Mechanism of the Blood Pressure–Raising Effect of Cocaine in Humans

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Background—Although the sympathomimetic actions and cardiovascular complications of cocaine are ascribed to inhibition of norepinephrine (NE) reuptake, this hypothesis has not been tested in humans. We asked (a) whether cocaine can inhibit NE reuptake in the human peripheral circulation and (b) whether the NE-mediated peripheral vasoconstriction is the main mechanism mediating blood pressure–raising effect of cocaine.

Methods and Results—In 15 healthy cocaine-naive subjects, we measured blood pressure, forearm blood flow, and forearm venous NE concentration during administration of (a) intrabrachial cocaine (0.15 and 15 mg), which produced no systemic neurohormonal effects, and (b) intranasal cocaine (2 mg/kg). Intrabrachial cocaine (0.15 mg) increased venous forearm NE concentration by 82% and vascular resistance by 71% (P<0.01). Increasing the intrabrachial cocaine dose by 100-fold to match the venous cocaine level of massive cocaine overdose caused a small additional increase in venous forearm NE concentration without causing significant additional vasoconstriction. Although intranasal cocaine (2 mg/kg) matched the venous cocaine concentrations caused by 0.15 mg of intrabrachial cocaine, venous NE concentration was unchanged as sympathetic nerve activity (SNA) decreased reflexively as the result of an increase in blood pressure. When SNA was restored to baseline by blunting the cocaine-induced rise in blood pressure (baroreflex activation) with nitroprusside, venous NE concentration increased to the same level caused by intrabrachial cocaine.

Conclusions—In healthy cocaine-naive individuals, cocaine can inhibit NE reuptake in the human peripheral circulation. However, this mechanism does not contribute importantly to the blood pressure–raising effect of cocaine because activation of baroreceptor reflexes decreases SNA, the neural stimulus for NE release. (Circulation. 2002;105:1054-1059.)

Key Words: cocaine ■ norepinephrine ■ nervous system, sympathetic ■ baroreceptors

Cocaine abuse is a major cause of life-threatening cardiovascular emergencies including ventricular arrhythmias, acute myocardial infarction, and hypertensive crisis.1–4 Although these emergencies are attributed to excessive adrenergic stimulation of the heart and blood vessels,5–7 the underlying mechanisms mediating the sympathomimetic actions of cocaine on the human cardiovascular system have not been well studied. The standard explanation is that cocaine blocks norepinephrine (NE) reuptake in peripheral sympathetic nerve terminals, thereby increasing the NE concentration in the synaptic cleft.1,8–10 However, the principal support for this theory is derived from studies in ex vivo rodent preparations, with an amazing paucity of direct experimental support in either intact animals or human subjects.9,11

Two observations led us to suspect that inhibition of NE reuptake is considerably less important than previously assumed in mediating the blood pressure–raising effects of cocaine in vivo: (1) In patients, tricyclic antidepressants, which are more effective than cocaine at blocking the NE transporter, do not raise blood pressure,12 and (2) in healthy humans, intranasal cocaine raises blood pressure and activates baroreceptor reflexes, thereby reflexively decreasing sympathetic nerve activity (SNA), the neural stimulus for NE release.13 If there is little stimulus for NE release into the synaptic cleft, there should be little NE available for reuptake by the transporter and thus little transporter activity to be blocked by cocaine.

Accordingly, we performed studies in 15 healthy cocaine-naive human subjects to determine if forearm venous NE concentrations and vascular resistance increase when cocaine is either (a) infused directly into the brachial artery, which avoids systemic spillover, or (b) administered systemically, which evokes baroreflex suppression of SNA. We hypothesized that the same forearm venous cocaine concentration results in a much smaller increase in venous NE concentration when SNA (measured with intraneural microelectrodes) is suppressed (intranasal cocaine alone) than when SNA is unchanged (intrabrachial cocaine).
Methods
We studied 15 healthy volunteers, 22 to 39 years of age. The Institutional Review Board of the University of Texas Southwestern Medical Center approved the protocol, and all subjects provided their informed written consent to participate. All subjects were normotensive and had no history of cardiovascular disease or substance abuse. None of the subjects was taking any prescription or nonprescription drugs with cardiovascular or autonomic effects. Subjects were instructed to refrain from smoking cigarettes or drinking alcohol or caffeine-containing beverages for at least 12 hours before the experiment.

