Central Sympatholysis as a Novel Countermeasure for Cocaine-Induced Sympathetic Activation and Vasoconstriction in Humans

Dileep V. Menon, MD, Zhongyun Wang, MD, Paul J. Fadel, PhD, Debbie Arbique, RN, David Leonard, PhD, Jia-Ling Li, MD, Ronald G. Victor, MD, FACC, Wanpen Vongpatanasin, MD, FACC

Dallas, Texas

Objectives
The aim of this study was to determine whether cocaine’s sympathomimetic actions can be reversed by a potent centrally acting \( \alpha_2 \) adrenergic receptor (AR) agonist (dexmedetomidine).

Background
We recently showed that cocaine stimulates the human cardiovascular system primarily by acting in the brain to increase sympathetic nerve activity (SNA), the neural stimulus to norepinephrine release. Thus, SNA constitutes a putative new drug target to block cocaine’s adverse cardiovascular effects at their origin.

Methods
In 22 healthy cocaine-naïve humans, we measured skin SNA (microneurography) and skin blood flow (laser Doppler velocimetry) as well as heart rate and blood pressure before and after intranasal cocaine (2 mg/kg) alone and in combination with dexmedetomidine or saline.

Results
During intranasal cocaine alone, SNA increased by 2-fold and skin vascular resistance increased from 13.2 \( \pm \) 2.3 to 20.1 \( \pm \) 2.2 resistance units while mean arterial pressure increased by 14 \( \pm \) 3 mm Hg and heart rate by 18 \( \pm \) 3 beats/min (p < 0.01). Dexmedetomidine abolished these increases, whereas intravenous saline was without effect. Dexmedetomidine was effective in blocking these sympathomimetic actions of cocaine even in all 7 subjects who were homozygous for the Del322-325 polymorphism in the \( \alpha_2C \) AR, a loss-of-function mutation that is highly enriched in blacks.

Conclusions
The data advance the novel hypothesis that central sympatholysis with dexmedetomidine constitutes a highly effective countermeasure for cocaine’s sympathomimetic actions on the human cardiovascular system, even in individuals carrying the \( \alpha_2C \)Del322-325 polymorphism. (Study to Improve Scientific Understanding of the Cardiovascular Actions of Cocaine; http://clinicaltrials.gov/ct/show/NCT00338546?order=1; NCT00338546) (J Am Coll Cardiol 2007;50:626–33) © 2007 by the American College of Cardiology Foundation

Cocaine abuse has reached epidemic proportions in the U.S., with 34.9 million Americans reporting having ever tried cocaine and an estimated 7.3 million regular users, including 15% of young adults ages 18 to 25 years (1). Cocaine is the dominant illicit drug causing life-threatening cardiovascular emergencies. These include acute coronary syndromes, sudden cardiac death, malignant hypertermia, and hypertensive crisis including stroke and aortic dissection. Although these emergencies all are related to excessive adrenergic stimulation of the cardiovascular system, our understanding of the underlying mechanisms mediating cocaine’s sympathomimetic effects is far from complete and current strategies for emergency management remain unsatisfactory.

The standard theory is that cocaine blocks norepinephrine (NE) reuptake in peripheral sympathetic nerve terminals, thereby increasing NE in the synaptic cleft (2). In contrast to this rather traditional view, our recent studies demonstrate that cocaine stimulates the human cardiovascular system primarily by acting in the brain to increase central sympathetic nerve activity (SNA) (3), the neural stimulus to NE release, with minimal contribution from peripheral NE transporter inhibition (4). Thus, SNA constitutes a putative new drug target for the acute management of cocaine-induced cardiovascular emergencies.

From the Hypertension Division and the Donald W. Reynolds Cardiovascular Clinical Research Center, University of Texas Southwestern Medical Center, Dallas, Texas. This work was supported by grants to Dr. Victor from the National Institute on Drug Abuse (RO-1 DA10064) and the American Society of Hypertension (Texas chapter) and to Drs. Vongpatanasin and Victor from the Donald W. Reynolds Foundation.

Manuscript received December 12, 2006; revised manuscript received March 14, 2007, accepted March 28, 2007.
Central sympatholytic drugs, particularly α-adrenergic receptor (AR) agonists such as clonidine, have been shown to reverse cocaine-induced increases in blood pressure and vascular resistance in experimental animals (5). Dexmedetomidine is a newer central sympatholytic agent with an α2 AR binding affinity that is 8 times higher than that for clonidine (6,7). This α2 AR agonist is increasingly used as an anesthetic agent and has proven to be particularly effective in minimizing acute hypertension and tachycardia in surgical and critically ill patients (8,9). Dexmedetomidine has been shown to markedly attenuate cocaine-induced coronary and systemic vasoconstriction in dogs (10), but translational human studies previously have not been reported.

