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# Cardiovascular responses to cocaine self-administration: acute and chronic tolerance

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**Abstract**

The nature and the mechanism of tolerance to the cardiovascular responses to cocaine self-administration were studied in rats implanted with telemetric devices. The first infusion of cocaine (1 mg/kg/infusion) on day 1 of testing produced rapid and brief increases in mean arterial blood pressure and in heart rate. Subsequent infusions in the same session produced minimal effects. With chronic testing, there were gradual reductions in cardiovascular responses to the first infusion in the daily session and enhancements in the daily cocaine intake, with significant changes occurring by the fourth week of the testing. Following saline extinction testing (for 5 days), reinstatement of cocaine during week 6 led to a partial and short lasting ($\leq 3$ sessions) recovery from the chronic tolerance to the rapid cardiovascular responses to cocaine. There were significant enhancements in cardiovascular responses to post-session norepinephrine during week 2 and marked reductions during week 6 as compared to corresponding control responses. There were marked reductions in the cardiovascular responses to post-session tyramine tested during week 3. These data indicate that self-administered cocaine produces rapid and brief cardiovascular responses which undergo both within-session acute tolerance and a between-session, reversible chronic tolerance. Adrenergic adaptive mechanisms mediate the chronic tolerance. The development of chronic cardiovascular tolerance to cocaine temporally parallels that of the apparent tolerance to its reinforcing effects. Doses of cocaine that maintain self-administration behavior inhibit the norepinephrine transporter at peripheral sympathetic nerve terminals. 

*Keywords:* Cocaine; Self-administration; Cardiovascular effect; Reinforcing effect; Acute tolerance; Chronic tolerance

## 1. Introduction

While numerous studies have investigated the cardiovascular effects of cocaine, the experimental conditions of most of these studies were different from human cocaine abuse conditions. Cocaine injections were typically administered by investigators in these studies, whereas cocaine is self-administered by humans. Human cocaine self-administration is preceded by a sequence of self-preparatory events. This self-preparation and the associated environmental events can have a significant modulatory influence on the behavior and physiology of subjects (Herd et al., 1976; Johanson, 1984). Substantial differences can exist between contingent and noncontingent presentation of environmental events or drugs on neurochemical, physiological and toxic consequences (Porrino et al., 1984; Smith and Dworkin, 1990). In this context, intravenous drug self-administration procedures using experimental animals have many similarities with cocaine abuse patterns in humans (Deneau et al., 1969; Wilson et al., 1971; Johanson et al., 1976). Several studies suggest that the investigation of pharmacological effects of cocaine using intravenous drug self-administration procedures has relevance for the etiology and the treatment of cocaine abuse and its associated toxicity (Thompson and Unna, 1977; Griffiths et al., 1980).

Another important concern is that most previous cardiovascular studies have dealt with the acute effects of a single dose of cocaine. However, it is known that cocaine

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is typically abused in a repetitive 'binge' pattern of administration. Repeated administration of cocaine has been known to produce either tolerance or sensitization to its behavioral effects (Stewart and Badiani, 1993; Hammer et al., 1997). Repetitive doses of cocaine have been shown to produce a within-session acute tolerance to its cardiovascular effects in some, but not all, studies (Fischman et al., 1985; Foltin et al., 1988; Noe and Kumor, 1991; Ambre, 1993; Smith et al., 1993; Shannon et al., 1996). However, the cardiovascular consequences of chronic multiple daily doses of cocaine administered over several weeks have not been investigated. Although the adrenergic system has been shown to play a central role in the acute cardiovascular effects of cocaine (Schwartz et al., 1988; Kiritsy-Roy et al., 1990, Stambler et al., 1993; Tella et al., 1993; Gillis et al., 1995), the mechanism of cardiovascular tolerance to cocaine remains unclear (Pitts et al., 1987; Jain et al., 1990; Smith et al., 1993; Shannon et al., 1996). Further, a majority of the experimental studies investigating the cardiovascular effects of cocaine were conducted with anesthetized animals. Since general anesthesia is known to markedly attenuate the cardiovascular effects of cocaine (Wilkerson, 1988; Tella et al., 1990), it is important to study these effects in conscious animals.

Norepinephrine transporters located in the postganglionic sympathetic presynaptic nerve terminals play an important role in the peripheral adrenergic control of the cardiovascular system. This transporter helps maintain the synaptic concentrations of norepinephrine at physiological levels by transporting synaptic norepinephrine back into the nerve terminals. Cocaine following its binding to the transporter inhibits this reuptake mechanism and thus increases synaptic norepinephrine. Following chronic cocaine exposure, disruption of this reuptake mechanism could potentially lead to chronic adaptive changes in peripheral adrenergic control of cardiovascular system. To our knowledge, studies addressing adaptive changes in the adrenergic nervous system following chronic cocaine self-administration have not been reported. It also is not known whether doses of cocaine that maintain self-administration behavior inhibit norepinephrine transporter function at peripheral sympathetic nerve terminals.