With the subjects supine, heart rate (HR) was recorded continuously from the ECG with a multichannel digital data recorder (MacLab/85 ML780, AD Instruments Inc). Blood pressure (BP) was measured either by an intra-arterial catheter or by the oscillometric technique.

Forearm Blood Flow
Forearm vascular responsiveness was assessed bilaterally by venous occlusion plethysmography with a mercury strain gauge (Hokanson EC 6). Hand blood flow was excluded by means of a wrist cuff inflated to 250 mm Hg during measurement of forearm blood flow. Forearm blood flow was expressed in milliliters per minute per 100 mL of forearm volume. Forearm vascular resistance (FVR) was calculated as mean arterial pressure (MAP) divided by forearm blood flow.

Plasma NE Concentration
Plasma concentrations of NE were determined by high-performance liquid chromatography14 (Mayo Medical Laboratories). The intra-assay coefficient of variation was 4.0%.

Measurement of SNA by Microneurography
Multiunit recordings of postganglionic SNA were obtained with unipolar tungsten microelectrodes inserted into muscle nerve fascicles of the peroneal nerves with the use of the microneurographic technique of Valbo et al.15 Briefly, the nerve signals are amplified, filtered (bandwidth 700 to 2000 Hz), rectified, and integrated to obtain a mean voltage display of SNA. The interobserver and intraobserver variations in identifying bursts of muscle SNA are 5% and <5%, respectively.16 Nerve traffic was expressed as (a) bursts per minute and (b) percent changes in the total activity (burst frequency times mean burst amplitude).

Experimental Protocols
Protocol 1: Intrabrachial Cocaine
Ten experiments were conducted in 10 subjects. After local anesthesia, the brachial artery of the nondominant arm was cannulated with a 20-gauge, 7.6-cm catheter (Argon) for intra-arterial blood pressure monitoring and local infusion of saline and cocaine. To obtain deep venous blood samples, retrograde cannulation of the antecubital vein was performed with the use of an 18-gauge catheter. Solutions of cocaine hydrochloride (0.01 mg/mL or 1.0 mg/mL) or vehicle (normal saline) were titrated to the same pH (5.5) and infused at a rate of 1 mL/min for 15 minutes through an infusion pump. In pilot experiments, we determined that an intrabrachial cocaine dose of 0.15 mg achieves a forearm venous cocaine concentration of ~100 ng/mL, which is similar to that produced by the intranasal cocaine (2 mg/kg) used in protocol 2. We also determined that an intrabrachial cocaine dose of 15 mg achieves forearm venous cocaine concentrations that approximate those seen in patients with severe cocaine intoxication (3000 to 6000 ng/mL)17 without producing systemic spillover. Forearm blood flow and intra-arterial pressure were measured and forearm venous blood samples were drawn for cocaine and NE levels at baseline and during the last 2 minutes of each infusion period.

Protocol 2: Intranasal Cocaine
Nineteen experiments were conducted in 10 subjects; 7 subjects had undergone intrabrachial infusion of cocaine and 3 had not. On two separate days, each subject received either intranasal (a) cocaine hydrochloride (2 mg/kg, 10% solution) or (b) lidocaine hydrochloride (2 mg/kg, 10% solution), with the latter used as an internal control for the local anesthetic property of cocaine. This dose of intranasal cocaine is half the standard clinical dose for rhinolaryngologic procedures.18 Forearm blood flow, HR, and BP were recorded continuously before and for 90 minutes after intranasal cocaine or lidocaine. Blood samples were obtained from a catheter inserted retrograde in an antecubital vein for measurement of cocaine and NE levels at baseline and 30 minutes after intranasal cocaine, the time of peak cocaine levels.

