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Cardiovascular effects of cocaine during operant cocaine self-administration

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Abstract

The aim of this study was to investigate the acute and chronic effects of cocaine self-administration behavior on cardiovascular function. Mean blood pressure and heart rate were measured by radio-telemetry during several experimental conditions. Initial control studies eliminated possible confounds related to the effects of saline injections and operant responding on heart rate and blood pressure. When rats were first allowed to self-administer 0.5-mg/kg injections of cocaine (FR(fixed ratio)10:TO 30 s), there was a significant increase in blood pressure. Tolerance developed to this effect within 3 daily sessions. A significant decrease in blood pressure and heart rate was observed during saline-substitution sessions. Increasing the injection dose of cocaine (1.0, 2.0 and 4.0 mg/kg per injection) did not produce a dramatic increase in blood pressure or heart rate despite significant cumulative cocaine intake (20–27 mg/kg). The cardiovascular effects of cocaine administration did not approach magnitudes previously reported. The results of the current study suggest that operant-conditioned behavior and/or the direct reinforcing effects of cocaine modulates the cardiovascular effects of cocaine.

Keywords: Cocaine; Heart rate; Blood pressure; Self-administration

1. Introduction

The widespread abuse of cocaine and its associated morbidity and mortality have stimulated interest in the potential toxic effects of cocaine on the cardiovascular system (Cregler, 1989; Isner and Chokshi, 1989). Clinical evidence suggests that cocaine administration can result in acute myocardial ischemia and infarction in cocaine abusers (Isner and Chokshi, 1989), as well as cardiac arrhythmias, myocarditis, dilated cardiomyopathy and cerebrovascular and pulmonary hemorrhage (Cregler, 1989; Lathers et al., 1988; Rezkella et al., 1990). Cocaine has vasoconstrictor actions due to its sympathomimetic properties which may be involved in the etiology of these adverse effects (Cregler, 1989).

Cocaine produces consistent increases in blood pressure and heart rate in conscious human subjects (Fischman et al., 1976; Javaid et al., 1978; Resnick et al., 1977), rhesus monkeys (Carroll et al., 1990; Matsuzaki et al., 1978), squirrel monkeys (Gonzales and Byrd, 1977; Schindler et al., 1991; Tella et al., 1990), dogs (Wilkerson, 1988) and rats (Tella et al., 1991, 1992, 1993) but the mechanisms underlying these cardiovascular actions of cocaine are not clear (Jones and Tackett, 1990; Kiritsy-Roy et al., 1990; Knuepfer and Branch, 1992; Pitts et al., 1987; Raczkowski et al., 1991; Tella et al., 1992, 1993). In a conscious animal model, the cocaine-induced increases in blood pressure and heart rate have been shown to be centrally mediated (Schindler et al., 1992; Tella et al., 1992, 1993).

Previous studies have shown that the behavioral and pharmacological effects of reinforcing events, such as cocaine or opioid injection, or electrical stimulation are significantly influenced by the conditions under which the subject receives the stimulus. For example, contingent (self-administered) vs. non-contingent (passive) administration may result in different neurochemical and toxicity profiles. Non-contingent vs. contingent morphine injection

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or electrical brain stimulation results in significantly different brain neurotransmitter turnover and glucose utilization rates (Porrino et al., 1984; Smith et al., 1982). Contingent injections of cocaine result in significantly greater glucose utilization than non-contingent injections in regions thought to mediate the reinforcing properties of cocaine, while non-contingent injections of cocaine in paired yoked subjects appear to produce significantly greater morbidity and mortality than self-administered (contingent) injections (Dworkin et al., 1995). Unfortunately, most pre-clinical studies of the cardiovascular actions of cocaine have almost exclusively used passive drug administration. The aim of the present study was to investigate the cardiovascular effects of cocaine under conditions where animals are actively self-administering i.v. injections of cocaine under operant schedules of reinforcement.

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (Harlan Sprague Dawley) weighing approximately 400–500 g at the start of their training were used. All animals were experimentally naive, housed individually in a temperature-controlled room (26°C) with a 12-h light-dark cycle (07:00–19:00 h lights on) and given free access to Purina laboratory chow and tap water prior to initiation of the experiments. Animals used in this study were maintained in facilities fully accredited by the American Association of the Accreditation of Laboratory Animal Care (AAALAC) and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the NIDA Intramural Research Program (NIH), and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23 (revised 1985).