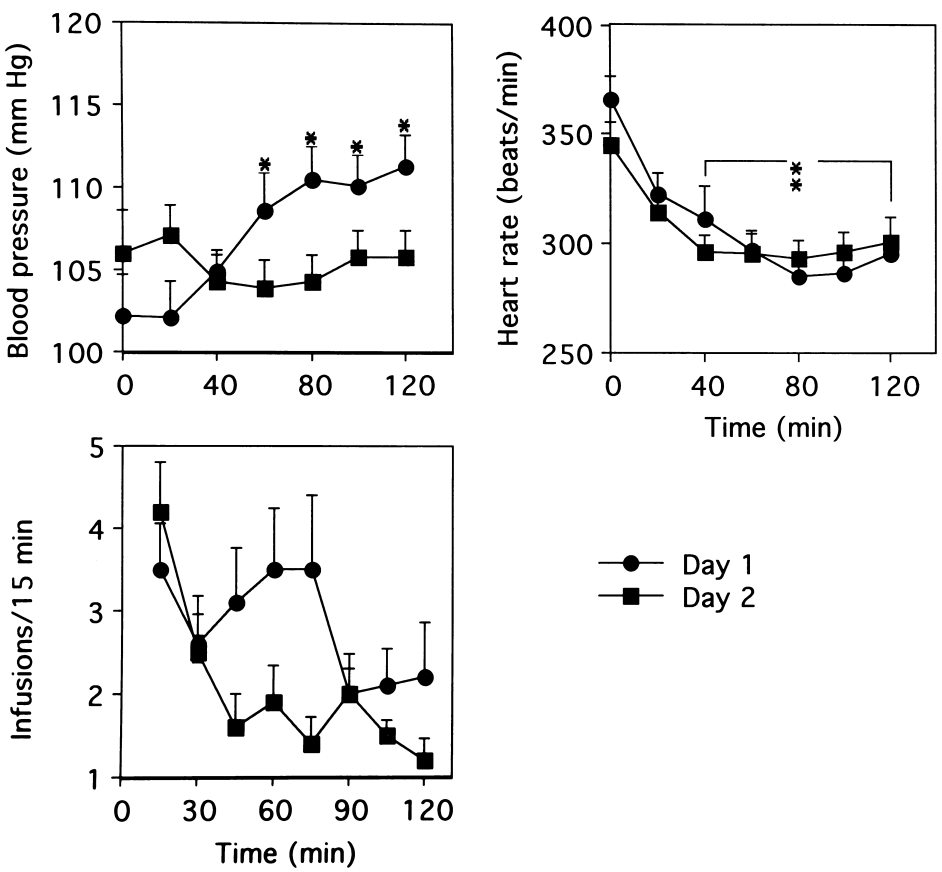


Fig. 1. The time-course of average (20-min blocks) blood pressure and heart rate during i.v. cocaine (1 mg/kg/infusion) self-administration on testing days 1 and 2. Also shown is the time-course of average (15-min blocks) cocaine intake on these test days. Each data point represents the mean ± 1 S.E.M. ($n = 10$). The cardiovascular measures at zero time represent the baseline measures prior to the first cocaine infusion in each session. There were significant ($P < 0.01$) within-session time-course differences in blood pressure on day 1, but not on day 2 of testing. There were significant within-session time-course differences in heart rate on both day 1 ($P < 0.001$) and day 2 ($P < 0.001$) of testing. $^{*}P < 0.05$; $^{**}P < 0.01$ as compared to their corresponding baseline cardiovascular measures at zero time by post hoc contrast tests. The time-courses of cardiovascular responses to cocaine self-administration and of cocaine intake on all other days of testing (data not shown) were similar to that of day 2.

The goal of the present study was to investigate both the acute and chronic cardiovascular effects of repetitive cocaine injections using intravenous drug self-administration techniques. The cardiovascular effects of reinstatement of cocaine self-administration following saline substitution test were also studied. We periodically monitored the cardiovascular responsiveness of the animals to norepinephrine in order to determine possible adaptive changes in the adrenergic system in response to chronic cocaine self-administration. To determine whether the doses of cocaine that maintain self-administration behavior are adequate to inhibit the function of the norepinephrine transporter at peripheral sympathetic nerve terminals, we investigated the cardiovascular effects of tyramine, a norepinephrine transporter substrate and an indirect adrenergic agonist, both before and after a cocaine self-administration session. Tyramine increases blood pressure indirectly by releasing norepinephrine from presynaptic sympathetic nerve terminals through a norepinephrine transporter-dependent mechanism. Therefore, a reduction in the cardiovascular response to tyramine can be used as a marker for the inhibition of norepinephrine transporter function at peripheral sympathetic nerve terminals.

## 2. Materials and methods

### 2.1. Subjects

Ten male Sprague–Dawley rats (Charles River Laboratories, Wilmington, DE) weighing 350–500 g were used. Animals were housed individually in temperature- and humidity-controlled rooms with a 12-h light (7:00 a.m. to 7:00 p.m.) and dark (7:00 p.m. to 7:00 a.m.) cycle.

### 2.2. Lever press training

Daily food intake was restricted until body weights gradually stabilized at 80–85% of free-feeding weights. Rats were then trained to press a lever for food pellets (45 mg) in standard operant chambers (Med Associates, East Fairfield, VT) each equipped with two levers. Responding on one of the levers resulted in delivery of a food pellet (reinforcement), while responding on the other lever was recorded, but had no programmed consequence. Training sessions were 1 h in duration. Rats were initially trained to respond under a fixed-ratio 1 schedule of food delivery (FR1; each lever press response produced a food pellet) and after every 50 such reinforcements, the FR was increased by 1 until FR10 (every tenth response produced a pellet) was reached. Following acquisition of lever-pressing under the FR10 schedule, rats were allowed food ad libitum to regain their free-feeding body weights. After the recovery of their body weights, each animal was surgically prepared with a head mount, an i.v. cannula and a transmitter as described below.

### 2.3. Surgical procedures

All surgeries were done according to the previously published procedures (Tella, 1996; Tella and Goldberg, 1998). Briefly, a small plastic pedestal was mounted on the rat skull under pentobarbital (50–60 mg/kg i.p.) anesthesia. The i.v. catheter was placed into the femoral vein and passed subcutaneously to exit at the back of the neck. Following 7 days of recovery, animals were surgically implanted with transmitters (Data Sciences International, St. Paul, MN) under halothane anesthesia. Briefly, an incision 4–5 cm long was made on the midline of the abdomen. The descending aorta was exposed below the renal arteries. A vascular clamp was placed immediately posterior to the renal artery. A curved 21-gauge needle was used to puncture the vessel anterior to the bifurcation. The catheter of the transmitter was inserted about 2 cm into the aorta. The area was dried and a drop of tissue adhesive (Vet Bond) was applied to the catheter entry point. The

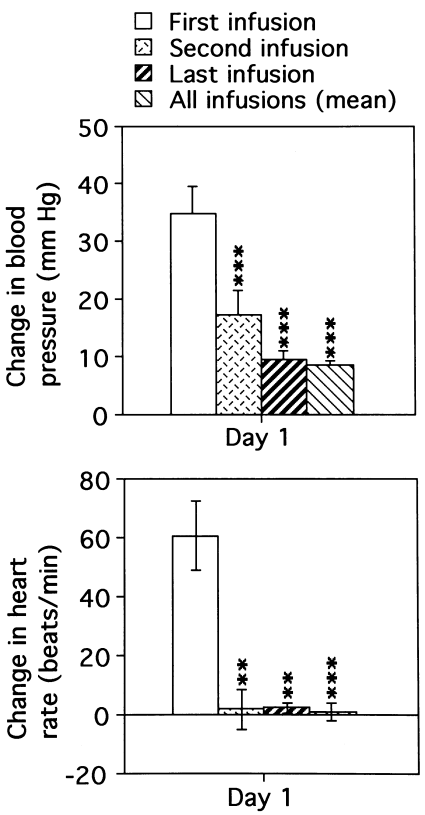


Fig. 2. Acute tolerance to the rapid increases in blood pressure and in heart rate produced by self-administered cocaine on the testing day 1. These rapid responses represent the maximal change within 30 s following each cocaine infusion. The first infusion of cocaine in a given session produced large increases in these measures, while the subsequent cocaine infusions in the same session produced significantly ($P < 0.001$) smaller effects. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ as compared to the first infusion effects by post hoc contrast tests. Each bar represents the mean ± 1 S.E.M. ($n = 10$). Cocaine self-administration produced qualitatively similar pattern of rapid responses on all other days of testing (data not shown).

