Cocaine Stimulates the Human Cardiovascular System via a Central Mechanism of Action

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Background—Cocaine is thought to stimulate the cardiovascular system by blocking peripheral norepinephrine reuptake. This study was designed to test the novel hypotheses that cocaine also stimulates the human cardiovascular system by (1) increasing central sympathetic outflow, or (2) decreasing parasympathetic control of heart rate.

Methods and Results—In 14 healthy cocaine-naive humans, we measured blood pressure, heart rate, and skin sympathetic nerve activity (SNA) with intraneural microelectrodes before, during, and for 90 minutes after intranasal cocaine (2 mg/kg, n=7) or lidocaine (2 mg/kg, n=7). Intranasal cocaine caused an initial but transient 3.3-fold increase in skin SNA during the period of intranasal administration followed by a sustained 2.4-fold increase lasting for up to 90 minutes after cocaine. Unlike cocaine, intranasal lidocaine caused only a small transient increase in skin SNA due to local nasal irritation. The cocaine-induced increase in SNA was accompanied by decreased skin blood flow, increased skin vascular resistance, and increased heart rate. In 11 additional subjects, we showed that the cocaine-induced increase in heart rate was eliminated by β-adrenergic receptor blockade (propranolol) but unaffected by muscarinic receptor blockade (atropine), indicating sympathetic mediation.

Conclusions—These studies provide direct microneurographic evidence in humans that intranasal cocaine stimulates central sympathetic outflow. This central sympathetic activation appears to be targeted not only to the cutaneous circulation promoting peripheral vasoconstriction but also to the heart promoting tachycardia. **(*Circulation*. 1999;100:497-502.)**

Key Words: cocaine ■ nervous system, sympathetic ■ microneurography

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Cocaine abuse is a major cause of life-threatening cardiovascular emergencies including ventricular arrhythmias, acute myocardial infarction, and hypertensive crises.[1–4] Although the assumption is that all these emergencies are caused by excessive adrenergic stimulation of the heart and blood vessels,[5–7] the underlying mechanisms mediating cocaine's excitatory actions on the human cardiovascular system are poorly understood. The standard explanation is that cocaine blocks the norepinephrine reuptake transporter in peripheral sympathetic nerve terminals, thereby increasing the norepinephrine concentration in the synaptic cleft.[8–12] However, additional mechanisms must be involved because other drugs (eg, tricyclic antidepressants), which are more effective than cocaine at blocking the norepinephrine transporter, do not cause the same catastrophic cardiovascular events.[13] One possibility is that cocaine exerts major effects on parasympathetic, as well as sympathetic, function. There seems to be a major vagolytic component to cocaine's tachycardic effects in dogs,[14,15] and previous study in humans has provided indirect evidence that cocaine may also exert a vagolytic effect on sinus node function.[16] Nonetheless, the relative contributions of parasympathetic withdrawal versus sympathetic activation in mediating the cardiovascular responses to cocaine in human have not been determined. Another possibility is that cocaine acts centrally to increase sympathetic nerve activity (SNA), the neural stimulus to norepinephrine release. When cocaine was infused directly into the human coronary arteries, in doses that produced large concentrations of cocaine in the heart but with minimal systemic spillover, no changes in heart rate, blood pressure, or coronary vasomotor tone were observed.[17] In contrast, when cocaine is administered systemically, even small doses cause robust increases in heart rate, blood pressure, and coronary vasomotor tone,[1,5–6] indirectly implicating a central site of action.

However, when SNA has been measured directly in either experimental animals or humans, an excitatory action of cocaine on central sympathetic outflow has been difficult to demonstrate. In anesthetized, decerebrate, or conscious animals, the predominant effect of intravenous cocaine is the decrease of SNA to a variety of vascular beds, with only a few studies showing a transient increase in SNA at the highest doses.[18–23] In conscious humans, intranasal cocaine previously was found to increase systemic arterial pressure

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and evoke a baroreflex-mediated decrease in SNA to the skeletal muscle bed.[24] The magnitude of the reflex decrease in SNA was smaller than expected for the increase in arterial pressure, suggesting a relative sympathoexcitation. Indeed, when blood pressure was clamped experimentally with intravenous nitroprusside to minimize baroreflex activation during cocaine, an increase in SNA was unmasked. These data provide provocative, but still indirect, evidence in humans for a central sympathoexcitatory action of cocaine.