Accordingly, the goal of the present study was to test whether controlling cocaine-induced central sympathetic activation with dexmedetomidine can effectively reverse the acute hemodynamic responses to cocaine. Here we conducted a prospective randomized placebo-controlled study in cocaine-naïve healthy subjects in whom we performed microelectrode recordings of skin SNA, a regional sympathetic outflow that is highly reactive to low-dose intranasal cocaine (3), and simultaneously measured skin vascular resistance as the primary hemodynamic end point. We titrated the dexmedetomidine dose to eliminate the cocaine-induced increase in skin SNA and determined whether this intervention would be sufficient to completely reverse the attendant increases in skin vascular resistance as well as in heart rate and blood pressure. To address applicability of the findings in broader ethnic population, we enriched the study samples with subjects who are homozygous for a loss-of-function mutation in the α2C AR (α2CDe322–325), a target of dexmedetomidine. This mutation occurs mainly in blacks (11), the population with the highest cardiovascular mortality in the U.S. (12).

Methods
We studied 22 healthy volunteers (9 men and 13 women, 21 to 56 years of age) after obtaining 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 supine. Blood pressure was measured by the oscilometric technique with the Vitalsigns Monitor (CE00050, Welch Allyn, Tycos Instruments, Inc., Skaneateles Falls, New York). Heart rate was monitored continuously by a cardiotachometer triggered by R wave of an electrocardiogram lead. Respiratory rate was monitored by a strain-gauge pneumograph positioned at the mid-chest level. Postganglionic efferent sympathetic nerve discharge, heart rate, respiratory rate, and skin blood flow were recorded continuously with a multi-channel digital data recorder (MacLab/8S ML780, AD Instruments Inc., Colorado Springs, Colorado). The level of alertness in subjects was monitored with the Observer’s Assessment of Alertness/Sedation (OAAS) scale. The OAAS comprises 4 scales that researchers use to assess alertness or sedation: speech, responsiveness, facial expression, and eyes. A composite score is determined by summing the scores of all 4 scales; score of 5 correlates with maximum alertness, and 1 indicates deep sleep (13).

Measurement of skin SNA. 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 Valbo (14). The neural signals were amplified 20,000 to 50,000 times, filtered (bandwidth 700 to 2,000 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, 0.2 s, 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 Valsalva maneuver. The intraobserver variabilities in identifying bursts of skin SNA is 3.4% (range 0% to 11%), as previously reported (3). 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/minute and total integrated activity/min, which is the sum of the integrated area under all the bursts detected in 1 min. Integration was performed with MacLab software.

Measurement of skin blood flow. Skin blood flow was measured by laser Doppler velocimetry (Advance Laser Flowmeter, ALF 2100, Advance Co., Tokyo, Japan) with the probe placed on the plantar aspect of the first toe. Skin
vascular resistance (expressed in resistance units) was calculated as the quotient of mean arterial pressure (MAP) and skin blood flow (expressed in perfusion units). The SNA and vascular resistance were studied in the same vascular bed of the same limb. This allowed us to ask whether elimination of the cocaine-induced sympathetic activation would effectively reverse its end-organ effect—namely cutaneous vasoconstriction.

Genotyping. Subjects carrying the α2C Del322-325 polymorphism were identified as previously described (15). Briefly, genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood with the Puregene kit (Gentra System, Minneapolis, Minnesota); oligonucleotides were purchased from Integrated DNA Technologies (Coralville, Iowa). All sequencing was performed with an ABI 3730 automated DNA Sequencing instrument and Big Dye Version 3.1 dye terminator chemistry (Applied Biosystems, Foster City, California). The 12 base pair (bp) in-frame deletion (Del322-325) allele of the α2C AR was identified by size fractionation assay. A DNA fragment spanning the polymorphic region was polymerase chain reaction (PCR)-amplified and fluorescence-labeled with a FAM-labeled sense primer 5'-FAM-GTCTACGCCGATCTACCGAGTTGGCCAAG-3' and unlabeled antisense primer 5'-CCCATGACCACAGCCACAAAGGTTGAAG-3'.