2.2. Surgery

Experimentally naive subjects were surgically prepared with an i.v. catheter placed in the jugular vein. Polyvinylchloride tubing (0.064 i.d.) was implanted in the right jugular vein approximately at the level of the atrium under halothane anesthesia (2.5%). The catheter was passed s.c. and exited in the midscapular region. The catheter then passed through a spring tether system (Alice King Chatham, Hawthorne, CA, USA) that was mounted to the skull of the rat with dental cement. All subjects were housed individually following surgery and given at least 7 days to recover. When rats were fully recovered from i.v. catheter implantation, a transmitter (model TA11PA-C40; Data Sciences International, St. Paul, MN, USA) was surgically implanted in the abdominal aorta for cardiovascular measurements by radio-telemetry according to previously described procedures (Tella, 1996). Rats were allowed another post-operative recovery period of 7 days before initiation of experimental procedures.

2.3. Apparatus

Four operant chambers were used for cocaine self-administration studies. Two levers designed to register a response when 3.0 g of force was applied were placed 14 cm apart on the front wall of the chamber. A microliter injection pump (Harvard 22) was used to deliver i.v. saline or drug injections to the rat. Drug delivery, operant data acquisition and storage were accomplished on IBM computers (Med Associates, East Fairfield, VT, USA). Cardiovascular data was collected from the TA11PA-C40 transmitter with a DSI radio-receiver placed under each chamber (RA1310 receiver/Dataquest Data Acquisition System; Data Sciences International). Cocaine-reinforced behavior and cardiovascular measurements were synchronized by using identical session start times and real time observation of self-administration injections.

2.4. Experimental procedure

Before surgical implantation of the i.v. catheter and TA11PA-C40 transmitter, animals were trained to lever press for food reinforcement under a FR(fixed ratio)10 schedule of reinforcement. Initially, a single lever press on the left-hand lever resulted in delivery of a food pellet (45 mg; Bio-Serv, Frenchtown, NJ, USA) and turned on both an overhead house light and stimulus lights above the lever for 15 s. After responding was initiated, the response requirement/food delivery was raised in increments to 10 and a programmed 30-s time-out period in which responses had no programmed consequences followed each food pellet delivery (FR10:TO 30 s). When behavior was maintained under the FR10 schedule of food-reinforced behavior, the catheter and transmitter were surgically implanted as described.

After the post-operative period, all rats were sequentially tested under 4 experimental conditions. In the 1st phase of the experiment, food-reinforced behavior was re-established. In the 2nd phase, the effects of multiple saline injections on cardiovascular function during operant food-reinforced behavior was determined by simultaneously injecting saline with pellet delivery at 1 of 3 injection volumes (25, 50 or 100 μl). The 3rd phase of the experiment involved initiation of cocaine-reinforced behavior. The 2-h session was divided into two 60-min periods. During the first 60-min period, behavior was reinforced as before by food reinforcement under an FR10 schedule of reinforcement. During the second 60-min period, operant behavior was reinforced by i.v. self-administration of either saline or cocaine injections (0.5 or 1.0 mg/kg). The final (4th) phase of the experiment involved

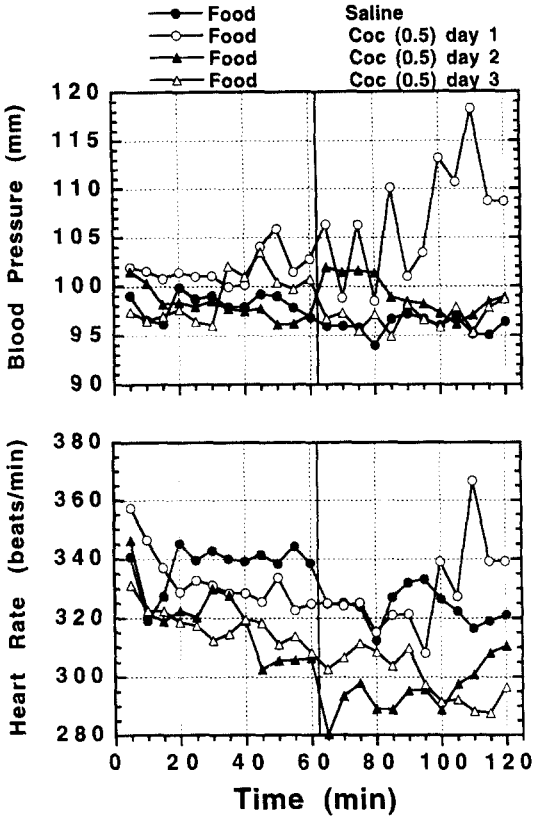

Fig. 1. Cardiovascular effects of self-administered cocaine during the first 3 days of exposure to cocaine. The 2-h session was divided into two 60-min periods. During the first 60 min, operant behavior was maintained by food reinforcement on an FR10 schedule of reinforcement. During the second 60-min period, operant behavior was maintained by either saline or cocaine administration (0.5 mg/kg per injection). Each point represents the mean of 4 rats.

measurement of cardiovascular changes during self-administration under an FR10 schedule of drug injection. The following sequence of injection doses (mg/kg per injection) was studied: 1.0, 0 (saline extinction), 2.0 and 4.0. Sessions were conducted between 15:00 and 19:00 h 7 days/week and each dosage condition was continued until stable behavior was established (±10% variability in the number of injections for 3 sequential days). The injection rate (400 μl/min) and injection duration (15 s) for all cocaine doses was held constant throughout the experiment.

