Dexmedetomidine as a Novel Countermeasure for Cocaine-Induced Central Sympathoexcitation in Cocaine-Addicted Humans

Andrew C. Kontak, Ronald G. Victor, Wanpen Vongpatanasin

Abstract—Cocaine-induced acute hypertension is mediated largely by increased central sympathetic nerve activity. We hypothesized that dexmedetomidine, a central sympatholytic, reverses cocaine-induced increases in sympathetic nerve activity, mean arterial pressure (MAP), and heart rate (HR) in cocaine-addicted subjects. First, we conducted a dose-finding study in 15 nontreatment-seeking cocaine-addicted subjects and 12 cocaine-naïve healthy controls to find doses of intranasal dexmedetomidine that lower MAP and HR in the absence of acute-cocaine challenge. We then conducted a placebo-controlled treatment trial in 26 cocaine-addicted subjects to determine whether dexmedetomidine reverses MAP and HR increases after intranasal cocaine (3 mg/kg). Skin sympathetic nerve activity (measured in the second protocol) and skin vascular resistance (measured in both protocols) served as indices of cocaine-sensitive central sympathoexcitation. In doses up to 0.6 µg/kg IV, dexmedetomidine alone caused comparable dose-dependent decreases in blood pressure in cases and controls but a 1.0 µg/kg dose was required to lower HR. In cocaine-addicted subjects, low-dose dexmedetomidine (0.4 µg/kg; n=14) abolished cocaine-induced increases in skin sympathetic nerve activity (156±26 versus −15±22%, cocaine/placebo versus cocaine/dexmedetomidine; P<0.05), skin vascular resistance (+10±2 versus −2±3 U; P<0.05), and MAP (+6±1 versus −5±2 mm Hg; P<0.01) without affecting HR (+13±2 versus +9±2 bpm; P=ns). When dexmedetomidine was increased to 1 µg/kg (high dose; n=12) to reverse cocaine-induced increases in HR, MAP did not fall further and increased paradoxically in 4 of 12 subjects. Thus, in a low nonsedating dose, dexmedetomidine constitutes a putative new treatment for cocaine-induced acute hypertension but higher sedating doses can increase blood pressure unpredictably during acute-cocaine challenge and should be avoided. (Hypertension. 2013;61:388-394.)● Online Data Supplement

Key Words: adrenergic receptors □ adrenergic receptor agonists □ cocaine □ sympathetic nervous system □ sympatholytics

Cocaine abuse is increasing worldwide among all income strata.1 By current estimates, 20% of Americans >12 years of age have tried cocaine, and 2.1 million Americans are current users.2 Cocaine is the most common illicit drug causing life-threatening cardiovascular emergencies, including acute coronary syndrome, stroke, sudden cardiac death, and hypertensive crisis.1,3,4 Current treatment recommendations for cocaine-induced acute hypertension and other cardiovascular emergencies are based on limited evidence,6 and standard first-line nitrate therapy is not always effective. Thus, new treatment targets and better evidence are required. The standard teaching is that cocaine blocks norepinephrine (NE) reuptake in peripheral sympathetic nerve terminals, thereby increasing (NE) in the synaptic cleft.7 On the contrary, studies by our group and others indicate that cocaine stimulates the mammalian cardiovascular system primarily by acting on the brain to increase central sympathetic nerve activity (SNA), with minimal contribution from peripheral NE transporter inhibition.8–12 Thus, SNA constitutes a putative new drug target for the management of cocaine-induced acute hypertension.