transmitter was then sutured to the abdominal musculature. The abdominal incision and the skin were closed by suturing. An injection of 50,000 U/kg i.m. dual penicillin was given to safeguard against infection. Throughout the self-administration testing phase, rats were fed their daily food requirement of 5 g/100 g body weight of standard rat chow as a single meal.

### 2.4. Experimental procedures

Seven days after the transmitter surgery, rats were tested for cocaine self-administration. During testing, animals were placed in operant boxes and venous catheters were connected to external tubing, which in turn were connected to 10-ml syringes filled with cocaine solution. The syringes were placed in infusion pumps (Pump 22, Harvard Apparatus, South Natick, MA), which were interfaced with the computer. Following the completion of a fixed number of lever presses (fixed ratio of 10; FR10) by the animal, the infusion pump was programmed to deliver a 1-s cocaine solution. The infusion volume was adjusted for each animal to deliver a cocaine dose of 1 mg/kg/infusion. Access to cocaine was on a FR10 schedule with a 20-s signaled time-out during which responding had no programmed consequences after each infusion. Self-administration sessions (2 h in duration) were conducted once daily Monday through Friday. Experimental sessions were controlled by Med-PC software (Med Associates, East Fairfield, VT). The data from telemetric devices were collected by placing transmitter receivers below the operant boxes. The sampling of telemetric measures from the receivers was done every 10 s and recorded on another computer using Dataquest software (Data Sciences International). The parameters recorded were diastolic, systolic and mean arterial blood pressures and heart rate. The results on diastolic and systolic blood pressure were essentially similar to that of mean arterial blood pressure. Therefore, only mean arterial blood pressure is usually presented.

Following 4 weeks of cocaine self-administration, cardiovascular responses to saline substitution were studied for 1 week (week 5) by replacing cocaine solution with saline in the infusion syringe. The cardiovascular effects of cocaine reinstatement (1 mg/kg/infusion) following saline substitution were then investigated for one week (week 6) by replacing saline with cocaine solution in the infusion syringe.

Control cumulative dose–response relationships to norepinephrine (0.01–1 μg/kg) were determined prior to the

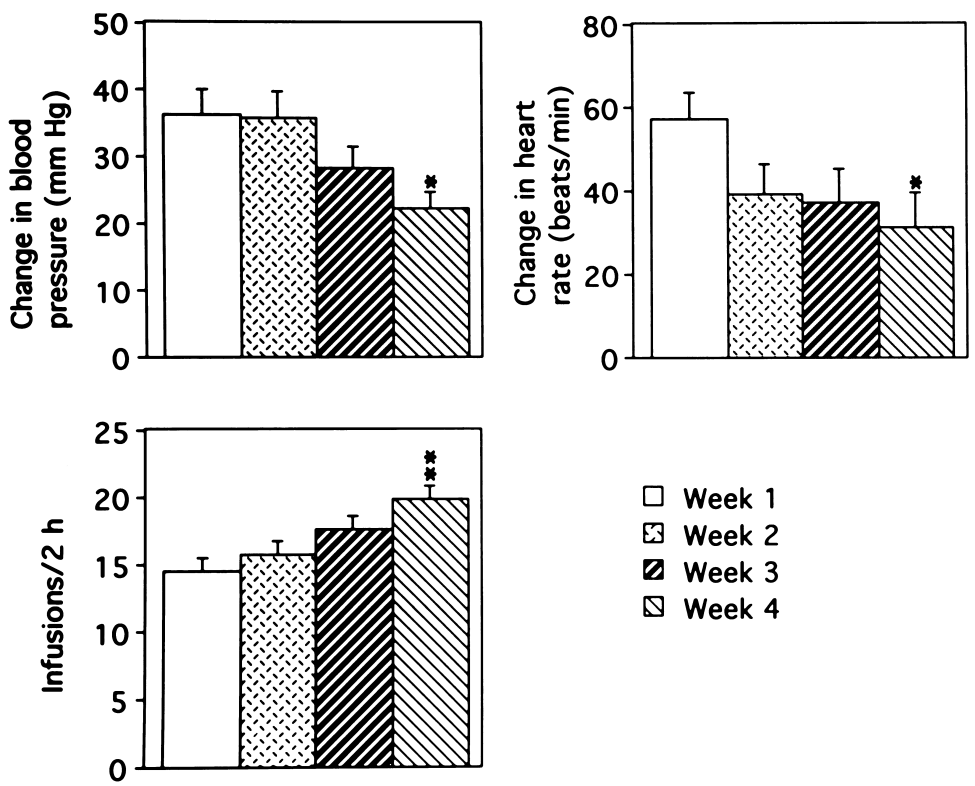


Fig. 3. The weekly averages of rapid increases in blood pressure and in heart rate produced by the first cocaine infusion in each session during weeks 1–4 of self-administration testing. Also shown are the weekly averages of daily total cocaine infusions during these 4 weeks of testing. Each bar represents the mean ± 1 S.E.M. ($n = 10$). There were significant differences in blood pressure ($P < 0.001$) and in heart rate ($P = 0.05$) effects of cocaine and in cocaine intake ($P < 0.01$) during the 4 weeks of testing. $^{*}P < 0.05$; $^{**}P < 0.01$ as compared to the corresponding measures during week 1 by post hoc contrast tests.