Amplicon sizes were determined with an ABI 3100 automated DNA sequencer without purification of the PCR product. The results of the fragment analysis were verified by directly sequencing PCR fragments amplified with unlabeled primers.

From a random population sample of 1,458 blacks in the Dallas Heart Study (16), 246 subjects were homozygous for the mutant allele. Of these, we enrolled 7 subjects from a pool of 128 subjects who met the following inclusion criteria: normotensive, non-diabetic, non-pregnant, and no history of cocaine or other drug abuse.

Experimental protocol. We performed the same experimental protocol in 2 groups of subjects. In group 1, all subjects were homozygous for the common α2C AR allele. In group 2, all were homozygous for the Del322-325 allele.

Effect of dexmedetomidine on skin SNA and cutaneous vasomotor responses to intranasal cocaine in subjects with common α2C AR alleles. After stable baseline data were obtained for 15 min, each subject received intranasal cocaine hydrochloride, 2 mg/kg in a 10% nasal solution (19 experiments in 15 subjects). This dose of intranasal cocaine is one-half the standard clinical dose for rhinologic procedures (17) and has been shown previously to cause reproducible increases in skin SNA and skin vascular resistance that last for 90 min (3). The cocaine solution was delivered into each nostril via a dropper over a period of 5 min. After completion of nasal administration of cocaine for 30 min, which is time to peak effect of intranasal cocaine, subjects were randomized to receive either a single bolus intravenous dose of dexmedetomidine (Abbott Laboratories, Abbott Park, Illinois; n = 11) at the dose of 0.1 and 0.3 μg/kg over 1 min or saline at the identical volume used during dexmedetomidine administration (0.025 and 0.075 ml/kg over 1 min, n = 8) with a time interval of 10 min between the 2 doses of the drugs. Heart rate, blood pressure, sympathetic nerve discharge, and skin blood flow were recorded continuously for 50 min. Subjects were monitored for the level of alertness with the OAAS after administration of both doses of the drugs.

Effects of dexmedetomidine in individuals with the α2C AR Del322-325 variant allele. We repeated the previously described protocol in homozygous carriers of the α2C Del322-325 allele with the identical procedures except that the saline control was not repeated in this group (7 experiments in 7 subjects).

Statistical analyses. The SAS/STAT software (SAS, Cary, North Carolina) version 9.1 was used for all analyses. Presented p values are based on tests of contrasts within a mixed linear model of each response variable with fixed treatment group × genotype × time effect and random subject effect. Treatment group had 2 levels: dexmedetomidine and saline. Genotype had 2 levels: wild and variant with respect to α2C Del322-325. Time had 4 levels: baseline, after cocaine, after 1st treatment dose, and after second treatment dose. The random subject effect allows for dependence among repeated measures on the same individual. The intervention effects (treatment group differences in second dose treatment—cocaine) were also tested with rank-sum tests to confirm the conclusions on the basis of the mixed linear models. Because the distributions of skin SNA (% integrated activity) were skewed, the data were analyzed after a natural logarithmic transformation. Two-sided p values <0.05 were considered to indicate statistical significance.

Results

None of the subjects developed chest pain, electrocardiographic evidence of ischemia, or arrhythmias or any other complications from this low dose of intranasal cocaine.

### Table 1. Baseline Characteristics of Subjects Treated With Intravenous Dexmedetomidine or Saline

<table>
<thead>
<tr>
<th></th>
<th>Cocaine + Dexmedetomidine (n = 11)</th>
<th>Cocaine + Saline (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>40 ± 3.2</td>
<td>35 ± 6</td>
</tr>
<tr>
<td>Male/female</td>
<td>4/7</td>
<td>3/5</td>
</tr>
<tr>
<td>White/black</td>
<td>4/7</td>
<td>1/7</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25 ± 1.2</td>
<td>26 ± 1.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 ± 2</td>
<td>58 ± 3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91 ± 2</td>
<td>87 ± 5</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE.
Effects of dexmedetomidine on skin sympathetic and vasoconstrictor responses. Baseline characteristics of subjects in the saline and dexmedetomidine group are shown in Table 1. Mean arterial pressure and heart rate increased significantly after intranasal cocaine administration alone, and skin SNA increased to a value that was approximately 2-fold of the baseline (p < 0.01 for both repeated measures analysis of variance [ANOVA] and nonparametric rank sum test) (Fig. 1, Table 2). Intravenous saline infusion had no effect on the cocaine-induced increase in skin SNA, MAP, and heart rate, which remained constant for the entire duration of the protocol (Figs. 1 and 2, Table 2). The cocaine-induced increase in skin SNA was accompanied by a sustained decrease in skin blood flow and increase in skin vascular resistance, which was also unaffected by intravenous saline administration (Fig. 2, Table 2). The magnitude and duration of the increases in SNA, skin vascular resistance, heart rate, and MAP during administration of intranasal cocaine + intravenous saline were comparable to those reported previously with intranasal cocaine alone (3,4), suggesting that intravenous saline had no impact on sympathetic and hemodynamic responses to cocaine.