Dexmedetomidine, an intravenous central sympatholytic drug that is a more potent α2 adrenergic agonist than clonidine, is approved for conscious sedation in the intensive care unit.13 The drug acts in the central nervous system to augment α2 adrenergoreceptor restraint on SNA to multiple tissues and vascular beds.14 Reasoning that dexmedetomidine might also be useful in the setting of cocaine overdose, we previously showed that even low nonsedating doses of dexmedetomidine can eliminate cocaine-induced increases in skin SNA, mean arterial pressure (MAP), and heart rate (HR).15 However, the clinical applicability of those data were limited by studying

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only cocaine-naive subjects receiving a low-dose cocaine (2 mg/kg) challenge, which is much lower than doses typically used by cocaine addicts.9

The aim of the current study was to test whether dexmedetomidine also reverses the increases in blood pressure (BP), HR, and skin SNA caused by a higher cocaine dose in non-treatment-seeking cocaine-addicted individuals, who represent the majority of patients presenting to emergency rooms with cocaine-induced cardiovascular complications.16 Two sequential series of studies were performed. First, we conducted a dose-finding study to detect the doses of intravenous dexmedetomidine needed to achieve controlled reductions in MAP and HR in the absence of acute-cocaine challenge. In this dexmedetomidine-suppression test, we compared responses of nontreatment-seeking cocaine-addicted subjects and age-matched cocaine-naive healthy controls. Because chronic cocaine exposure has been shown to reduce central α2 adrenergic receptor density17 and agonist sensitivity in rodents,17,18 we needed to know whether dexmedetomidine would be less effective as a central sympatholytic and thus higher doses needed in the setting of chronic cocaine addiction. We then conducted a placebo-controlled single-blind parallel arm treatment trial in a total of 26 cocaine-addicted subjects, to determine whether low- or high-dose dexmedetomidine reverses the acute increases in MAP and HR evoked by intranasal cocaine challenge (3 mg/kg).

Methods
We studied a total of 12 cocaine-naive control subjects and 30 non-treatment-seeking cocaine-addicted subjects (32 men and 10 women, 31–58 years). The protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center at Dallas. All subjects were recruited through newspaper advertisements. Subjects were normotensive and had no history of cardiovascular disease. Cocaine addiction was documented by detection of cocaine or metabolites in urine samples (without other positive urine toxicology) at screening. All cocaine-addicted subjects refused any prescription or nonprescription drugs with cardiovascular or cerebrovascular disease. Cocaine addiction was documented by detection of cocaine or metabolites in urine samples (without other positive urine toxicology) at screening. All cocaine-addicted subjects who expressed any interest in drug rehabilitation were excluded from drug rehabilitation; for ethical reasons, cocaine-addicted subjects expressing any interest in drug rehabilitation were excluded from the study. All cocaine-addicted subjects were asked to abstain from cocaine or any other illicit drug use for 72 hours before study; cocaine abstinence was confirmed by undetectable plasma cocaine levels at the time of the study. None of the subjects from either group 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. The HR, SNA, skin blood flow, and respiratory rate were recorded continuously with a multichannel digital data recorder (MacLab/SS ML780, AD Instruments, Inc, Colorado Springs, CO); BP was measured with a validated oscillometric Welch Allyn Vitalsigns Monitor (Tycos Instruments Inc, Skaneateles Falls, NY).

Recording of SNA
Multunit recordings of postganglionic SNA were obtained with uni-polar tungsten microelectrodes inserted selectively into muscle or skin nerve fascicles of the peroneal nerve, according to the technique by Valbo.19 The neural signals were amplified, filtered, rectified, and integrated with a nerve traffic analyzer to obtain a mean voltage display of sympathetic discharge. The criteria for acceptable recordings of skin SNA and muscle SNA have been described previously19,20 and detailed in the online-only Data Supplement.

All records were analyzed by the same investigator (A.K.), who scored the recorded data in a blinded fashion. The interobserver and intraobserver variability in identifying bursts are ≤10% and 5%, respectively.20

Measurement of Skin Blood Flow
Skin blood flow was measured by laser Doppler velocimetry (Advance Laser Flowmeter, Advance Co, Tokyo, Japan) with the probe placed on the plantar aspect of the first toe. Skin vascular resistance (resistance unit) was calculated as MAP X 100/skin blood flow (perfusion units).