2.5. Data analysis

The operant session and cardiovascular recordings were started simultaneously. Real time observation of injection time was recorded and coordinated with cardiovascular recordings. Due to the long duration of the study and computer limitations, cardiovascular measurements were not taken every session. Direct observation of cardiovascular parameters across conditions suggested highly stable measurements once each condition was initiated. Cardiovascular measurements were collected during the following sessions: phase 1, the last 2 days of food-reinforced behavior; phase 2, the last 2 days of food-reinforced behavior with simultaneous injections of saline; phase 3, the last 2 days of the food:saline sessions and the first 3 sessions of food: 0.5 mg/kg cocaine; phase 4, the first 4 sessions of 1.0 mg/kg cocaine, a representative day during 1.0 mg/kg cocaine (during stable behavior), the 1st and 3rd days of saline extinction and a representative day during the 2.0 and 4.0 mg/kg cocaine self-administration sessions.

Blood pressure and heart rate values were recorded every 15 s for the entire 2-h session. The mean of the heart rate and mean blood pressure values recorded during each 5-min interval of the session was used as the dependent measure in all analyses. Statistical analysis of condition- and dose-related effects of cocaine self-administration on mean blood pressure and heart rate were determined by a two-factor repeated-measures analysis of variance (dose and time). The 1st and 2nd hours of the phase 3, food:cocaine sessions, were analyzed separately. Planned comparisons of condition effects (dose or day) were conducted using contrast analysis (SuperAnova; Abacus Concepts, CA, USA). For all conditions prior to testing the 2.0-mg/kg dose, $n = 4$; $n = 3$ at the 2.0- and 4.0-mg/kg doses. The level of significance was considered to be $P < 0.05$ for all analyses.

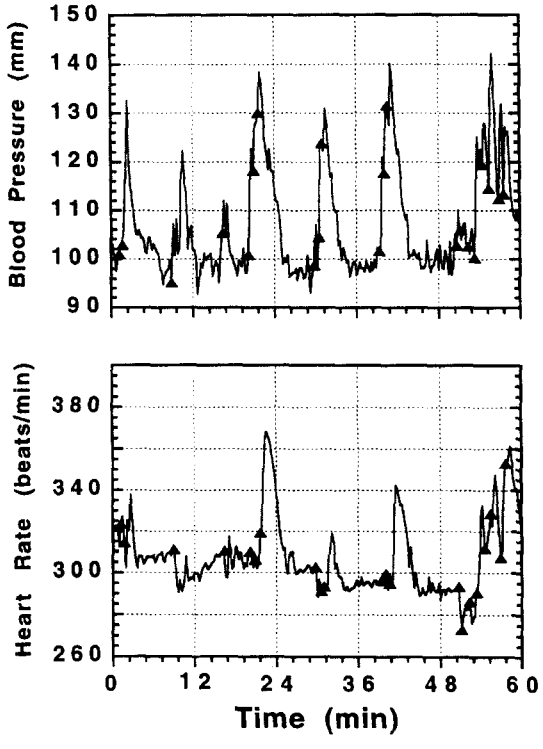

Fig. 2. Cardiovascular effects of self-administered cocaine (0.5 mg/kg per injection) during the first exposure to cocaine in a representative rat (R12). The data represent blood pressure and heart rate values taken every 15 s during the latter 60 min of the self-administration session (see Fig. 1). Solid triangles represent the time of each cocaine injection.

3. Results

3.1. Cardiovascular measures during food-reinforced responding (phases 1 and 2)

On average, animals received 168.4 ± 23 (S.E.M.) food reinforcements which required 1684 ± 230 (S.E.M.) lever presses during the course of the 2-h session. The mean values for blood pressure and heart rate were 98.9 ± 1.3 mm Hg (S.E.M.) and 329 ± 21 (S.E.M.) beats/min, respectively. These values did not change significantly during the course of the 2-h session (data not shown). Simultaneous administration of saline did not significantly alter cardiovascular measures. Animals received 151 ± 26 (S.E.M.) food reinforcements which required 1510 ± 260 (S.E.M.) lever presses during the course of the 2-h session. There was no significant volume-dependent effect of saline administration on cardiovascular parameters (data not shown). All subsequent injections were 100 μl/injection.

