Dev. Res. 25:39-53; 1992.
48. Pollack, M. H.; Rosenbaum, J. F. Fluoxetine treatment of cocaine abuse in heroin addicts. J. Clin. Psychiatry 52:31-33; 1991.
49. Post, R. M.; Weiss, S. R. B.; Pert, A.; Uhde, T. W. Chronic cocaine administration: Sensitization and kindling effects. In: Rusher, S.; Raskin, A.; Uhlenhuth, E. H., eds. Cocaine: Clinical and behavioral aspects. New York: Oxford University Press; 1987:109-173.
50. Reith, M. E. A. 5-HT_3 antagonists attenuate cocaine-induced locomotion in mice. Eur. J. Pharmacol. 186:327-330; 1990.
51. Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A. Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Biochem. Pharmacol. 35:1123-1129; 1986.
52. Reith, M. E. A.; Weiner, H. L.; Fischette, C. T. Sertraline and cocaine-induced locomotion in mice. I. Acute studies. Psychopharmacology (Berlin) 103:297-305; 1991.
53. 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.
54. 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.
55. Rothman, R. B.; Greig, N.; Kim, A.; De Costa, B. R.; Rice, K. C.; Carroll, F. I.; Pert, A. Cocaine and GBR 12909 produce equivalent locomotor responses at different occupancy of the dopamine transporter. Pharmacol. Biochem. Behav. 43:1135-1142; 1992.
56. Rutten, A. J.; Nancarrow, C.; Mather, L. E.; Ilsley, A. H.;

Runciman, W. B.; Upton, R. N. Hemodynamic and central nervous system effects of intravenous bolus doses of lidocaine, bupivacaine, and ropivacaine in sheep. Anesth. Analg. 69:291–299; 1989.
57. 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.
58. 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.
59. 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.
60. 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.
61. Schnell, C. R.; Wood, J. M. Measurement of blood pressure and heart rate by telemetry in conscious, unrestrained marmosets. Am. J. Physiol. 264:H1509–H1516; 1993.
62. 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.
63. Silverman, P. B.; Schultz, K. A. Comparison of cocaine and procaine discriminative stimuli. Drug Dev. Res. 16:427–433; 1989.
64. Spealman, R. D. Antagonism of behavioral effects of cocaine by selective dopamine receptor blockers. Psychopharmacology (Berlin) 101:142–145; 1990.
65. 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.
66. 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.
67. Strichartz, G. R.; Ritchie, J. M. The action of local anesthetics on ion channels of excitable tissues. In: Strichartz, G. R., ed. Local anesthetics. New York: Springer Verlag; 1987:21–52.
68. Szabo, B.; Schultheiss, A. Desipramine inhibits sympathetic nerve activity in the rabbit. Naunyn Schmiedebergs Arch. Pharmacol. 342:469–476; 1990.
69. Svingos, A. L.; Hitzeman, R. 5-HT$_3$ antagonists block cocaine-induced locomotion via a PCPA-sensitive mechanism. Pharmacol. Biochem. Behav. 43: 871–879; 1992.
70. Tejani-Butt, S. Z. [^{3}H]nisoxetine: A radioligand for quantitation of norepinephrine uptake sites by autoradiography or by homogenate binding. J. Pharmacol. Exp. Ther. 260:427–436; 1992.
71. Tella, S. R. Differential blockade of chronic vs. acute effects of intravenous cocaine by dopamine receptor antagonists. Pharmacol. Biochem. Behav. 48:151–159; 1994.
72. Tella, S. R.; Korupolu, G. R.; Schindler, C. W.; Goldberg, S. R. Pathophysiological and pharmacological mechanisms of acute cocaine toxicity in conscious rats. J. Pharmacol. Exp. Ther. 262: 936–946; 1992.
73. 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.
74. 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.
75. 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.
76. 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.
77. Tennant, F. S.; Sagherian, A. A. Double-blind comparison of amantadine hydrochloride and bromocriptine mesylate for ambulatory withdrawal from cocaine dependence. Arch. Int. Med. 147: 109–112; 1987.
78. Tessel, R. E. Noradrenergic processes in the behavioral actions of psychomotor stimulants. Drug Dev. Res. 20:359–368; 1990.
79. Van Der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-dialk(en)ylpiperazines as selective and very potent inhibitors of dopamine uptake. Eur. J. Med. Chem. 15:363–370; 1980.
80. Van Haaren, F. Effects of cocaine alone and in combination with prazosin or ondansetron on multiple fixed-interval fixed-ratio performance in pigeons. Pharmacol. Biochem. Behav. 42:849–853; 1992.
81. Weddington, W. W.; Brown, B. S.; Haertzen, C. A.; Hess, J. M.; Mahaffey, J. R.; Kolar, A. F.; Jaffe, J. H. Comparison of amantadine and desipramine combined with psychotherapy for treatment of cocaine dependence. Am. J. Drug Alcohol Abuse 17:137–152; 1991.
82. 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.
83. 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.
84. Wilkinson, L. SYSTAT: The system for statistics. Evanston, IL: SYSTAT, Inc.; 1989.
85. Wiklund, L. Human hepatic blood flow and its relation to systemic circulation during intravenous infusion of lidocaine. Acta Anesthesiol. Scand. 21:148–160; 1977.
86. Winger, G. Dopamine antagonist effects on behavior maintained by cocaine and alfentanil in rhesus monkeys. Behav. Pharmacol. 5:141–152; 1994.
87. Witkin, J. M.; Nicholos, D. E.; Terry, P.; Katz, J. L. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J. Pharmacol. Exp. Ther. 257:706–713; 1991.
88. Wong, D. T.; Bymaster, F. P.; Horng, J. S.; Molloy, B. B. A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine. J. Pharmacol. Exp. Ther. 193:804–811; 1975.
89. Wong, D. T.; Bymaster, F. P.; Reid, L. R.; Threlkeld, P. G. Fluoxetine and two other serotonin uptake inhibitors without affinity for neuronal receptors. Biochem. Pharmacol. 32:1287–1293; 1983.
90. Wong, D. T.; Threlkeld, P. G.; Best, K. L.; Bymaster, F. P. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J. Pharmacol. Exp. Ther. 222:61–65; 1982.
91. 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.
92. Yokoyama, M.; Benson, K. T.; Arakawa, K.; Goto, H. Effects of flumazenil on intravenous lidocaine-induced convulsions and anticonvulsant property of diazepam in rats. Anesth. Analg. 75: 87–90; 1992.
93. Yoshida, K. I.; Morimoto, A.; Makisumi, T.; Murakami, N. Cardiovascular, thermal and behavioral sensitization to methamphetamine in freely moving rats. J. Pharmacol. Exp. Ther. 267: 1538–1543; 1993.