Lower Body Negative Pressure
With the subject’s lower body enclosed in an airtight chamber, lower body negative pressure (LBNP) was applied at −40 mm Hg to unload the baroreceptors, thereby reflexively increasing HR.25

Laboratory Assays
Plasma (NE) was determined by high-performance liquid chromatography (Quest Diagnostics, San Juan Capistrano, CA). The intraassay coefficient of variation was ≤5%. Plasma cocaine was determined by gas chromatography/mass spectrometry (Quest Diagnostics, Pittsburgh, PA). The interassay and intraassay variability of cocaine readings are ≤10%.

Assessment of Level of Sedation
During infusion of dexmedetomidine, the level of alertness/sedation was monitored with the Observer’s Assessment of Alertness/Sedation scale. A score of 5 correlates with maximum alertness and 1 indicates deep sleep.22

Specific Protocols
Dose-Finding Case–Control Study (19 Experiments in 15 Cocaine-Addicted Subjects and 15 Experiments in 12 Cocaine-Naive Subjects)
Dexmedetomidine-suppression testing was conducted to determine whether the drug would be less effective as a central sympatholytic and thus higher doses needed in the setting of chronic cocaine addiction.

Protocol 1A: We measured BP and HR at baseline and 10 minutes after intravenous infusion of dexmedetomidine (Hospira Inc, Lake Forest, IL) at a dose of 0.1, 0.2, and 0.3 μg/kg (each given over 1 minute), separated by 10 minutes, for a cumulative dose of 0.6 μg/kg (Figure S3 in the online-only Data Supplement). In this protocol, we also measured skin blood flow (using skin vascular resistance as an index of skin SNA), as well as muscle SNA and plasma NE to confirm that the dexmedetomidine acts centrally to reduce SNA to multiple vascular beds.

Protocol 1B: Because HR was unaffected by these 3 doses of dexmedetomidine in both groups of subjects, we conducted additional experiments in which we assessed HR and MAP responses to a higher dose of dexmedetomidine: 1 μg/kg infused intravenously over 10 minutes; HR and MAP were measured before and 10 minutes after dexmedetomidine infusion. These measurements were made both at rest and during 3 minutes of LBNP at −40 mm Hg, the latter to reflexively elevate the ambient HR level on which dexmedetomidine infusion was superimposed (Figure S4).

Randomized Controlled Treatment Trial (42 Experiments in 26 Cocaine-Addicted Subjects)
A single-blind, randomized, placebo-controlled, parallel, treatment trial was conducted to determine whether dexmedetomidine reverses increases in MAP and HR as well as skin SNA and skin vascular resistance after acute-cocaine challenge in cocaine-addicted subjects.

Based on our past work, skin SNA, rather muscle SNA, is the appropriate indicator of cocaine-induced central sympathetic activation. Because muscle SNA is tightly regulated by arterial baroreflexes, cocaine-induced sympathoexcitation is obscured by baroreflex-mediated sympathoinhibition such that muscle SNA actually decreases as BP rises with acute-cocaine challenge.23 Thus, cocaine causes no clear-cut increase in muscle SNA or plasma (NE) to test for its modulation by dexmedetomidine. In contrast, skin SNA is devoid of baroreflex regulation and therefore shows a consistently large and sustained increase after acute-cocaine challenge, thereby
Results

The baseline characteristics of subjects in the case–control study of dexmedetomidine-suppression testing are shown in Table 1. The 2 groups were well matched on most characteristics including age, sex, race/ethnicity (most being black men), body mass index, and baseline HR; however, cocaine-addicted subjects (who had a mean duration of cocaine addiction of 17±2 years) had higher systolic BP at baseline (P<0.05). The baseline characteristics of the cocaine-addicted subjects in the treatment trial are shown in Table 2.

In the initial dose-finding study, we studied 15 cases and 12 controls. Of these subjects, 10 cases and 7 controls participated in protocol 1A and 9 cases and 8 controls in protocol 1B.
Dexmedetomidine-induced decreases in MAP and skin vascular resistance (or increase in skin blood flow). In contrast, HR was unaffected by cumulative doses of dexmedetomidine up to 0.6 μg/kg in both groups. Changes in muscle SNA and plasma NE are shown in the online-only Data Supplement (Table S1 and Figure S6).