Protocol 3: Intranasal Cocaine With SNA Clamped
Five experiments were conducted in 5 subjects; 3 subjects had undergone protocols 1 and 2, and 2 had not. After baseline muscle SNA was stable for 15 minutes, each subject received 2 mg/kg intranasal cocaine. When BP peaked and SNA decreased to its nadir 30 minutes after intranasal cocaine administration, intravenous nitroprusside was started. The infusion rate (0.25 to 3 µg/kg per minute) was titrated to attenuate the cocaine-induced rise in BP sufficiently to restore SNA to (but not above) the baseline value. Deep venous blood samples were taken from the contralateral antecubital veins for measurement of cocaine and NE levels at baseline, after administration of intranasal cocaine alone, and after SNA had been returned to baseline with concomitant infusion of nitroprusside.

Statistical Analysis
For protocol 1, repeated-measures ANOVA models were used to assess differences between baseline, saline, 0.15 mg cocaine, and 15.0 mg cocaine. Contrasts from these models were used for pairwise comparisons. Wilcoxon signed rank tests were implemented for venous cocaine levels because the data were skewed. The 0.05 level of significance was used for ANOVA, and the 0.01 level of significance was used for pairwise tests to adjust for multiple testing. For protocol 2, 2-factor repeated-measures ANOVA was used to assess differences between cocaine and lidocaine at the 0.05 significance level. Where significant treatment by time interactions were found, 2-sample t tests with Bonferroni correction were used to evaluate the difference between the cocaine and lidocaine groups at specific time points. Changes induced by cocaine or lidocaine at different time points compared with baseline were assessed by a single-factor, repeated-measures ANOVA with Bonferroni post hoc test for multiple comparisons, with a significance level of 0.01. For protocol 3, changes in muscle SNA, NE, and cocaine concentrations from baseline induced by intranasal cocaine alone and intranasal cocaine plus nitroprusside were compared with a paired t test with Bonferroni correction at the 0.01 level of significance. Results are expressed as mean±SEM. Statistical analysis was performed with SAS version 8.0 (SAS Institute Inc).

Results
None of the subjects had chest pain, electrocardiographic evidence of ischemia or arrhythmias, or other complications of cocaine.

Responses to Intrabrachial Cocaine
Intrabrachial infusion of cocaine at doses of 0.15 and 15.0 mg produced dramatic dose-dependent increases in the deep venous cocaine concentration in the ipsilateral forearm but highly nonlinear increases in forearm venous NE concentration and vascular resistance, with the majority of the responses occurring at the low dose (Figure 1). Venous cocaine concentration in the experimental forearm increased to 102±30 ng/mL after 0.15 mg of intrabrachial cocaine and to...
3596±458 ng/mL after 15 mg of intrabrachial cocaine (P<0.01) without causing any systemic spillover even at the highest dose (Table 1). The low dose of cocaine caused deep venous NE levels in the experimental forearm to increase by 82% (from 163±26 to 296±45 pg/mL, P<0.01) and FVR to increase by 71% (from 38±3 to 65±8 U, P<0.01). A 100-fold increase in the cocaine dose caused an additional increase in forearm NE concentrations of only 20%. There was a tendency for additional increase in FVR, but this tendency did not reach statistical significance of 0.01 (P=0.03 versus intrabrachial cocaine of 0.15 mg).

**Differential Responses to Intranasal Versus Intrabrachial Cocaine**

Despite producing comparable forearm venous cocaine concentrations (104±29 versus 102±30 ng/mL), intranasal and intrabrachial cocaine (0.15 mg) produced directionally opposite responses in FVR in the same subjects (Figure 2). With intrabrachial cocaine, BP was unchanged (P=NS versus saline) and FVR increased substantially, whereas with intranasal cocaine, MAP increased (from 87±1.4 to 98±1.9 mm Hg, P<0.01), triggering a reflex decrease in FVR of 25% (38.2±2.3 to 28.7±2.5 U, P<0.01; as forearm blood flow increased from 2.39±0.14 to 3.64±0.27 mL/min per 100 mL of forearm tissue). This forearm vasodilator response peaked 30 minutes after intranasal cocaine and persisted for 90 minutes. In contrast, intranasal lidocaine was without effect (Table 2).