Table 1
Baseline cardiovascular measures prior to the first, the second and the last infusion of cocaine during its self-administration on days 1, 2, 10 and 20

| Test day | Parameter | Prior to | | |
|---|---|---|---|---|
| | | First infusion | Second infusion | Last infusion |
| Day 1 | Blood pressure | 101.5 ± 2.4 | 102.5 ± 2.4 | 110.5 ± 2.8[a] |
| | Heart rate | 347 ± 15.7 | 344 ± 13.8 | 290 ± 9.4[c] |
| Day 2 | Blood pressure | 103.8 ± 3.6 | 104.7 ± 2.8 | 103.9 ± 1.6 |
| | Heart rate | 326 ± 16.3 | 322 ± 14.3 | 297 ± 13.7[b] |
| Day 10 | Blood pressure | 105.4 ± 2.9 | 110.8 ± 2.6 | 105.1 ± 2.0 |
| | Heart rate | 315 ± 7.8 | 302 ± 9.11 | 273 ± 8.2[c] |
| Day 20 | Blood pressure | 104.1 ± 2.2 | 110 ± 3[a] | 105 ± 2 |
| | Heart rate | 314 ± 9.6 | 314 ± 9.5 | 277 ± 9.3[b] |

[a] $P < 0.05$.
[b] $P < 0.001$.
[c] $P < 0.01$.

start of cocaine self-administration sessions. This dose–response testing with norepinephrine was repeated following the end of the cocaine self-administration session on day 1 of week 2 and on the last day of week 6. Norepinephrine was injected i.v. in a volume of 0.1 ml/kg followed by a 0.3-ml saline flush. The inter-dose interval was 10 min. The effects of tyramine were studied on day 14 (day 4 of week 3) by administering 0.3 mg/kg of tyramine both before and 10 and 60 min after the end of the cocaine self-administration session. This dose of tyramine produces consistent increases in blood pressure of similar magnitudes following each of three consecutive infusions at 10-min intervals without any tachyphylaxis (Tella et al., 1992).

### 2.5. Data analysis

The rapid changes in blood pressure and heart rate within the first 30 s following each infusion of cocaine in a given session were calculated and compared. To determine the long term changes in the rapid cardiovascular effects of the first cocaine infusion in each session, the corresponding measures for all 5 days (4 days for week 3) of a given week were averaged and compared. Similarly, the total number of daily cocaine infusions for all 5 days (except day 1 of the first week) of a given week were averaged and compared. Since the temporal pattern of cocaine intake on day 1 of week 1 appeared to be different from that of subsequent days of testing (Fig. 1), the data on this day was not included in the calculation of weekly averages of daily cocaine intake. To determine the time-course of within-session changes, cardiovascular measures were averaged every 20 min. Similarly, to determine the time-course of cocaine intake in a given session, the number of infusions delivered during each 15 min of the session were summed and presented. The cardiovascular responses to the first infusion during each session of saline substitution or cocaine reinstatement were compared with the corresponding cardiovascular responses to cocaine obtained on the last day of cocaine self-administration prior to initiation of saline substitution (day 20; i.e., last day of week 4). Cardiovascular responses to post-session norepinephrine were compared with corresponding control responses determined prior to the start of cocaine self-administration testing. Post-session responses to tyramine were compared with the corresponding pre-session control responses to tyramine. Statistical analyses were done using an analysis of variance for repeated measures followed by post hoc contrasts (Wilkinson, 1989). The post hoc contrast tests were done by comparing individual mean value with the corresponding control mean value. The doses of norepinephrine that increased blood pressure by 30 mm Hg ($ED_{30}$) and reduced heart rate by 100 beats/min ($ED_{100}$) were determined using least squares linear regression bioassay procedures (Finney, 1964; Snedecor and Cochran, 1967). All values are expressed as mean ± 1 S.E.M.

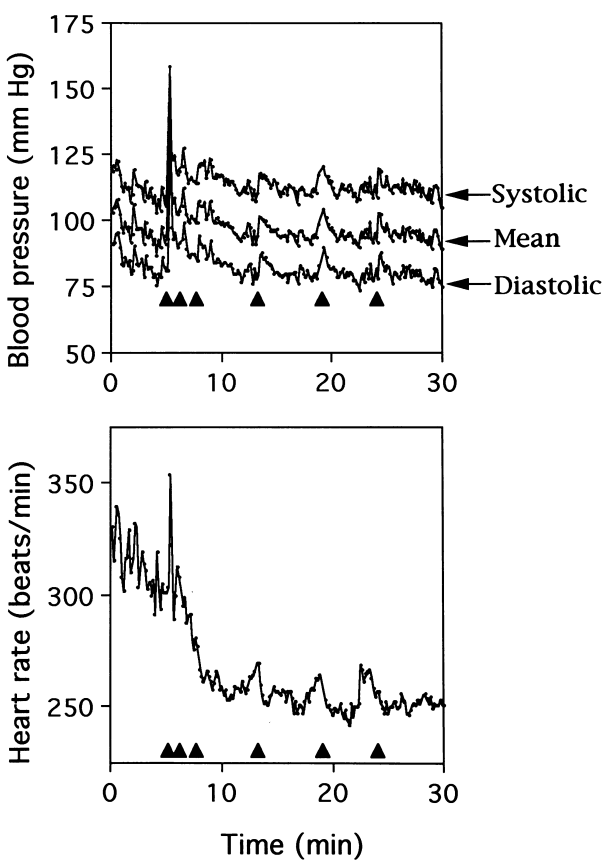


Fig. 4. Temporal response pattern of cocaine self-administration and the accompanying changes in diastolic, systolic, and mean arterial blood pressures and in heart rate during the first half-hour of a typical session in a rat. Each triangle represents an infusion of self-administered cocaine at that time point in the session. Note the rapid increases in diastolic, systolic and mean arterial blood pressures and in heart rate following the first cocaine infusion and the markedly attenuated responses to its subsequent infusions.

## 3. Results

### 3.1. Cocaine self-administration and cardiovascular measures

Rats reliably maintained consistent cocaine self-administration. With the exception of the first day, there were a relatively large number of cocaine infusions in quick succession at the start of each session followed by a moderate and consistent intake at regular time intervals for the remainder of the session (Fig. 1). Differences in the intake of cocaine between the beginning of the session versus the remainder of the session were less evident on the first day of testing.