When the dose was increased to 1 μg/kg in cocaine-addicted subjects, dexmedetomidine lowered HR by 4 bpm (P<0.05), both in the absence and presence of LBNP, whereas, in the cocaine-naive subjects, 1 μg/kg dexmedetomidine lowered HR only during LBNP (by 4.5 bpm; P<0.05; Figure 1B).

Randomized Controlled Treatment Trial in Cocaine-Addicted Subjects: Effects of Low- and High-Dose Dexmedetomidine Versus Placebo on Responses to Acute-Cocaine Challenge

With acute intranasal cocaine, the plasma cocaine level increased from 0 to 0.05±0.01 μg/mL in cocaine-addicted subjects. As shown in Figures 2A, 2B, and 3, placebo (n=16) was without effect whereas low-dose dexmedetomidine (0.4 μg/kg; n=14) abolished cocaine-induced increases in MAP (+6±1 versus −5±2 mm Hg, cocaine/placebo versus cocaine/dexmedetomidine; P<0.01), skin SNA (+156±26 versus −15±22%; P<0.05), and skin vascular resistance (+10±2 versus −2±3 U; P<0.05) without affecting HR (+13±2 versus +9±2 bpm; P=ns; Table S2).

When the dexmedetomidine dose was increased sufficiently (1 μg/kg; n=12) to reverse the cocaine-induced increase in HR (+13±2 versus +3±2 bpm, cocaine/placebo versus cocaine/dexmedetomidine; P<0.01), the average level of MAP did not fall further, with MAP increasing paradoxically in 4 of 12 subjects (Figure 3).

The subjects’ mean sedation score was unchanged from baseline with low-dose dexmedetomidine (5.0±0 versus 4.8±0.12) but decreased to 3.83±0.46 (P<0.05) with the higher dose.

Discussion

In the absence of acute-cocaine challenge, we found that cocaine-naive and cocaine-addicted subjects show very similar depressor responses to dexmedetomidine but striking differences become apparent during acute-cocaine challenge. In cocaine-naive subjects, we had previously found that a low nonsedating dose of dexmedetomidine (0.4 μg/kg) readily reverses the acute cocaine-induced increase in both BP and HR, as well as skin SNA and skin vascular resistance reflecting cocaine’s central mechanism of action;14 on the contrary, the current study on cocaine-addicted subjects shows that the same low dose of dexmedetomidine reverses the cocaine-induced increases in MAP, skin SNA, and skin vascular resistance but it fails to affect the HR increase. We discovered that a much higher sedating dose of dexmedetomidine (1.0 μg/kg) is needed to counteract the modest HR rise with low-dose cocaine challenge but at the expense of increasing BP in one third of cocaine-addicted subjects. These new findings have important implications for considering dexmedetomidine as a putative new countermeasure for acute cocaine-induced hypertension in the clinical setting.
Although cocaine has been shown to block NE reuptake in peripheral sympathetic nerve terminals in ex vivo preparations, previous studies by our group in conscious humans and primates, as well as studies in conscious dogs by other groups indicate that cocaine stimulates the mammalian cardiovascular system in vivo mainly by a central rather than a peripheral mechanism of action. Thus, a central sympatholytic drug might eliminate the adverse cardiovascular response at its central origin.

Although chronic cocaine exposure has been reported to cause downregulation of central α2 adrenergic signaling in rodents, we found no such evidence under the experimental conditions of these translational research studies in humans. Chronic cocaine exposure, for even 2 decades, did not impair the ability of dexmedetomidine to cause dose-dependent decreases in BP. Specifically, our initial dose-finding case-control study informed the subsequent treatment trial by showing that the 0.4 μg/kg dose of dexmedetomidine (used in previous study of cocaine-naive subjects) was sufficient to cause large reductions in MAP in cocaine-addicted subjects but that a >2-fold higher dose was needed to lower HR.