This study was designed to further test our novel hypothesis that cocaine stimulates the human cardiovascular system via a central mechanism of action. The major aims were 2-fold. First, we asked if cocaine increases SNA targeted to skin, a regional sympathetic outflow that, unlike muscle SNA, is not so tightly regulated by arterial baroreflexes.[25] In the absence of major baroreflex modulation, an unequivocal increase in SNA would provide straightforward evidence for cocaine-induced sympathoexcitation. Second, we asked if a cocaine-induced increase in this regional sympathetic outflow is accompanied by a parallel increase in sympathetic drive or a decrease in parasympathetic drive to the heart. Because heart rate is not increased with intracoronary cocaine,[17] a sizeable β-adrenergic component to the increase in heart rate seen with intranasal cocaine would provide evidence that cocaine increases central sympathetic outflow to the heart as well as the skin.

To accomplish these aims, we (1) measured skin SNA with intraneural microelectrodes in cocaine-naive healthy human subjects in response to intranasal cocaine, and (2) probed the relative contributions of sympathetic versus parasympathetic influences on sinus node function by studying the heart rate responses to intranasal cocaine alone and in combination with β-adrenergic receptor blockade (propranolol) or muscarinic receptor blockade (atropine).

Methods

We studied 22 healthy volunteers (12 men and 10 women, 22 to 44 years of age) after informed written consent. The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. All subjects were normotensive and had no history of cardiovascular disease, cocaine abuse, or other recreational drug abuse. None of the subjects was taking any prescription or nonprescription drugs with cardiovascular or autonomic effects.

All experiments were performed under normothermic conditions (22°C), with the subjects in the supine position. Blood pressure was measured by the oscillometric technique with the Vitalsigns Monitor (CE00050, Welch Allyn, Tycos Instruments, Inc). Heart rate was monitored continuously by a cardiotachometer triggered by R wave of an ECG lead. Respiratory rate was monitored by a strain-gauge pneumograph positioned at the mid-chest level. Skin temperature was measured with a type-T thermocouple thermometer (BAT-10, Physitemp Inc) that can detect differences in temperature with a resolution and accuracy of 0.1°C. In each experiment, probes were placed in the both shoulders, anterior and posterior chest wall, and ventral and dorsal surface of right leg; skin temperature was calculated as the arithmetic mean of the temperature from all 6 probes. The skin blood flow was measured by laser Doppler velocimetry (Advance Laser Flowmeter, ALF 2100, Advance Co), with the probe placed on ventral surface of forearm. Postganglionic efferent sympathetic nerve discharge, heart rate, respiratory rate, skin blood flow, and skin temperature were recorded continuously using a multi-channel digital data recorder (MacLab/8S ML780, AD Instruments Inc). Core temperature was recorded periodically with an ear-probed thermometer (Thermoscan Pro-1, Thermoscan Inc). Skin vascular resistance (expressed in resistance units) was calculated as the quotient of mean arterial pressure and skin blood flow (expressed in perfusion units).

Measurement of Sympathetic Nerve Activity by Microneurography

Multiunit recordings of postganglionic sympathetic nerve discharge were obtained with unipolar tungsten microelectrodes inserted selectively into skin nerve fascicles of the peroneal nerve posterior to the fibular head, according to the technique of Vallbo et al.[26] The neural signals were amplified 20 000 to 50 000 times, filtered (bandwidth 700 to 2000 Hz), rectified, and integrated (time constant, 0.1 s) with a nerve traffic analyzer (Bioengineering Department, University of Iowa) to obtain a mean voltage display of sympathetic discharge. A recording of skin sympathetic nerve discharge was considered acceptable when (1) weak electrical stimulation (0.5 to 3.2 V, 0.2s, 1 Hz) through the electrode elicited paresthesias without muscle contraction; (2) tactile stimuli within the receptive field of the impaled nerve fascicle elicited afferent mechanoreceptive impulses, whereas no impulses could be evoked by muscle stretch or contraction; and (3) the mean voltage neurogram revealed bursts of neural activity (with a signal-to-noise ratio of $>$3:1) that increased during arousal stimuli (loud noise, skin pinch) but not during the Valsava maneuver. The intraobserver variabilities in identifying bursts of skin SNA is 3.4% (range, 0 to 11%), as previously reported.[27] All the records were analyzed by the same investigator who scored the recorded data in a blinded fashion. Inadvertent contraction of the leg muscles adjacent to the recording electrode produces electromyographic artifacts that are easily distinguished from sympathetic bursts; neurograms that revealed such artifacts were excluded from analysis. Nerve traffic was expressed as both bursts per minute and total integrated activity per minute, which is the sum of the integrated area under all the bursts detected in 1 minute. Integration was performed using MacLab software.