Cocaine self-administration on day 1 of testing produced two temporally distinct cardiovascular effects. One effect consisted of rapid and brief ($< 2$ min) increases in blood pressure and heart rate following the first infusion of cocaine (Fig. 2). These rapid cardiovascular responses to the second and the subsequent infusions of cocaine within the same session were of significantly smaller magnitudes. The other effect on day 1 of testing consisted of a gradual within-session increase in blood pressure and a gradual reduction in heart rate that was sustained until the end of the session (Fig. 1). On day 2 of self-administration testing, there were similar rapid effects (data not shown) and within session gradual reductions in heart rate but there was no within session progressive increase in blood pressure (Fig. 1). On subsequent days of testing, cocaine self-administration produced effects similar to those on day 2, but with some quantitative differences. There were gradual reductions in the rapid responses to the first cocaine infusion of a given daily session with statistically significant changes occurring during week 4. In parallel to the gradual reductions in the rapid cardiovascular responses to the first cocaine infusion, there were gradual increases in the weekly averages of daily cocaine intake, with a statistically significant increase occurring during week 4 (Fig. 3). There were no significant differences in weekly averages of pre-session baseline blood pressure and heart rate during the 4 weeks of cocaine self-administration testing (data not shown). However, there was a significant elevation in baseline blood pressure prior to last infusion as compared to that of the first infusion on day 1,

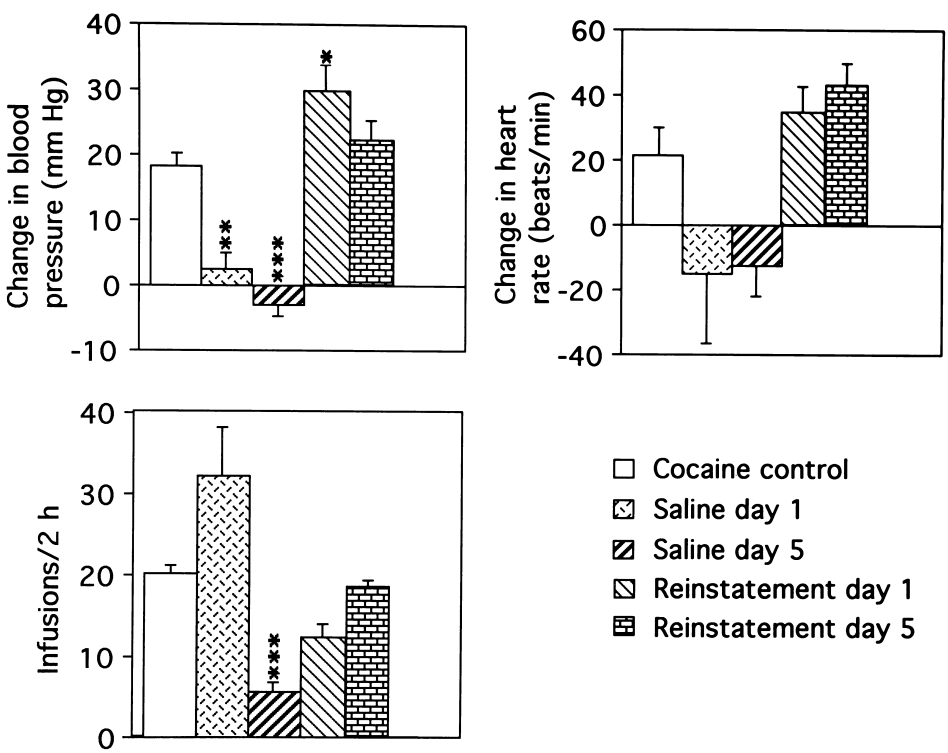


Fig. 5. Cardiovascular responses to substitution of saline for cocaine for five consecutive daily sessions followed by reinstatement of cocaine for five consecutive daily sessions during self-administration testing. For the sake of clarity, the data of the first and the last session of saline substitution and of cocaine reinstatement were presented. The maximal changes in blood pressure and in heart rate within 30 s following the first infusion of saline or cocaine on a given day were calculated and presented. Cocaine control represents the corresponding data obtained on the last cocaine self-administration day (day 20) prior to saline substitution test. Also shown are the average daily self-administered infusions of cocaine or saline on these days of testing. Each bar represents the mean $\pm$ 1 S.E.M. ($n = 10$). Unlike cocaine, saline produced little or no changes in cardiovascular measures. There were significant ($P < 0.001$) reductions in the total daily self-administered saline infusions as compared to the corresponding cocaine infusions on the day prior to the saline substitution test. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ as compared to their corresponding cocaine control measures by post hoc contrast test. The data on saline days 2, 3 and 4 (data not shown) are similar to that recorded on day 5. Cocaine produced larger increase in blood pressure on day 1 of reinstatement following saline test. This enhancement lasted for two to three sessions (data for days 2, 3 and 4 are not shown).

but not on the other days of testing (Table 1). There were gradual and significant reductions in baseline heart rate on all days of testing. A representative response pattern of cocaine self-administration and the accompanying heart rate and diastolic, systolic and mean blood pressure changes during the first half-hour of a typical daily session are shown in Fig. 4.

### 3.2. Saline substitution and cardiovascular measures

Substitution of saline for cocaine led to a temporary and small, but not significant increase in the rate of self-administration responding on day 1 (Fig. 5). In contrast, there were marked reductions in the rates of responding from day 2 and onwards (data for saline days 2, 3 and 4 are not shown). Unlike in cocaine sessions, there were no significant changes in blood pressure and heart rate following the first saline infusion in any given saline session (Fig. 5). However, there were gradual and sustained within-session reductions in blood pressure and in heart rate during all the saline substitution days (Fig. 6; data for saline days 2, 3 and 4 are not shown). The gradual reduction in heart rate on day 1 of saline substitution appeared to have a delayed onset. The pre-session baseline blood pressure and heart rate values during the 5 days of saline substitution were not significantly different from those on the last day (day 20) of cocaine self-administration, prior to saline substitution (data not shown).

### 3.3. Cardiovascular responses to reinstatement of cocaine self-administration

Following saline-substitution test, replacement of saline with cocaine led to a prompt reinstatement of self-administration responding (Fig. 5). The cardiovascular responses to cocaine reinstatement were qualitatively similar to those obtained with cocaine prior to saline-substitution testing, with some quantitative differences (Figs. 5 and 6). The magnitude of the rapid increase in blood pressure after the first infusion of cocaine on day 1 of reinstatement was significantly larger than the corresponding increase in blood pressure after the first cocaine infusion on the day prior (day 20) to saline substitution. However, after 3 days of cocaine reinstatement testing, these rapid responses to cocaine on days 4 and 5 of reinstatement were not significantly different from the corresponding responses obtained on the day prior (day 20) to saline substitution (Fig. 5; data for reinstatement days 2, 3 and 4 are not shown). The pre-session baseline blood pressure and heart rate values during the 5 days of cocaine reinstatement were not significantly different from those on saline-substitution days and on the last day of cocaine self-administration (day 20), prior to saline substitution (data not shown).