In contrast, low dose of dexmedetomidine (0.1 μg/kg/min) abolished effects of cocaine on the skin SNA and returned SNA to baseline; whereas the higher dose of dexmedetomidine (0.3 μg/kg/min) reduced SNA further to 35% of baseline activity (p < 0.01 for both repeated measures ANOVA and nonparametric rank sum test) (Fig. 1, Table 3). Dexmedetomidine also reversed the cocaine-induced increases in skin vascular resistance, MAP, and heart rate in a dose-dependent fashion, which was not observed with saline (Fig. 2, Tables 2 and 3). There were no changes in subjects’ alertness as evidenced by OAAS scale with either dose of dexmedetomidine (Table 3).

Table 2  Dose-Dependent Effects of Saline on Responses to Intranasal Cocaine

<table>
<thead>
<tr>
<th>Saline Group (n = 8)</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>Plus Saline 0.025 ml/kg</th>
<th>Plus Saline 0.075 ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>87 ± 5</td>
<td>101 ± 3*</td>
<td>98 ± 3*</td>
<td>97 ± 4*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>58 ± 3</td>
<td>76 ± 3*</td>
<td>72 ± 2*</td>
<td>71 ± 3*</td>
</tr>
<tr>
<td>Skin SNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated activity, %</td>
<td>100</td>
<td>246 ± 46</td>
<td>231 ± 40</td>
<td>217 ± 29</td>
</tr>
<tr>
<td>Ln % integrate activity</td>
<td>4.61 ± 0</td>
<td>5.42 ± 0.21*</td>
<td>5.38 ± 0.19*</td>
<td>5.34 ± 0.15†</td>
</tr>
<tr>
<td>Skin blood flow (perfusion units)</td>
<td>8.03 ± 1.78</td>
<td>5.24 ± 0.59†</td>
<td>4.98 ± 0.57†</td>
<td>4.71 ± 0.53*</td>
</tr>
<tr>
<td>Skin vascular resistance (resistance units)</td>
<td>13.24 ± 2.30</td>
<td>20.16 ± 2.16*</td>
<td>20.69 ± 2.16*</td>
<td>21.69 ± 2.19*</td>
</tr>
<tr>
<td>OAAS scale</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE. *p < 0.01 versus baseline; †p < 0.05 versus baseline. OAAS = observer’s assessment of alertness and sedation; SNA = sympathetic nerve activity.
**Table 3**  Dose-Dependent Effects of Dexmedetomidine on Responses to Intranasal Cocaine

<table>
<thead>
<tr>
<th>Dexmedetomidine Group (n = 11)</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>Plus Dexmedetomidine 0.1 µg/kg</th>
<th>Plus Dexmedetomidine 0.3 µg/kg</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91 ± 2</td>
<td>100 ± 2†</td>
<td>93 ± 3‡§</td>
<td>89 ± 2†§</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 ± 2</td>
<td>77 ± 2†</td>
<td>76 ± 2†</td>
<td>68 ± 2†</td>
<td>NS</td>
</tr>
<tr>
<td>Skin SNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated activity, %</td>
<td>100</td>
<td>174 ± 10</td>
<td>103 ± 11</td>
<td>35 ± 8</td>
<td>&lt;10⁻⁶</td>
</tr>
<tr>
<td>Ln % integrate activity</td>
<td>4.61 ± 0</td>
<td>5.15 ± 0.06</td>
<td>4.0 ± 0.11‡§</td>
<td>3.37 ± 0.28‡§</td>
<td>&lt;10⁻⁶</td>
</tr>
<tr>
<td>Skin blood flow (perfusion units)</td>
<td>6.03 ± 0.56</td>
<td>4.83 ± 0.50</td>
<td>6.87 ± 2.34</td>
<td>8.50 ± 2.22‡§</td>
<td>NS</td>
</tr>
<tr>
<td>Skin vascular resistance (resistance units)</td>
<td>16.20 ± 1.38</td>
<td>22.26 ± 1.78†</td>
<td>19.58 ± 2.2</td>
<td>15.10 ± 2.24‡§</td>
<td>0.001</td>
</tr>
<tr>
<td>OAAS scale</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
<td>5 ± 0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE. *Interaction between treatment group and time effect and represents difference in response between dexmedetomidine and saline; †p < 0.01 vs. baseline; ‡p < 0.01 vs. cocaine; §p < 0.01 versus saline; |p < 0.05 versus baseline; †p < 0.05 versus cocaine; ‡p < 0.05 versus saline. NS = non-significance at the level of p > 0.05; OAAS = observer’s assessment of alertness and sedation; SNA = sympathetic nerve activity.