Experimental Protocols

Protocol 1: Skin Sympathetic and Vasomotor Responses to Intranasal Cocaine Versus Intranasal Lidocaine (14 Experiments on 14 Subjects)

After stable baseline data were obtained for 15 minutes, each subject was randomized, using a double-blind design, to receive intranasal (1) cocaine hydrochloride, 2 mg/kg in a 10% solution (n=7) or (2) lidocaine hydrochloride, also 2 mg/kg in a 10% solution (n=7), 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.[28] Heart rate, blood pressure, sympathetic nerve discharge, skin blood flow, and skin temperature were recorded continuously for 90 minutes. Core temperature was recorded at baseline and at 90 minutes. At the end of the study, each subject was asked to complete a questionnaire to report whether a sensation of heightened arousal or euphoria had developed after drug administration.

Protocol 2: Effects of β-Adrenergic Receptor and Muscarinic Receptor Blockade on Heart Rate Responses to Cocaine (25 Experiments on 11 Subjects)

To examine the sympathetic and parasympathetic influences on the positive chronotropic response to cocaine, heart rate was measured before and 20 minutes after administration of intranasal cocaine (2 mg/kg) in 11 subjects on 3 separate days: (1) cocaine alone (n=11), (2) cocaine after muscarinic receptor blockade with intravenous atropine (0.04 mg/kg IV followed by small supplemental doses, n=7), and (3) cocaine after β-adrenergic receptor blockade with intravenous propranolol (0.2 mg/kg, n=7)

Statistical Methods

All data are expressed as mean±SEM. Statistical analyses were performed with the SAS software (SAS Institute Inc) using 2 factor

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TABLE 1. Responses to Intranasal Cocaine

	Time After Administration, min							ANOVA
	Baseline	During	5	10	30	60	90	P‡
Mean arterial pressure, mm/Hg	80±3	92±3*	88±4*	90±4*	92±4*	92±4*	90±3*	$<10^{-4}$
Heart rate, bpm	64±3	73±3	70±3*†	73±3*†	76±3*†	75±3*†	76±3*†	0.02
Skin sympathetic nerve activity								
Bursts/min	12±3	17±3	18±3*†	17±3†	20±3*†	21±2*†	22±2*†	$<10^{-4}$
Integrated activity, %	100	325±76	161±33	202±65	234±49	217±39	236±47	
Ln % integrate activity	4.61±0.0	5.78±0.28*	5.08±0.16	5.31±0.25	5.46±0.2*†	5.38±0.15*†	5.46±0.17*†	0.005
Skin blood flow, perfusion units	4.3±0.4	4.0±0.4	3.9±0.4	4.1±0.4	3.7±0.4*	3.6±0.4*	3.4±0.4*	0.025
Skin vascular resistance, resistance units	20±3	25±3	24±3	24±2	27±3*	28±3*	29±3*	0.065

*$P<0.05$ vs baseline, after Bonferroni adjustment; †$P<0.05$ vs lidocaine, after Bonferroni adjustment; ‡Group by time interaction from 2 factor repeated measures ANOVA, indicating the difference in response between cocaine and lidocaine.

repeated measures ANOVA with one repeated factor (time) and one grouping factor (cocaine versus lidocaine) at 0.05 significance level. Where significant treatment by time interactions were found, 2 sample *t* tests with Bonferroni's correction were used to evaluate the difference between the cocaine and lidocaine groups at specific time points. Within-group effects (ie, changes induced by cocaine or lidocaine at different time points compared with baseline) were assessed by a single factor repeated measure ANOVA with Bonferroni's post hoc test for multiple comparisons over time, using a significance level of 0.05. Because the distributions of skin sympathetic nerve activity (% integrated activity) were skewed, the data were analyzed after a natural logarithmic transformation. Changes in skin and core temperature induced by cocaine or lidocaine between baseline and 90 minutes were assessed with a paired *t* test at the 0.05 level of significance. The difference in changes in heart rate induced by cocaine alone, combined cocaine and propranolol, or combined cocaine and atropine were compared with unpaired *t* test with Bonferroni's correction at the 0.01 level of significance.