3.2. Cardiovascular measures during food-reinforced responding (1st hour) followed by cocaine self-administration (2nd hour) (phase 3)

Fig. 1 (top and bottom panels) show blood pressure and heart rate, respectively, during the 1st and 2nd hours of the 2-h session. There was no significant effect of condition (rats receiving food or cocaine during the 2nd hour) during the 1st hour of the session on blood pressure or heart rate. There was a condition (saline, 0.5 mg/kg cocaine days 1–3) × time-dependent effect during the 2nd hour of the session on blood pressure ($F(33,191) = 2.4$, $P < 0.01$). On the 1st day in which cocaine was self-administered during the 2nd hour of the session, there was a significant increase in blood pressure ($F(1,2) = 5.2$, $P < 0.05$; cocaine day 1 compared to saline). Blood pressure was not significantly affected during cocaine self-administration in the 2nd hour of the session on the 2nd and 3rd days. There was a marginally significant condition (saline, 0.5 mg/kg cocaine days 1–3) × time-dependent effect during the 2nd hour of the session on heart rate ($F(33,191) = 1.58$, $P < 0.056$). There was an increase across the session in heart rate during the 1st day of cocaine self-administration. Fig. 2 shows a representative graph of blood pressure and heart rate during the 2nd hour of the 1st day exposure to 0.5 mg/kg in rat R12. The graph represents telemetry values collected every 15 s.

3.3. Cardiovascular measures during cocaine self-administration alone (phase 4)

3.3.1. First 4 days of 1.0 mg/kg cocaine

Fig. 3 (panels A and B, and panels C and D), shows the effects of self-administered cocaine (1.0 mg/kg per injec-

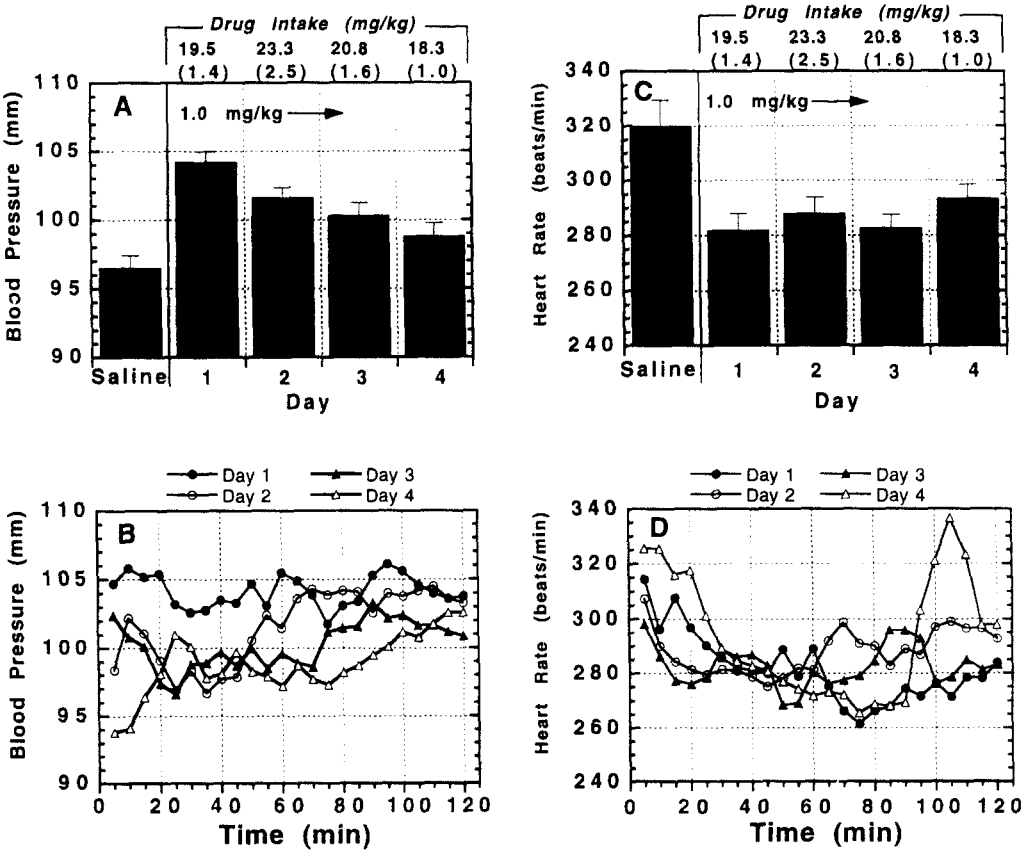

Fig. 3. Cardiovascular effects of self-administered cocaine during the first 4 days of exposure to 1.0 mg/kg cocaine. Operant behavior (FR10) was maintained by either saline or cocaine administration. Each bar represents the session blood pressure or heart rate mean ($n = 4$) (panels A and C). Each point represents the mean of 4 rats (panels B and D). Drug intake (S.E.M.) during each session is shown at the top of panels A and C.