Dexmedetomidine, as hypothesized, proved to be a potent countermeasure to the central sympathomimetic action of cocaine in cocaine-addicted subjects. The low-dose dexmedetomdine completely abolished the large cocaine-induced increase in skin SNA—a regional sympathetic outflow that is not buffered by arterial baroreflexes and is thus exquisitely sensitive to central neural stimuli including small, nonintoxicating doses of cocaine. Low-dose dexmedetomidine also abolished the modest cocaine-induced increase in BP, although the cocaine dose was 50% higher than in a previous study of cocaine-naive subjects.

However, dexmedetomidine was less potent against the chronotrophic action of cocaine, because a higher sedating dose...
of dexmedetomidine (1 µg/kg) was required to reverse the cocaine-induced increase in HR in the cocaine-addicted subjects. The precise explanation for the HR–BP dissociation in our study is unclear, as both responses to cocaine are mediated by central sympathetic activation with no contribution from vagal withdrawal. Because higher doses of dexmedetomidine were also needed to slow HR in the absence of cocaine, our data suggest that the dexmedetomidine dose–response relation for decreased cardiac SNA targeted to the sinus node is shifted to the right or is less steep than the dose–response relation for decreased vasconstrictor SNA targeted to the cutaneous and skeletal muscle circulations and possibly other vascular beds that regulate BP.

With the 1 µg/kg dose of dexmedetomidine needed to control HR during cocaine, the paradoxical increase in BP observed in one third of our cocaine-addicted subjects is most likely explained by direct agonist stimulation of vascular α2 adrenergic receptors that increase vascular resistance in regional beds other than the cutaneous circulation. The less potent α2 adrenergic agonist clonidine has been shown to evoke a large paradoxical pressor response caused by peripheral vasoconstriction in patients with sympathetic denervation because of primary autonomic failure. We speculate that in cocaine-addicted subjects low-dose dexmedetomidine consistently lowered BP during acute-cocaine challenge because the predominant effect was to stimulate α2 adrenergic receptors in the central nervous system, thereby lowering central sympathetic vasoconstrictor drive to multiple vascular beds, with little or no effect on vascular α2 receptors, whereas, with high-dose dexmedetomidine, SNA is suppressed, allowing direct peripheral vasoconstriction (via vascular α2 receptors) to be the dominate effect on BP in some subjects. However, neither skin SNA nor any of the other variables measured in these studies were predictive of the dexmedetomidine-induced pressor response.

Our study has several limitations. The 3-mg/kg dose of intranasal cocaine, though higher than used in past research, is still only ~75% of the average dose used for rhinolaryngeal procedures. Whether dexmedetomidine can control acute severe hypertension at higher doses typically used by cocaine addicts or with massive cocaine overdose is unknown. Because most study subjects were black men, further studies would be needed to determine whether our findings are generalizable; however, cocaine addiction is more prevalent among blacks than whites (pushers having targeted low-income inner-city blacks with inexpensive crack cocaine) and more prevalent among black men than women. Moreover, there is no evidence that the cardiovascular effects of cocaine vary by race or gender. Skin SNA per se is not a major determinant of BP but constitutes a sensitive marker of central generated sympathetic activation targeted to the heart and multiple vascular beds during cocaine challenge. Muscle SNA plays at most a permissive role in the pressor response to cocaine, because the activity does not increase with cocaine but rather shows a smaller-than-expected decrease. An inherent limitation of microneurography is that the technique cannot be used to measure SNA in visceral nerves that drive BP such as the renal nerves; in experimental animals, multi-fiber renal SNA is regulated both by barorereflexes (like human muscle SNA) and by central nervous system stimuli (like human skin SNA). Because our study focused on BP and HR, the determinants of myocardial oxygen demand, additional studies will be needed to test dexmedetomidine’s ability to counteract cocaine-induced coronary vasoconstriction, a major mechanism of cocaine-related chest pain and acute coronary syndrome.