### 3.4. Cocaine self-administration and cardiovascular responses to adrenergic drugs

Norepinephrine (0.01–1 μg/kg) produced dose-dependent, rapid and brief (< 2 min) increases in blood pressure and reductions in heart rate, when tested prior to the initiation of cocaine self-administration testing (Fig. 7). Norepinephrine, when tested post-session on day 1 of week 2, was found to be more potent in increasing blood pressure and decreasing heart rate as compared to its corresponding potencies prior to cocaine self-administration testing (Table 2). In contrast, it was considerably less potent in increasing blood pressure during week 6 of cocaine self-administration testing as compared to its corresponding potency prior to cocaine self-administration testing. There was also a trend for reduced potency in decreasing heart rate during week 6.

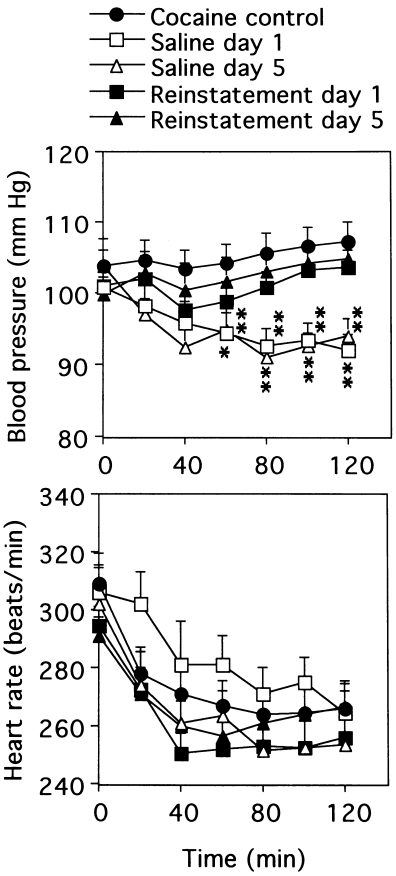


Fig. 6. The time-course of within-session changes in average (20-min blocks) blood pressure and heart rate on cocaine control day and on the first and the last day of both the saline substitution and the cocaine reinstatement. Responses to saline substitution and cocaine reinstatement on all other days (data not shown) were similar to their corresponding responses recorded on the last day of these tests. Each data point represents the mean ± 1 S.E.M. ($n = 10$). The cardiovascular measures at zero time represent the baseline measures prior to the first cocaine or saline infusion in each session. There were significant (day 1: $P < 0.01$; day 5: $P < 0.001$) within-session reductions in blood pressure on saline days. There were also significant within-session reductions in heart rate on cocaine control ($P < 0.001$), saline days 1 ($P < 0.001$) and 5 ($P < 0.001$), reinstatement days 1 ($P < 0.01$) and 5 ($P < 0.001$). $^{*}P < 0.05$; $^{**}P < 0.01$ as compared to their corresponding baseline measures by post hoc contrast tests. The $P$ values of post hoc contrast tests for heart rate ranged from 0.04 to 0.001 and are not shown in the figure for the sake of clarity.

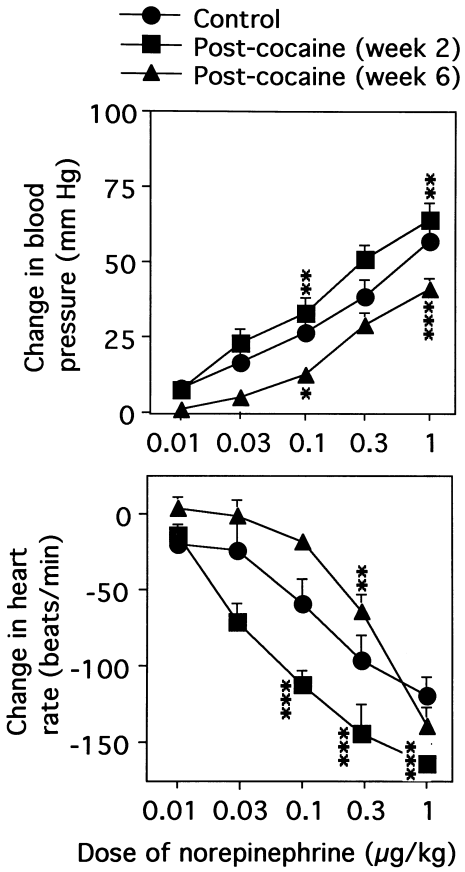


Fig. 7. Effect of cocaine self-administration on cardiovascular responses to norepinephrine tested post-session on day 1 of week 2 and on the last day of week 6. Control responses represent the effects of norepinephrine obtained prior to the initiation of cocaine self-administration testing. Each data point represents the mean ± 1 S.E.M. ($n = 7$). On blood pressure, there were signicant effects at 0.1 ($P < 0.01$), and 1.0 ($P < 0.05$) μg/kg doses of norepinephrine. On heart rate, there were signicant effects at 0.1 ($P < 0.01$), 0.03 ($P < 0.05$) and 1.0 ($P < 0.05$) μg/kg doses of norepinephrine. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ as compared to their corresponding control responses by post hoc contrast tests.

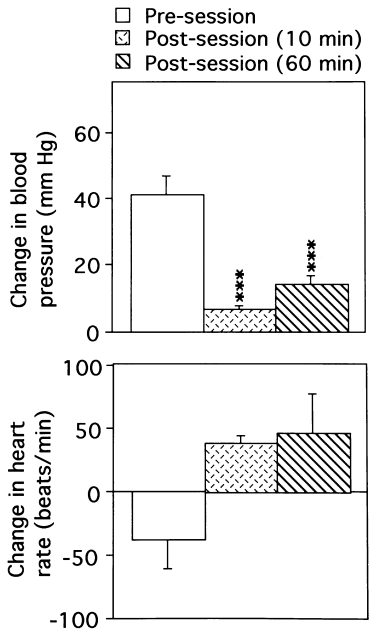


Fig. 8. Effect of cocaine self-administration on cardiovascular responses to tyramine (0.3 mg/kg) tested pre- and post-session (10 and 60 min) during week 3 ($n = 7$). There were significant ($P < 0.001$) differences in tyramine-induced changes in blood pressure. $^{***}P < 0.001$ as compared to their corresponding pre-session control measures by post hoc contrast test.