Results

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

Effects of Intranasal Cocaine on Skin Sympathetic and Vasomotor Responses

Mean arterial pressure increased after intranasal cocaine administration and remained elevated for at least 90 minutes (Table 1); the magnitude of these increases was comparable to those reported previously.[6,24,29] Intranasal cocaine caused an initial but transient 3.3-fold increase during the period of intranasal administration followed by a sustained 2.4-fold increase lasting for up to 90 minutes after cocaine (Table 1 and Figure 1). Unlike intranasal cocaine, intranasal lidocaine caused only an initial increase in skin SNA, which returned promptly to baseline after completion of intranasal administration (Table 2 and Figure 1). After lidocaine, blood pressure, heart rate, skin blood flow, and skin vascular resistance were unchanged (Table 2). After cocaine, the sustained increase in skin SNA was accompanied by significant decreases in skin blood flow, increases in skin vascular resistance, and increases in heart rate (Table 1). The temporal pattern of cocaine-induced increase in heart rate closely paralleled the pattern of increase in skin SNA (Figure 2). No changes in skin or core temperature were observed (skin temperature: 33.2±0.3 at baseline versus 33.5±0.3°C at 90 minutes after cocaine administration; core temperature: 36.5±0.3 at baseline versus 36.5±0.3°C at 90 minutes). Euphoria or heightened arousal was reported by 3 of 7 subjects given cocaine but also by 2 of 7 who received lidocaine. The other subjects reported no subjective sensations during the study.

Effects of β-adrenergic Receptor and Muscarinic Receptor Blockade on Heart Rate Responses to Cocaine

Cocaine alone increased heart rate by 11±2 bpm ($P<0.05$). The cocaine-induced increase in heart rate was abolished by propranolol but unaffected by atropine (Table 3 and Figure 3).

Discussion

Although cocaine is generally assumed to stimulate cardiovascular function by blocking the peripheral norepinephrine transporter, the drug also has been hypothesized to both increase central sympathetic outflow and cause parasympathetic withdrawal. The major new findings of our study are

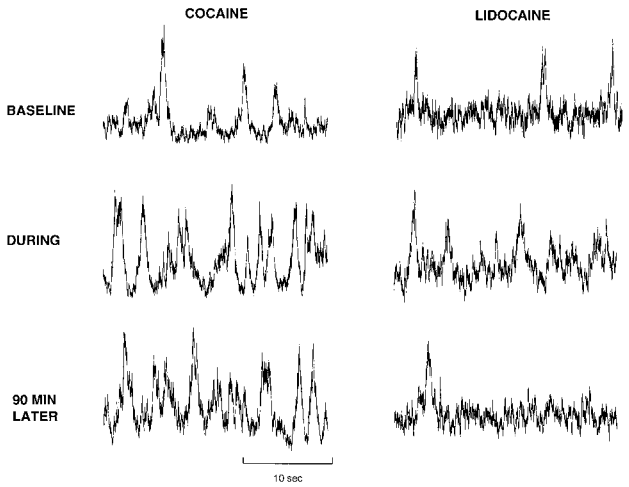

Figure 1. Recordings of skin SNA before, during, and after intranasal administration of cocaine or lidocaine. Intranasal cocaine evoked a rapid and sustained increased in skin SNA up to 90 minutes afterwards, whereas lidocaine caused only an initial transient increase which returned promptly to baseline after completion of administration.

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TABLE 2. Responses to Intranasal Lidocaine

	Time After Administration, min						
	Baseline	During	5	10	30	60	90
Mean arterial pressure, mm Hg	82±3	85±3	82±2	84±2	83±2	85±3	84±3
Heart rate, bpm	60±5	63±5	59±5	58±5	58±5	58±5	58±5
Skin sympathetic nerve activity							
Bursts/min	9±1	16±2*	9±1	7±1	7±1	9±2	11±2
Integrated activity, %	100	210±54	94±13	79±15	89±14	97±20	105±14
Ln % integrated activity	4.61±0.0	5.35±0.27	4.54±0.2	4.37±0.25	4.49±0.21	4.57±0.29	4.65±0.17
Skin blood flow, perfusion units	3.7±0.2	3.6±0.4	3.8±0.4	3.8±0.4	3.7±0.4	3.8±0.6	3.8±0.5
Skin vascular resistance, resistance units	22±2	26±4	23±3	24±2	24±3	25±4	24±3

*$P<0.01$ vs baseline, after Bonferroni adjustment.