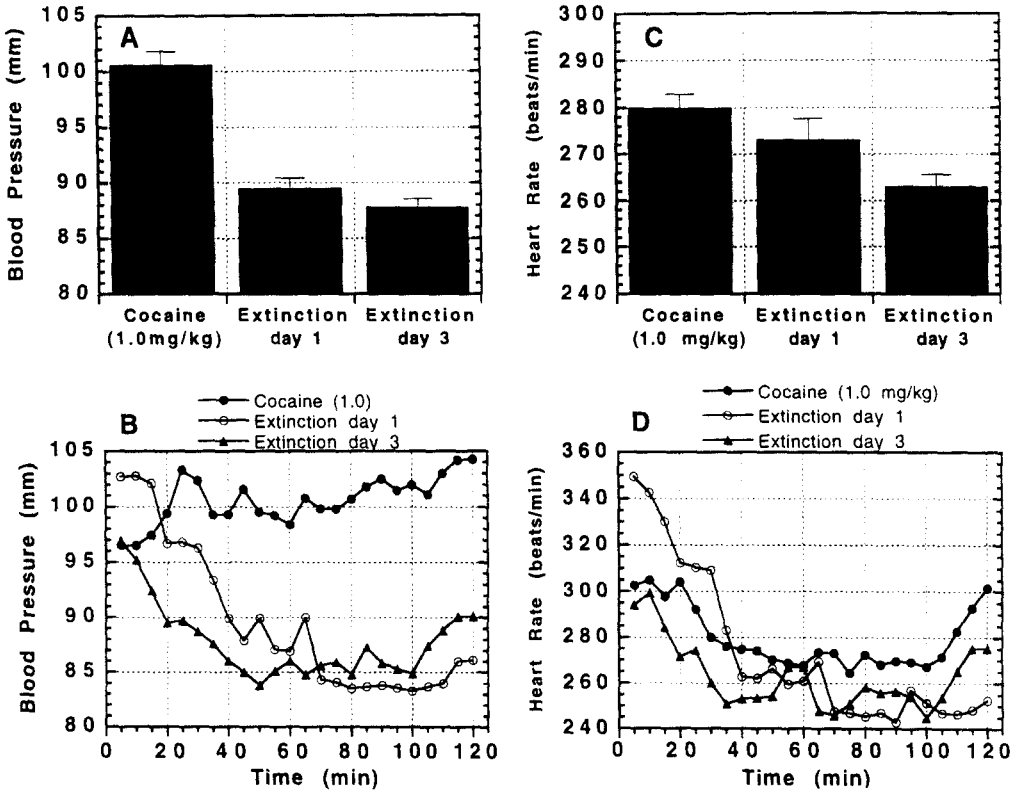

Fig. 4. Cardiovascular effects of self-administered cocaine and saline substitution during days 1 and 3 of the saline extinction period. Each bar represents the session blood pressure or heart rate mean ($n = 4$) (panels A and C). Each point represents the mean of 4 rats (panels B and D).

tion) on blood pressure and heart rate, respectively, during the first 4 days. There was a condition × time-dependent effect across the 4 days on blood pressure ($F(69,287) = 2.4$, $P < 0.04$). There was a significant increase in blood pressure during the 1st day of 1.0 mg/kg cocaine self-administration ($F(1,2) = 5.9$, $P < 0.05$; cocaine 1.0 mg/kg day 1 compared to saline), an effect which was apparent within the first 5 min of the session. The effects of cocaine on blood pressure decreased each successive day although there was a tendency for blood pressure to increase latter in the session. There was no significant difference in the effect of 1.0 mg/kg cocaine across the 4 days on heart rate.

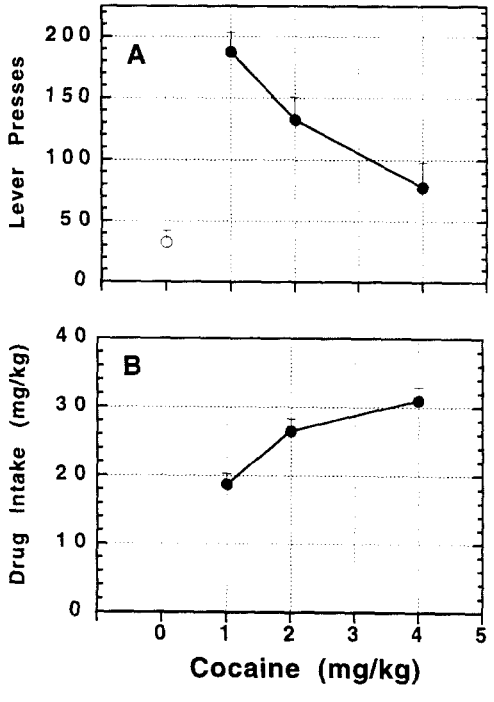

Fig. 5. Drug self-administration behavior (lever pressing) and drug intake as a function of cocaine dose. Each point represents the condition mean (S.E.M.) over the last 3 days at each condition.