Tyramine (0.3 mg/kg), when tested prior to the 14th cocaine self-administration session (day 4 of week 3), produced a large but brief (< 3 min) increase in blood pressure and a reduction in heart rate (Fig. 8). There were significant reductions in tyramine-induced increases in blood pressure, when tested at 10 and 60 min post-session on the same day, compared to the corresponding pre-session control values. Unlike pre-session testing, tyramine did not decrease heart rate during post-session testing, but instead increased it.

Table 2
The doses (μg/kg) of norepinephrine to produce an increase of 30 mm Hg ($ED_{30}$) in blood pressure and a reduction of 100 beats/min ($ED_{100}$) in heart rate prior (control) to and during the second and the sixth week of cocaine self-administration testing
The numerals in parentheses indicate the 95% confidence intervals. Control responses to norepinephrine were determined prior to the initiation of self-administration testing. The responses to norepinephrine during weeks 2 and 6 were determined post-session.

| Condition | Blood pressure [$ED_{30}$ (μg/kg)] | Heart rate [$ED_{100}$ (μg/kg)] |
|---|---|---|
| Control | 0.106 (0.078–0.143) | 0.45 (0.27–0.97) |
| Week 2 | 0.063 (0.05–0.077) | 0.093 (0.067–0.13) |
| Week 6 | 0.379 (0.287–0.379) | 0.613 (0.91–0.447) |

## 4. Discussion

We recently reported that intravenous cocaine produces two temporally distinct effects on blood pressure and heart rate with different underlying neurobiological mechanisms in conscious rats (Tella, 1996; Tella and Goldberg, 1998). One is a dopamine receptor-independent rapid and brief increase in blood pressure and heart rate which occurs within 30 s following a cocaine injection. The other effect is a dopamine receptor-dependent sustained and moderate increase in blood pressure and heart rate. In the present study, we found that similar to noncontingent cocaine, the first self-administered cocaine infusion in a given session produces rapid and brief increases in blood pressure and in heart rate. This suggests that both contingent and noncontingent infusions of cocaine produce the initial rapid responses and the operant procedure per se does not appreciably alter them. Acute tolerance to the rapid effects of

self-administered cocaine in the present experiment occurred quickly, as there were markedly diminished responses to subsequent cocaine infusions within the same 2-h session. The diminished responses to the second and subsequent infusions are not due to elevations in baseline measures following the first infusion as these measures promptly returned to pre-infusion control values following the first infusion.

Chronic tolerance to these rapid effects of the first infusion of cocaine also occurred as evidenced by significant reductions in the magnitudes of these responses by the fourth week of self-administration. The present study also indicates that cocaine self-administration produces gradual and sustained increase in blood pressure on day 1 of testing, but not on subsequent days. One possible factor underlying this sustained increase in blood pressure may be the large cocaine intake during the middle of the session on day 1 of testing. Alternatively, it is possible that this sustained increase in blood pressure on day 1 is the counterpart to the dopamine receptor-dependent prolonged increase in blood pressure produced by noncontingent cocaine (Tella, 1996; Tella and Goldberg, 1998). This is indicated by our additional recent findings that the self-administration of GBR-12909, a dopamine-selective uptake inhibitor, also produces a sustained increase in blood pressure on day 1, but not the subsequent days of testing (unpublished results). This further supports our original hypothesis of the dopaminergic nature of the prolonged increase in blood pressure produced by cocaine (Tella, 1996; Tella and Goldberg, 1998).

Unlike noncontingent cocaine infusions, self-administered cocaine infusions did not produce a prolonged increase in heart rate during the course of any session in the present study. This may be due to repeated infusions of self-administered cocaine in rapid succession, thereby increasing the likelihood of a local anesthetic-dependent inhibitory effect on cardiac pacemaker activity (Crumb and Clarkson, 1990; Erzouki et al., 1993). The substitution of saline for cocaine caused a sustained reduction in blood pressure. This is consistent with our previous report (Ambrosio et al., 1996).

Acute within-session tolerance to the rapid cardiovascular responses to cocaine infusion readily occurred following a single self-administered infusion. Similarly, with noncontingent infusions of cocaine, acute tolerance to its excitatory cardiovascular effects has been reported (Pitts et al., 1987; Ambre, 1993; Smith et al., 1993; Shannon et al., 1996). Thus, acute tolerance is not unique to the response-contingent procedures used in the present study. Although, we did not measure plasma concentrations of cocaine and its metabolites, it is unlikely that the acute tolerance is due to enhanced metabolism of cocaine following repeated cocaine infusions. Acute tolerance to cardiovascular effects occurred rapidly as evidenced by the marked reductions in the responses to the second infusion received within minutes following the first cocaine infusion in a given session. It is highly unlikely that the induction of cocaine metabolizing enzymes occurs within this rapid time-course. Further, previous studies have shown that repeated noncontingent i.v. administration of cocaine results in increases in plasma cocaine concentrations (Wilkerson, 1988; Shannon et al., 1996), not reductions.

One potential mechanism that may be relevant to the acute tolerance is the stimulation of presynaptic norepinephrine release-regulating inhibitory $\alpha_2$-adrenoceptors at sympathetic nerve terminals (Jain et al., 1990; Smith et al., 1993). Based on their findings in conscious dogs that acute tolerance to cocaine-induced increases in plasma catecholamines occurs not only to norepinephrine, but also to epinephrine of adrenal medullary origin, Shannon et al., (1996) argued that the presynaptic $\alpha_2$-adrenoceptor mechanism is inadequate to completely account for the acute tolerance phenomenon. These authors reported acute cardiovascular tolerance following the first infusion of five repeated cocaine infusions given at 25-min intervals. They also found no alteration in the cardiovascular effects of isoproterenol, a β-adrenoceptor agonist, and phenylephrine, an α-adrenoceptor agonist, following five repeated doses (1 mg/kg) of cocaine. Further studies are needed to determine whether or not a similar lack of alteration in cardiovascular responsiveness to adrenoceptor stimulation following a single self-administered cocaine infusion in a given session occurs. In light of several previous reports implicating the involvement of the central nervous system in the cardiovascular effects of cocaine, another potential site for the acute rapid tolerance to the pressor and tachycardiac effects of cocaine could be the central nervous system (Wilkerson, 1988; Kiritsy-Roy et al., 1990; Knuepfer and Branch, 1992; Tella et al., 1992, 1993).