2-fold. First, in conscious humans intranasal cocaine stimulates central sympathetic outflow, as measured by intraneural recordings of SNA to the cutaneous circulation. Second, the increase in SNA is accompanied by a parallel increase in heart rate that is abolished by β-adrenergic receptor blockade but unaffected by muscarinic receptor blockade, indicating sympathetic rather than parasympathetic mediation.

In our experiments, a low dose of intranasal cocaine, equivalent to one-half the standard dose used for rhinolaryngologic procedures, was a potent stimulus to skin SNA. The initial transient increase in skin SNA was a nonspecific response to local nasal irritation, because a similar response was elicited by the local nasal irritation caused by intranasal lidocaine. In contrast, the subsequent prolonged increase in skin SNA represents a specific effect of cocaine because it was not duplicated by intranasal lidocaine, which also serves as an internal control for the local anesthetic properties of cocaine. Whereas animal studies have demonstrated at most a transient (<5 minutes) sympathoexcitatory response to cocaine,[18,19,30] our study in humans provides straightforward evidence that cocaine can elicit a rather long-lasting increase in SNA (>90 minutes).

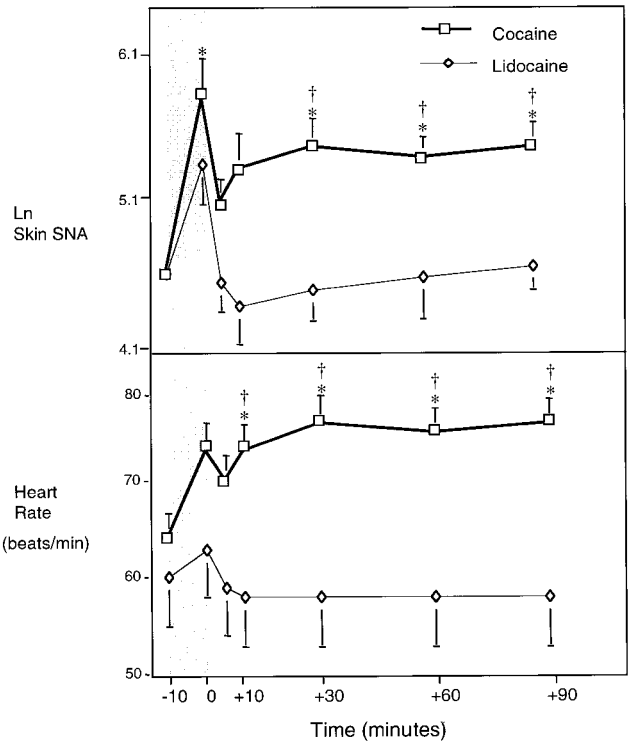

Figure 2. Summary data showing changes in skin SNA and heart rate, plotted as a function of time after intranasal administration of cocaine (n=7) or lidocaine (n=7). Data are mean±SE. *$P<0.05$ vs baseline (time −10). †$P<0.05$ versus lidocaine. Intranasal cocaine caused an initial but transient increase during the period of intranasal administration (shaded area) followed by a sustained increased lasting up to 90 minutes. This was accompanied by a parallel increase in heart rate. Unlike cocaine, intranasal lidocaine caused only a transient increase in skin SNA and had no effect on heart rate.

We considered the possibility that the cocaine-induced increase in SNA might be caused by a peripheral thermoregulatory reflex rather than a direct central mechanism of action. If cocaine effectively blocked norepinephrine reuptake in the cutaneous circulation, the resultant α-adrenergic vasoconstriction and decrease in skin temperature could activate cutaneous afferents that reflexively increase skin SNA. This possibility is unlikely because intranasal cocaine had no detectable effect on skin or core temperature and produced increases in skin vascular resistance that closely paralleled but did not precede the increases in skin SNA. Thus, we suggest that the increased skin vascular resistance was the consequence and not the cause of the increased SNA.

TABLE 3. Heart Rate Responses to Intranasal Cocane Alone and In Combination With Propranolol or Atropine

	Heart rate, bpm*	*P*
Session 1: Cocaine alone		
Baseline	61±3	<0.05
Cocaine	72±3	
Session 2: Combined with propranolol		
Baseline	64±4	
Propranolol	55±3	
Propranolol plus cocaine	57±3	
Session 3: Combined with atropine		
Baseline	69±3	
Atropine	127±6	<0.05
Atropine plus cocaine	141±6	

*Data are mean±SE.