**Responses to Intranasal Cocaine With SNA Clamped**

In the 5 subjects in whom SNA and NE were measured simultaneously during intranasal cocaine, MAP increased by 15 mm Hg (P=0.001 versus baseline), muscle SNA decreased reflexively by 72±7% (from 17±5 to 5±2 bursts/min, P<0.01 versus baseline), and forearm venous NE was unchanged (from 225±55 to 227±63 pg/mL, P=NS). When
healthy cocaine-naive subjects challenges this conventional hypothesis. The major new findings are 2-fold: (1) Intrabrachial cocaine causes regional increases in venous NE and vascular resistance that are consistent with NE transporter inhibition; however, (2) with intranasal cocaine, these increases are eliminated because even a modest cocaine-induced rise in blood pressure activates the arterial baroreceptors and reflexively suppresses postganglionic SNA, the neural stimulus for NE release. When we clamped SNA at baseline levels by minimizing baroreflex activation during intranasal cocaine, venous NE concentrations increased significantly, matching the increase seen with intrabrachial cocaine. These data demonstrate that in humans, the baroreceptor reflex plays a pivotal role in modulating the effects of cocaine on NE reuptake and peripheral vascular resistance.

By infusing cocaine directly into the brachial artery, we were able to study the effects of two vastly different doses on the forearm circulation without systemic neurohormonal effects, thereby eliminating both safety issues and baroreceptor reflex perturbation associated with systemic administration of high doses of cocaine. That intrabrachial cocaine caused dose-dependent parallel increases in venous NE and regional vascular resistance is entirely consistent with the traditional hypothesis that cocaine blocks NE reuptake in the human peripheral circulation. However, the dose-response curves were surprisingly flat, with most of the effects occurring with a venous cocaine concentration equivalent to that produced by only one-half the small intranasal dose used clinically in rhinolaryngologic procedures. That a 100-fold higher intrabrachial dose caused little or no additional effects suggests that inhibition of NE transporter is already near maximum because forearm venous NE concentration does not increase with the very low dose and is not a major mechanism causing hypertensive crisis with massive cocaine overdose.

With low-dose intranasal cocaine, inhibition of peripheral NE reuptake does not explain the modest increase in BP because forearm venous NE concentration does not increase and FVR decreases. This unexpected forearm vasodilator response is secondary to the cocaine-induced rise in BP, which activates the arterial baroreceptor reflex, thereby suppressing sympathetic vasoconstrictor drive to skeletal muscle. Despite substantial reduction in muscle SNA, intranasal

### Discussion

Although all the dramatic sympathomimetic actions and attendant cardiovascular complications of cocaine have long been ascribed to inhibition of peripheral NE reuptake, this conventional hypothesis previously has not been tested rigorously in humans. The present clinical investigation in

#### TABLE 2. Responses to Intranasal Cocaine vs Lidocaine (n=10)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
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<tr>
<td>Responses to intranasal cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>87.0±1.4</td>
<td>95.0±1.9†</td>
<td>98.0±1.9†</td>
<td>95.0±1.6†</td>
<td>95.0±1.7†</td>
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<td>Heart rate, bpm</td>
<td>65.0±2.1</td>
<td>72.0±1.8*</td>
<td>77.0±3.2†</td>
<td>72.0±3.0*</td>
<td>73.0±2.5*</td>
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<tr>
<td>Forearm blood flow, mL/min per 100 mL</td>
<td>2.39±0.14</td>
<td>3.39±0.34†</td>
<td>3.64±0.27†</td>
<td>3.48±0.23†</td>
<td>3.19±0.26†</td>
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<tr>
<td>Forearm vascular resistance, units</td>
<td>38.2±2.4</td>
<td>31.3±3.2†</td>
<td>28.7±2.5†</td>
<td>29.0±2.4†</td>
<td>32.6±3.0†</td>
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<tr>
<td>Responses to intranasal lidocaine</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
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<td>86.0±1.0</td>
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<tr>
<td>Heart rate, bpm</td>
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<td>67.0±2.9</td>
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<td>63.0±2.4</td>
<td>64.0±2.8</td>
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<tr>
<td>Forearm blood flow, mL/min per 100 mL</td>
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<td>Forearm vascular resistance, units</td>
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<td>40.3±2.1</td>
<td>41.5±2.6</td>
<td>43.5±2.1</td>
<td>41.7±3.2</td>
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</table>