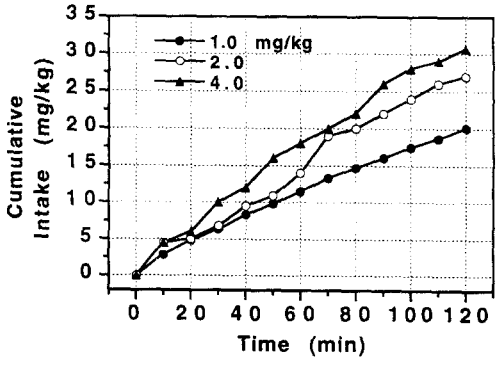

Fig. 6. Cumulative cocaine intake (mg/kg) during operant cocaine self-administration sessions. Each point represents the mean of 4 rats.

3.3.2. Saline substitution

Fig. 4 (panels A and B, and panels C and D), shows the effects of self-administered cocaine (1.0 mg/kg per injection) and of saline injections during the 1st and 3rd days of saline substitution on blood pressure and heart rate, respectively. There was a condition × time-dependent effect across the 3 conditions on blood pressure ($F(46,287) = 3.6$, $P < 0.01$). Blood pressure decreased significantly during the 1st and 3rd days of saline substitution ($F(1,2) = 8.3$ and 8.6, $P < 0.05$; extinction days 1 and 3, respectively, vs. cocaine). Saline substitution values were below those maintained during all previous conditions. There also was a condition × time-dependent effect across the 3 conditions on heart rate ($F(46,287) = 1.9$, $P < 0.05$). Heart rate increased in the first 30 min of the 1st session of saline substitution. There was a general decrease in heart rate during the 1st and 3rd sessions of saline substitution. Again, saline substitution values were below those maintained during all previous conditions.

3.3.3. Cocaine self-administration behavior: dose-effect data

Fig. 5 (panels A and B) shows the mean number of lever presses and drug intake during the last 3 stable self-administration sessions at each dose. There was a significant effect of cocaine dose on the number of lever presses/session ($F(3,8) = 9.6$, $P < 0.01$). Importantly, drug maintained significantly greater amounts of behavior than vehicle at each dose of cocaine. Thus, cocaine was serving as a positive reinforcer under these conditions. There was a corresponding significant effect of cocaine dose on drug intake (panel B; $F(2,5) = 6.1$, $P < 0.05$). Cumulative within session drug-intake for the 1.0, 2.0 and 4.0 mg/kg groups are shown in Fig. 6. Total drug intake for the 1.0, 2.0 and 4.0 mg/kg group averaged 18.8, 26.9 and 31.0 mg/kg, respectively, during the 2-h sessions. Rats in the 1.0 mg/kg group self-administered 2–3 injections of cocaine during the first 5 min of the session, then averaged approximately 1 injection every 5–10 min for the rest of the session. Inter-injection intervals for the 2.0- and 4.0-mg/kg session averaged 8–14 min. In general, the inter-injection interval was very stable across the 2-h session.

3.3.4. Cardiovascular effects of cocaine self-administration behavior: dose-effect data

Fig. 7 (panels A and B, and panels C and D), show the dose-related effects of self-administered cocaine injections