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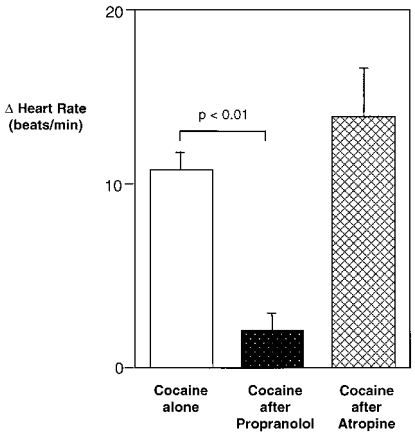

Figure 3. Effects of β-adrenergic receptor blockade and muscarinic receptor blockade on heart rate response to cocaine. Values are changes in heart rate 20 minutes after cocaine vs baseline and are displayed as mean±SE. *$P<0.01$. Heart rate increased significantly 20 minutes after cocaine alone (n=11). Propranolol abolished heart rate response to cocaine in the same group of subjects (n=7), whereas this response was still preserved after atropine (n=7), suggesting sympathetic stimulation mediating chronotropic response to cocaine.

Because skin SNA typically is very sensitive to emotional or arousal stimuli, we considered the possibility that increased SNA is a nonspecific response to heightened arousal related to the behavioral properties of cocaine. However, in our study the skin SNA response did not correlate with subjective reports of euphoria, which with this low dose of cocaine were minimal or none. Whereas arousal responses typically adapt over time, there was no adaptation to the SNA response after cocaine.

From these human experiments, we cannot localize cocaine's sympathoexcitatory action. Because we recorded SNA from postganglionic nerves, we cannot exclude the possibility that cocaine might enhance ganglionic transmission. However, there is no precedent for such a mechanism and animal experiments suggest that cocaine, if anything, decreases rather than increases ganglionic transmission.[12,31] Our data, therefore, are consistent with the hypothesis that cocaine acts centrally to increase SNA.

The underlying cellular mechanism mediating cocaine's excitatory effects on the human sympathetic nervous system is unknown. Animals studies have provided evidence that blockade of the norepinephrine transporter in brain stem as well as activation of brain stem N-methyl-D-aspartate receptors play important roles in mediating the decreases in cardiac, renal, and adrenal SNA evoked by intravenous cocaine.[18,23] It is difficult to conceive how mechanisms mediating sympathoinhibitory responses could explain cocaine-induced sympathoexcitation in conscious humans. On the other hand, there is some evidence to suggest that blockade of central dopamine transporters mediates cocaine-induced sympathoexcitation, at least in conscious rabbits.[18]

There also is evidence to suggest that a portion of cocaine's cardiovascular effects are caused by parasympathetic withdrawal due either to blockade of cardiac muscarinic receptors or decreased central parasympathetic outflow.[16,32] In conscious dogs, the tachycardic response to intravenous cocaine was only partially attenuated by propranolol, the remainder being blocked by atropine.[14,15] In conscious humans who chronically abused cocaine, power spectral analysis of heart rate indicated that cocaine decreases high frequency component, which is an indirect index of cardiac parasympathetic activity.[16] In our cocaine-naive subjects, however, the cocaine-induced increase in heart rate was sympathetically-mediated because this chronotropic response was abolished by propranolol but unaffected by atropine. Because in cocaine-naive subjects heart rate is unaffected by intracoronary (unlike intranasal) cocaine,[17] we interpret the present data to suggest that intranasal cocaine increases central sympathetic outflow to the heart as well as to the skin.

Taken together, these data and our previous microneurographic data prompt a new view about the neural mechanisms mediating the short-term effects of a low dose of intranasal cocaine on the human cardiovascular system. We speculate that cocaine acts centrally to increase sympathetic outflow both to the cutaneous and skeletal muscle beds, promoting peripheral vasoconstriction, and to the heart, promoting tachycardia.

The present data by no means refute the traditional hypothesis that cocaine stimulates the cardiovascular system by blocking the peripheral norepinephrine transporter. Indeed, increased SNA, the neural stimulus to norepinephrine release, would amplify any peripheral sympathomimetic action of cocaine.

Several aspects of these experiments performed on healthy human subjects limit our ability to draw inferences about the mechanisms of cocaine-induced cardiovascular emergencies in patients. First, for ethical reasons, our cocaine dose is small; we cannot challenge human subjects with higher doses of cocaine, which may engage different mechanisms. Second, a given dose of cocaine might produce quantitatively different responses in long-term cocaine abusers than in healthy volunteers with no history of prior exposure to cocaine.

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