**Effectiveness of dexmedetomidine on responses to cocaine in the presence of the α2CDe322-325 polymorphism.** Table 4 presents the baseline characteristics of subjects homozygous for α2CDe322-325 allele and compares with those of 11 subjects with common allele, which are the same subjects who received cocaine + dexmedetomidine in Table 1. Table 5 presents the responses to cocaine alone and in combination with dexmedetomidine in the homozygous carriers, whereas Table 3 presents the comparable data for the control subjects carrying only the common allele. The responses to cocaine and the effects of dexmedetomidine on these responses were similar in the 2 groups, with no evidence of attenuated dexmedetomidine action in the subjects homozygous for the mutant allele (Tables 3 and 5, Fig. 3). The OAAS was also unaffected by dexmedetomidine in this group of subjects as well.

**Discussion**

The major new findings of this study are 2-fold. First, the centrally acting α2 agonist dexmedetomidine was effective and safe in abolishing both the sympathoexcitatory and corresponding hemodynamic effects of cocaine in healthy cocaine-naïve human subjects. Second, the α2-agonist remained equally effective in subjects homozygous for a loss-of-function mutation in the α2C AR (Del322-325) present in the majority of blacks, suggesting the importance of other α2 AR subtypes and the applicability of the study results to a diverse multi-ethnic population.

**Effectiveness and safety of dexmedetomidine as a countermeasure to the sympathomimetic actions of cocaine.** Although cocaine is well known to block NE reuptake in peripheral sympathetic nerve terminals in experimental preparations, in conscious humans cocaine’s sympathomimetic effects on the heart and peripheral circulation seem to be caused primarily by central activation of SNA (3,4). The latter central mechanism of cocaine action provided the rationale for implicating central sympatholytic drugs as a potential new countermeasure, the effectiveness of which previously has been demonstrated only in experimental animals. In anesthetized rats, clonidine has been shown to reverse the pressor response to cocaine (5). In dogs, dexmedetomidine—a central sympatholytic agent with 8-times-higher binding affinity for α2 ARs than clonidine (6,7)—reversed cocaine-induced vasoconstriction in both the peripheral and coronary circulations (10).

The cutaneous circulation provided an excellent opportunity to extend these mechanistic observations to conscious humans. We previously showed that even a small subeuphoric dose of intranasal cocaine produces large increases in both skin SNA and skin vascular resistance that last for at least 90 min (3). Thus, this experimental approach provided a stable, centrally generated vasomotor response to examine its modulation by a central sympatholytic drug such as dexmedetomidine. In humans, skin SNA is highly reactive to central neural influences such as cocaine but unreactive to changes in baroreceptor activity, which would otherwise complicate the interpretation of centrally mediated responses (18,19). Under normothermic conditions, cocaine-induced increases in skin SNA are vasoconstrictor impulses. Thus, the combination of microneurographic and laser Doppler techniques allowed us to study SNA and its downstream vasoconstrictor effect in the same human vascular bed.

Dexmedetomidine allowed us to readily control and completely eliminate the SNA response to cocaine. This is a potent effect, because it occurred with doses of dexme-
Cocaine and Dexmedetomidine

Table 5  Dose-Dependent Effects of Dexmedetomidine in Subjects With the α2CDe322-325 Variant Allele

<table>
<thead>
<tr>
<th>α2CDe322-325 Variant Allele (n = 7)</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>Dexmedetomidine Plus 0.1 μ/kg</th>
<th>Dexmedetomidine Plus 0.3 μ/kg</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>93 ± 3</td>
<td>101 ± 3†</td>
<td>95 ± 3‡</td>
<td>89 ± 2‡</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69 ± 5</td>
<td>79 ± 8†</td>
<td>78 ± †</td>
<td>72 ± †</td>
<td>NS</td>
</tr>
</tbody>
</table>