**Perspectives**

Despite these limitations, the current data provide proof-of-concept for repurposing a central sympatholytic drug as a novel countermeasure for the acute cardiovascular complications of cocaine in cocaine-addicted humans, who represent the majority of patients encountered in the emergency room setting for drug-abuse related visits. The study of nontreatment-seeking cocaine-addicted persons allowed examination of higher doses of both cocaine and of dexmedetomidine than is feasible in cocaine-naive subjects. The new data move this work closer to clinical translation and reveal a nonlinearity in the dexmedetomidine–BP dose–response relation that highlights an important cautionary note for potential future clinical application. Specifically, dexmedetomidine would not be suitable as monotherapy because higher doses can cause unpredictable increases in BP, which could increase myocardial oxygen demands and exacerbate cocaine-induced myocardial ischemia. However, at nonseeding doses of 0.6 µg/kg or less, dexmedetomidine could be a useful adjunct in treating cocaine-induced acute hypertension that is refractory to standard first-line treatment with nitrates. As dexmedetomidine holds promise to impact treatment recommendations, further clinical research is warranted.

**Acknowledgments**

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**Disclosures**

None.

**References**

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DEXMEDETOMIDINE AS A NOVEL COUNTERMEASURE FOR COCAINE-INDUCED CENTRAL SYMPATHOEXCITATION IN COCAINE-ADDICTED HUMANS

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Methods

In all cases in Protocol 2 we proved that we were recording only skin SNA by showing that: 1) weak electrical stimulation (-.5 to 3.2V, 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.

Skin SNA bursts can appear to take on a pulse-synchronous appearance (even though they are not) when a high level of activity is displayed on a compressed time scale as in Figure 2A. The brisk increase in SNA burst frequency with cocaine cannot be muscle SNA, which decreases sharply with acute cocaine challenge.

The parallel increase in skin vascular resistance argues convincingly that the cocaine-induced increase in skin SNA is mainly vasoconstrictor activity. Though we did not measure sweat rate in this study which was performed at room temperature, in a previous paper we showed that intranasal cocaine has no effect on sudomotor activity at room temperature (but does attenuate sudomotor activation in the forearm during heat stress\(^1\)).

Results

Reduction in muscle SNA and plasma [NE] by each dose of dexmedetomidine was also indistinguishable from cocaine-naïve subjects (ANOVA p = 0.37, supplemental figure). The baseline plasma [NE] level was significantly higher in the cocaine-addicted subjects than in the cocaine-naive controls (619 ± 73 pg/ml vs. 406 ± 45 pg/ml, respectively, p<0.05).
References

Table S1.

**Cocaine-Addicted Cases (n=10)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Dex 0.1</th>
<th>Dex 0.3</th>
<th>Dex 0.6</th>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>97 ± 2</td>
<td>91 ± 2*</td>
<td>82 ± 2*</td>
<td>79 ± 3*</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>63 ± 3</td>
<td>63 ± 3</td>
<td>63 ± 3</td>
<td>62 ± 2</td>
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<tr>
<td>Muscle SNA, total activity/min, % bursts/min</td>
<td>100</td>
<td>84 ± 7†</td>
<td>67 ± 10*</td>
<td>49 ± 13*</td>
</tr>
<tr>
<td>NE, ng/ml</td>
<td>619 ± 73†</td>
<td>485 ± 67†</td>
<td>292 ± 48*</td>
<td>251 ± 30*</td>
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<tr>
<td>Forearm Blood Flow, ml/min⁻¹</td>
<td>71 ± 11</td>
<td>80 ± 12</td>
<td>123 ± 20*</td>
<td>134 ± 38*</td>
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<tr>
<td>Forearm Vascular Resistance, resistance units</td>
<td>160 ± 23</td>
<td>136 ± 20</td>
<td>81 ± 14*</td>
<td>90 ± 16*</td>
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</tbody>
</table>

Data expressed as mean ± SE. *p <0.01 vs. baseline, †p <0.05 vs. baseline. ‡p <0.05 vs. Cocaine-Naive. Dex = dexmedetomidine. MSNA = muscle sympathetic nerve activity. NE = norepinephrine.