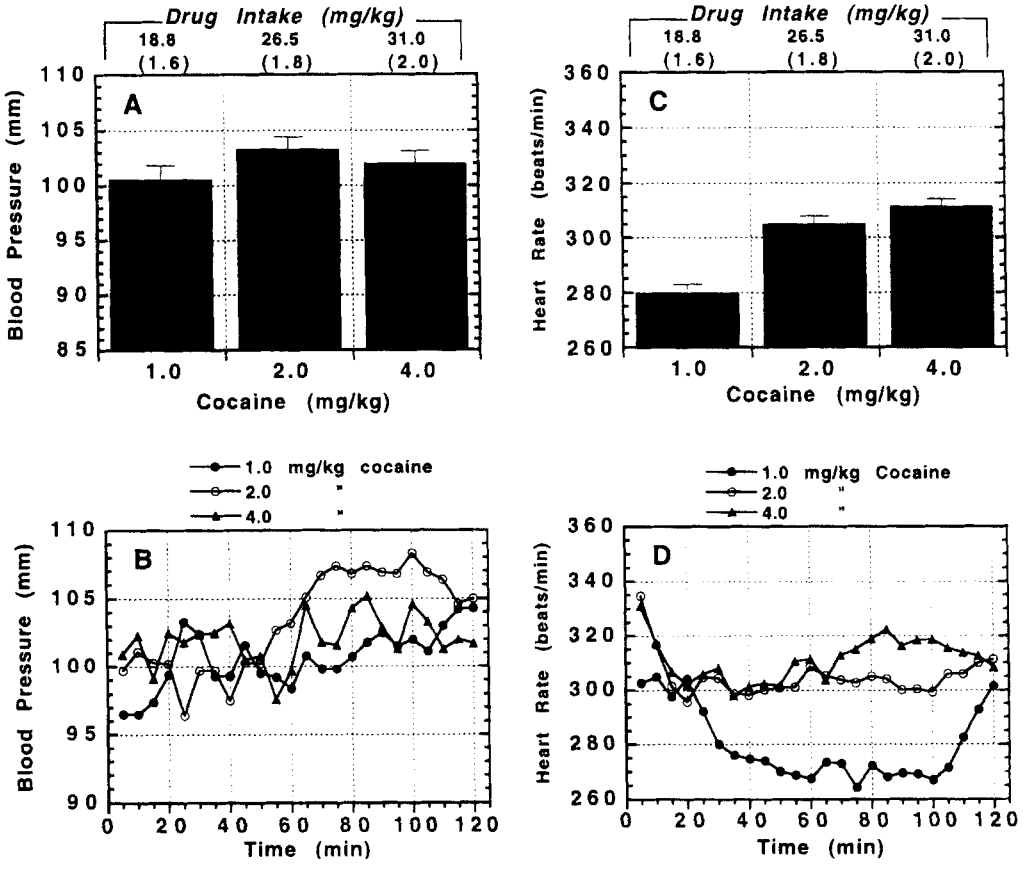

Fig. 7. Dose-effect function of the cardiovascular effects of cocaine self-administration. Each bar represents the session blood pressure or heart rate mean ($n = 3$) (panels A and C). Each point represents the mean of 4 rats (panels B and D). Drug intake (S.E.M.) during each session is shown at the top of panels A and C.

on blood pressure and heart rate, respectively. There was no significant effect of changes in cocaine dose (1.0, 2.0 or 4.0) on blood pressure. There was a marginally significant effect of changes in cocaine dose (1.0, 2.0 or 4.0) on heart rate ($F(46,215) = 3.4$, $P < 0.090$, an effect primarily due to the decrease in heart rate across the session at the 1.0 mg/kg per injection dose.

4. Discussion

The aim of this study was to investigate the acute and chronic effects of cocaine self-administration behavior on cardiovascular function. When rats were allowed to self-administer 0.5-mg/kg injections of cocaine, there was a significant increase in blood pressure; increases in blood pressure progressively declined and were not significant over the next 3 daily sessions of cocaine self-administration, despite cumulative intake of 8–12 mg/kg cocaine/session. This progressive decrease across days in cocaine's effects on blood pressure was observed again when animals were switched to 1.0 mg/kg. Cocaine significantly increased blood pressure during the 1st day of access to this dose but its effects on blood pressure decreased on each subsequent day and returned to saline levels by the 4th day. These results are in agreement with previous reports of acute tolerance to cardiovascular actions of cocaine in humans and rats (Fischman et al., 1985; Smith et al., 1993). For example, in the study by Smith et al. (1993) acute blood pressure and maximal heart rate changes produced by 1.0-mg/kg injections of cocaine diminished completely by the 3rd injection when rats were given repeated injections at 5-min intervals (Smith et al., 1993). Similarly, the acute heart rate and subjective effects of cocaine in humans given i.v. injections of 16, 32 or 48 mg/kg cocaine diminished significantly when they were given intranasal cocaine (96 mg/kg) 60 min prior to the i.v. injection (Fischman et al., 1985). These previous findings, as well as those of the current study, demonstrate that acute tolerance to the actions of cocaine on blood pressure and heart rate occur under a variety of experimental situations and in various species.

One of the most pronounced effects observed in the current study was the dramatic decrease in blood pressure and heart rate during saline-substitution sessions. Blood pressure decreased approximately 10 mm and heart rate decreased 24 beats/min on the 3rd day of extinction following self-administration of 1.0 mg/kg cocaine. The decrease in blood pressure was maximal during the latter half of each session. Interestingly, during the 1st day of extinction, heart rate increased an average of 35 beats/min during the first 15 min of the session.