Another pharmacodynamic action of cocaine that may be relevant to its cardiovascular effects is the release of norepinephrine from peripheral sympathetic nerve terminals, similar to the action of indirect sympathomimetic agent such as tyramine (Campos et al., 1963; Maengwyn-Davies and Koppanyi, 1966; Trendelenburg, 1968; Tessel et al., 1978). Studies using anesthetized animals provide some evidence in support of the involvement of this mechanism in the cardiovascular effects of cocaine (Teeters et al., 1963; Pitts et al., 1987). However, it should be pointed out that the use of general anesthesia largely attenuates the cardiovascular effects of cocaine (Wilkerson, 1988; Tella et al., 1990). Our studies using conscious animals do not lend support for this mechanism (Tella et al., 1992). Further, the concentration of cocaine required to produce a tyramine-like indirect sympathomimetic action is severalfold higher than that needed to inhibit norepinephrine transporter function (Campos et al., 1963; Maengwyn-Davies and Koppanyi, 1966; Trendelenburg, 1968; Tessel et al., 1978). In light of these considerations, it is unlikely that a tyramine-like indirect sympath-

omimetic action of cocaine is involved in the acute tolerance to its cardiovascular effects.

The present data indicate that in addition to acute tolerance, chronic tolerance to the rapid cardiovascular effects of cocaine also occurs, as evidenced by marked reductions in blood pressure and heart rate responses to cocaine during the fourth week of self-administration as compared to the first week. An impaired cardiovascular responsivity to norepinephrine in animals self-administering cocaine may underlie this chronic tolerance for several reasons. First, chemical sympathectomy with 6-hydroxy dopamine or pretreatment with α-adrenoceptor antagonists phentolamine or prazosin have been shown to attenuate to a large extent the rapidly occurring peak pressor responses to cocaine (Tella et al., 1993; Chen et al., 1995). This suggests that endogenous norepinephrine of sympathetic nerve terminal origin plays a main role in the rapid peak pressor effects of cocaine. Secondly, although cocaine potentiated the pressor responses to post-session norepinephrine during early stages of its testing, it lacked this effect following its chronic self-administration for several weeks in the present study. Instead, there were attenuations in the pressor response to norepinephrine. Thirdly, there was a time-course correspondence between the reduction in the pressor response to norepinehprine and the development of chronic tolerance to cocaine's rapid pressor responses. Both of these responses developed tolerance following several weeks, but not during the initial weeks of cocaine self-administration. The nature and the site of pre- or postsynaptic adaptive changes in the peripheral adrenergic system underlying this chronic tolerance remains to be investigated. One potential postsynaptic mechanism may be the downregulation of adrenoceptors following chronic daily cocaine exposure (Avakian et al., 1990). Although peripheral adrenergic adaptation leading to impaired cardiovascular responses to norepinephrine may be invoked to explain the chronic tolerance to cocaine's rapid pressor responses, this mechanism is not adequate to explain the acute within-session tolerance. This is because the acute tolerance to cocaine's rapid pressor responses occurred following a single infusion of cocaine on all days starting from day 1, while no such tolerance to norepinephrine's effects occurred during the early weeks of self-administration testing.

There was a significant increase in the daily cocaine intake during week 4 of cocaine self-administration as compared to the corresponding intake during the first week of its self-administration. This suggests that tolerance may develop to the reinforcing effects of cocaine following its chronic self-administration and is in agreement with previous reports (Hammer et al., 1997). Alternatively, rats may be developing tolerance to certain disruptive effects of cocaine on behavior which may limit responding or might be showing a progressive improvement in learning the operant task. However, based on the presence of tolerance to both high and low doses of cocaine, other investigators favored the hypothesis of tolerance to the reinforcing effects of cocaine (Hammer et al., 1997). It has been further suggested that adaptive changes in the mesocorticolimbic dopaminergic system may mediate such a chronic tolerance to the reinforcing effects of cocaine. This system is thought to play a central role in the acute behavioral and reinforcing effects of cocaine (Kuhar et al., 1991; Koob, 1992). The results of the present study also indicate that the time-course of development of apparent chronic tolerance to cocaine's reinforcing effects parallels that of its rapid cardiovascular effects. This suggests that the neurobiological adaptive changes underlying the chronic tolerance to cocaine's rapid cardiovascular effects follows a time-course similar to that underlying the chronic tolerance to its reinforcing effects. Alternatively, a common neurobiological mechanism may, at least in part, mediate both the reinforcing and rapid cardiovascular effects of cocaine and thus could explain the similar time-course of tolerance development to these effects.

One important pharmacodynamic action of cocaine is the inhibition of norepinephrine reuptake at peripheral sympathetic nerve terminals (Furchgott et al., 1963). Although the contribution of this pharmacodynamic action of cocaine to the initiation of its excitatory cardiovascular effects is controversial (Schindler et al., 1992; Tella et al., 1993; Gillis et al., 1995), this action, nevertheless, has the potential to modulate the ongoing cardiovascular effects of cocaine. For example, in the present study, the doses of cocaine that maintained self-administration behavior clearly inhibited the peripheral norepinephrine transporter function as evidenced by the potentiation and the inhibition of pressor responses to norepinephrine and tyramine, respectively. Similar studies on norepinephrine uptake have not been done in humans self-administering cocaine. However, based on well-established pharmacological similarities between intravenous drug self-administration in animals and human drug abuse patterns (see Section 1), it is likely that this effect occurs in humans and thus needs to be considered in the pharmacological evaluation of cocaine abuse.

In summary, the present experiments demonstrate that self-administered-cocaine produces rapid and brief increases in blood pressure and in heart rate. Acute (within-session) as well as chronic (between-sessions) tolerance occur to these cardiovascular effects of cocaine. Both these phenomena are reversible. Peripheral adrenergic adaptive changes leading to impaired responses to norepinephrine appear to mediate the between-session chronic tolerance to cocaine's pressor responses, while these mechanisms do not seem to be critical for within-session acute tolerance. Further studies are needed to determine the role of central mechanisms in the acute tolerance to cocaine. The doses of cocaine that reinforce self-administration behavior are adequate to inhibit the norepinephrine transporter function at peripheral sympathetic nerve terminals. Chronic tolerance may develop to the reinforcing effects of cocaine. The time-course of development of this apparent tolerance to

cocaine's reinforcing effects parallels that of chronic tolerance to its rapid cardiovascular effects. There are similarities as well as differences between the cardiovascular effects of self-administered versus noncontingent cocaine infusions.

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