*P<0.01 vs baseline.
†P<0.01 vs lidocaine.
‡Group by time interaction from 2-factor repeated-measures ANOVA, indicating the difference in response between cocaine and lidocaine.
cocaine did not cause a parallel reduction in venous NE levels, indicating that inhibitory effects of cocaine on NE reuptake was still present but counterbalanced by decreased sympathetic nerve firing rates. Indeed, when we restored muscle SNA to baseline levels after intranasal cocaine by attenuating the rise in BP (and thus baroreflex activation) with nitroprusside, the increase in venous NE concentrations also was restored, matching the increase seen with intrabrachial cocaine. It is unlikely that the rise in venous NE is explained by nitroprusside-induced forearm vasodilation because, in the absence of cocaine, more than 2-fold elevations in forearm blood flow with intrabrachial nitroprusside alone had no effect on forearm venous NE concentration. Thus, a salient finding of our study is that the same venous cocaine concentration can produce very different effects on venous NE concentrations and directionally opposite vasomotor responses in the same regional vascular bed, depending on the level of baroreflex activation.

Because blockade of peripheral NE reuptake is much less important than previously assumed in producing the blood pressure–raising effects of systemic cocaine, other mechanisms must be involved. Recent studies indicate that cocaine acts in the central nervous system to increase SNA to the heart, causing increased heart rate, contractility, and cardiac output. In anesthetized dogs, intravenous cocaine blocks NE reuptake as measured by PET with a C11-NE analog, but without affecting hemodynamic variables or coronary blood flow. In patients undergoing cardiac catheterization, infusion of cocaine into the coronary arteries at the same high dose used in our forearm studies had no effect on coronary blood flow or heart rate, possibly because of (a) lesser intrinsic sensitivity of &alpha;2-adrenergic receptors on coronary than peripheral blood vessels, and (b) attenuated adrenergic vasoconstriction in the beating heart by vasodilator metabolites.

Because our study was performed only in cocaine-naive healthy subjects, the results may not be extrapolated to chronic cocaine abusers. However, systemic administration

**Figure 3.** Summary data showing MAP, SNA, and venous NE concentrations (n=5, top) and recordings of muscle SNA in one subject (bottom) at baseline, after intranasal cocaine alone, and after intranasal cocaine plus intravenous nitroprusside (NTP). With intranasal cocaine alone, MAP increased and muscle SNA decreased reflexively, whereas forearm venous NE concentration was unchanged. When SNA was carefully returned to baseline level by attenuating the cocaine-induced rise in MAP with nitroprusside, a significant increase in venous NE concentration was observed. *P*<0.01 vs baseline.

**Figure 4.** Summary data comparing increases in forearm venous NE concentration from baseline produced by intrabrachial cocaine (0.15 mg, n=10), intranasal cocaine alone (n=7), and intranasal cocaine with SNA clamped (n=5). For equivalent forearm venous cocaine concentrations, the increase in forearm venous NE concentration produced by intranasal cocaine alone was greatly attenuated compared with intranasal cocaine when SNA was clamped at baseline level with nitroprusside (*P*<0.01), the latter value being indistinguishable from that produced by intrabrachial cocaine.
of smaller doses of cocaine has been shown to markedly increase plasma norepinephrine and epinephrine in chronic cocaine abusers, indicating a reverse tolerance or augmented response.25

In conclusion, the major new concept arising from this study of healthy cocaine-naive subjects is that baroreceptor reflexes normally play a key role in buffering the sympathomimetic actions of cocaine in the human peripheral circulation. The degree of peripheral vasoconstriction induced by a given dose of cocaine is critically dependent on the ambient level of central sympathetic outflow, which is suppressed in individuals with intact baroreceptor function. In the absence of baroreflex buffering, unrestrained central sympathetic outflow coupled with inhibition of peripheral NE reuptake would produce a state of excessive adrenergic vasoconstriction. This notion is supported by recent study in conscious dogs indicating that baroreceptor denervation leads to augmented pressor and tachycardic response to intravenous cocaine.27 We therefore speculate that the risk of hypertensive crisis and other catastrophic cardiovascular complications from cocaine is excessive in patients with long-standing hypertension, heart failure, or other pathophysiological conditions accompanied by impaired baroreceptor reflexes.

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References
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