Increasing the injection dose of cocaine above 1.0 mg/kg did not produce corresponding increases in blood pressure or heart rate despite cumulative cocaine intake/session to 20–27 mg/kg. There was no consistently significant dose-related effect of cocaine on blood pressure. There was a marginally significant effect of cocaine dose on heart rate, in particular, 1.0 mg/kg cocaine decreased heart rate. The decreased heart rate remained consistent throughout the first 4 days of exposure to this dose of cocaine in contrast to effects seen with blood pressure. The decrease in heart rate may be particular to a specific range of drug accumulation. The heart rate-decreasing effects of cocaine were most prominent at the end of the 3rd session during self-administration of 0.5-mg/kg cocaine injections (Fig. 1, cumulative intake 8–10 mg/kg) and during the 1st hour of self-administration of 1.0-mg/kg cocaine injection session (Fig. 2, cumulative intake 8–10 mg/kg). A similar pattern was found after several days of self-administration of 1.0-mg/kg cocaine injection when the subjects reached stable self-administration behavior (Fig. 7). The decrease in heart rate continued to be most prominent during the first 100 min of the session (cumulative intake 8–21 mg/kg). These data may represent an acute tolerance phenomenon similar to that seen after 3 injections in the report of Smith et al. (1993). The self-administration data collected at the 1.0-mg/kg injection dose of cocaine is relevant to the drug abuse literature since this dose is commonly used in operant self-administration studies and readily maintains a significant amount of self-administration behavior in the rat (see Fig. 5; Depoortere et al., 1993; Dworkin et al., 1992; Pickens and Thompson, 1968).

The decrease in heart rate at 1.0 mg/kg could be due to the local anesthetic properties of cocaine (Tella et al., 1990). The local anesthetic effect of cocaine results in a widening of the QRS complex and an increase in the P-R interval (Gillis et al., 1992). Interestingly, it has been suggested that acute tolerance to the local anesthetic effect of cocaine does not occur (Bachenheimer et al., 1988). In general, the local anesthetic effects of cocaine and the pharmacological effects of its metabolites should be taken into account when considering cardiovascular complications that can occur with accumulation of high cocaine doses that routinely occur following repeated self-administration episodes.

Previous reports using anesthetized or conscious freely moving rats have reported substantial increases in blood pressure (Branch and Knuepfer, 1994) and heart rate (Tella et al., 1991, 1992, 1993) under passive administration conditions. In addition, repeated administration of low doses of cocaine has been shown to produce sensitization to the pressor effects of cocaine (Tella et al., 1991). The cardiovascular effects of cocaine during operant cocaine self-administration did not approach the magnitude previously reported. In addition, repeated administration of cocaine did not appear to produce the type of sensitization demonstrated in the previous study. The differences between the present and previous reports are likely due to dosing differences and/or the effects of contingent vs. non-contingent administration. Several reports support the

latter hypothesis. For example, the individual response to the effects of non-contingent cocaine administration on cardiovascular output are positively correlated with the effects of a stressful stimuli (air jet), thus suggesting that the cardiovascular effects of cocaine are related to the stress of receiving the non-contingent stimulant (Knuepfer et al., 1993). In addition, contingent cocaine self-administration produces a significant increase in glucose utilization throughout the mesocorticolimbic system whereas passive yoked cocaine infusion produces increases in portions of the extrapyramidal motor system and not in forebrain structures (Dworkin et al., 1992; Porrino et al., 1991). Thus, the neurochemical events associated directly with cocaine-induced reinforcement are an important component to the behavioral and physiological response to cocaine injection. In addition, the acute lethal and anorectic effects of cocaine appear to be more prominent in yoke control vs. animals self-administering contingent cocaine injections (Dworkin et al., 1995). It is possible that operant-conditioned behavior modulates the cardiovascular effects of cocaine. For example, the effects of i.v. infusions of *l*-norepinephrine on cardiovascular parameters can be modulated by operant-conditioned behavior (Kelleher et al., 1974). Infusions of *l*-norepinephrine produced episodic increases in blood pressure and heart rate only when the animals were in the phase with schedule-controlled responding and not in the resting phase. Thus, a number of studies suggest that the physiological effects of cocaine injections may be markedly different when drugs are self-administered than when they are passively administered.

Most studies to date have recorded cardiovascular parameters in anesthetized animals or in conscious animals under passive cocaine administration conditions. Thus, in these studies, the factors associated with active self-administration of cocaine that could influence its cardiovascular effects have not been evaluated. Since various behavioral, physiological and toxic actions of cocaine may be dependent on the contingent vs. non-contingent administration, experimental paradigms that investigate the cardiovascular actions of cocaine under operant self-administration conditions are an important contribution. In general, operant self-administration of abused drugs with simultaneous recordings of cardiovascular parameters may be a useful model to search for and assess clinical treatments for cocaine addiction.

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