Skin SNA

| Integrated activity, %               | 100      | 416 ± 192 | 251 ± 102 | 92 ± 35 | NS      |
| Ln % integrate activity              | 4.61 ± 0 | 5.62 ± 0.38§| 5.12 ± 0.41| 4.02 ± 0.51‡§| NS      |
| Skin blood flow (perfusion units)    | 9.41 ± 2.05| 8.66 ± 1.37§| 0.37 ± 2.11| 13.37 ± 3.61‡| NS      |
| Skin vascular resistance (resistance units) | 12.68 ± 2.30| 17.88 ± 2.53‡| 15.52 ± 3.14| 11.70 ± 3.5‡| NS      |
| OAS scale                            | 5 ± 0    | 5 ± 0    | 5 ± 0      | 5 ± 0      | NS      |

Data expressed as mean ± SE. *Interaction between genotype and time effect and represents difference in response between subjects with the α2CDe322–325 variant and the common α2C allele; †p < 0.01 versus baseline; ‡p < 0.01 versus cocaine; §p < 0.05 versus baseline.

NS = non-significance at the level of p > 0.05; OAS = observer’s assessment of alertness and sedation; SNA = sympathetic nerve activity.

Figure 3  Changes in Skin SNA and Vascular Resistance in Subjects With α2CDe322–325 Allele

Intranasal cocaine caused a similar increase in skin sympathetic nerve activity (SNA) and skin vascular resistance in both groups of subjects. Dexmedetomidine (Dex) reversed effects of cocaine on SNA and skin vascular resistance similarly in both groups. Data are mean ± SE. *p < 0.05 versus baseline, †p < 0.01 versus baseline.

Study limitations. Despite the strengths of the study, there are several factors that limit the clinical applicability of the present findings. First, for obvious ethical reasons, the cocaine dose used in these studies was small, requiring only low doses of dexmedetomidine. Further clinical trials are needed to determine the efficacy and safety of larger doses of dexmedetomidine in counteracting the cardiovascular effects of higher recreational doses of cocaine. However, even very large doses of dexmedetomidine—10 times higher than that approved for anesthesia—are well-tolerated without causing respiratory depression (13), an advantage over the sedatives currently used to treat cocaine intoxication (i.e., morphine, benzodiazepines). Second, because we studied healthy cocaine-naïve subjects, the results cannot be extrapolated to chronic cocaine abusers. However, in isolated case reports dexmedetomidine has been effective in reducing agitation, tachycardia, and hypertension in poly-substance abusers undergoing withdrawal from cocaine, alcohol, and opiates (26,27). Third, here we focused on the human cutaneous circulation and skin sympathetic activity. Additional studies are needed to determine whether dexmedetomidine is equally effective in the human coronary circulation and cardiac sympathetic activity as well as other regional sympathetic outflow. Interestingly, a recent meta-analysis showed that dexmedetomidine and other α2 AR agonists...
reduced the risk of peri-operative myocardial infarction in high-risk patients (28).

**Clinical implications and conclusions.** The present data provide a conceptual framework for suggesting a new use for an old class of cardiovascular drugs—central sympatholytics as a novel countermeasure for the acute cardiovascular complications of cocaine. Currently, nitrates are considered first-line therapy (Class I indication) for cocaine-associated acute coronary syndrome (29); however, they can worsen myocardial oxygen demands by causing reflex tachycardia (30,31). Benzodiazepines (Class IIa indication) and morphine might help to reverse cocaine-induced coronary ischemia as well as agitation (31,32), but they are ineffective against cocaine-induced acute hypertension and tachycardia (31,33) and can cause respiratory depression. Beta blocker drugs are generally contraindicated in the setting of cocaine intoxication to avoid unopposed α1 adrenergic coronary vasoconstriction. Labeltalol, a combined α-/β-blocker, might attenuate cocaine-induced acute hypertension but unfortunately is not effective in reversing cocaine-induced coronary vasoconstriction (34). Calcium channel blockers such as verapamil are effective in reversing cocaine-induced coronary vasoconstriction but not in reversing effects of cocaine on the heart rate (35). In contrast, by eliminating cocaine’s multiple sympathomimetic actions at their origin, dexmedetomidine might constitute effective monotherapy for this common clinical problem by providing a controlled reduction in blood pressure and heart rate and reversing peripheral vasoconstriction.

**References**