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**Cocaine-Naive Controls (n=7)**

<table>
<thead>
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<th>Baseline</th>
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<th>Dex 0.3</th>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>90 ± 3</td>
<td>84 ± 3*</td>
<td>81 ± 3*</td>
<td>77 ± 2*</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>58 ± 4</td>
<td>57 ± 3</td>
<td>60 ± 4</td>
<td>58 ± 4</td>
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<tr>
<td>Muscle SNA, total activity/min, % bursts/min</td>
<td>100</td>
<td>86 ± 8</td>
<td>63 ± 10*</td>
<td>42 ± 9*</td>
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<tr>
<td>NE, ng/ml</td>
<td>406 ± 45</td>
<td>372 ± 26</td>
<td>303 ± 45</td>
<td>237 ± 15</td>
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<tr>
<td>Forearm Blood Flow, ml/min⁻¹</td>
<td>68 ± 11</td>
<td>83 ± 11</td>
<td>74.6†</td>
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<tr>
<td>Forearm Vascular Resistance, resistance units</td>
<td>145 ± 19</td>
<td>113 ± 21†</td>
<td>88 ± 9*</td>
<td>82 ± 5*</td>
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</table>

Data expressed as mean ± SE. *p <0.01 vs. baseline, †p <0.05 vs. baseline. Dex = dexmedetomidine. MSNA = muscle sympathetic nerve activity. NE = norepinephrine.
### Placebo (n=16)

<table>
<thead>
<tr>
<th>Variables</th>
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<th>Cocaine</th>
<th>Cocaine + Placebo</th>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96 ± 3</td>
<td>103 ± 2*</td>
<td>102 ± 2*</td>
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<td>Heart rate, beats/min</td>
<td>64 ± 2</td>
<td>75 ± 2*</td>
<td>77 ± 3*</td>
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<tr>
<td>Skin SNA, total activity/min, %</td>
<td>100</td>
<td>228 ± 30†</td>
<td>256 ± 26*</td>
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<tr>
<td>bursts/min</td>
<td>19 ± 2</td>
<td>29 ± 2†</td>
<td>29 ± 1*</td>
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<tr>
<td>Skin blood flow, perfusion units</td>
<td>9.63 ± 2.12</td>
<td>5.95 ± 1.21*</td>
<td>5.15 ± 0.91*</td>
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<td>Skin vascular resistance, bursts/min</td>
<td>14.55 ± 2.11</td>
<td>23.15 ± 2.45*</td>
<td>24.81 ± 2.30*</td>
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<td>OAAS scale</td>
<td>5.00 ± 0.00</td>
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</table>

Data expressed as mean ± SE. *p <0.01 vs. baseline. †p <0.05 vs. baseline.

SNA = sympathetic nerve activity

### Low Dose Dexmedetomidine (n=14)

<table>
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<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>Cocaine + Dexmedetomidine 0.4 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98 ± 2</td>
<td>102 ± 2*</td>
<td>93 ± 3†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60 ± 3</td>
<td>68 ± 3‡</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>Skin SNA, total activity/min, %</td>
<td>100</td>
<td>218 ± 28*</td>
<td>85 ± 22§</td>
</tr>
<tr>
<td>bursts/min</td>
<td>25 ± 2</td>
<td>34 ± 2*</td>
<td>18 ± 3§</td>
</tr>
<tr>
<td>Skin blood flow, perfusion units</td>
<td>7.92 ± 2.48</td>
<td>6.28 ± 2.11</td>
<td>7.12 ± 2.00†</td>
</tr>
<tr>
<td>Skin vascular resistance, bursts/min</td>
<td>20.74 ± 2.93</td>
<td>26.77 ± 3.32*</td>
<td>19.22 ± 2.58†</td>
</tr>
<tr>
<td>OAAS scale</td>
<td>5.00 ± 0.00</td>
<td>5.00 ± 0.00</td>
<td>4.82 ± 0.12</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE. *p <0.05 vs. baseline, †p <0.01 vs. saline, §p <0.05 vs. saline.

SNA = sympathetic nerve activity

### High Dose Dexmedetomidine (n=12)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Cocaine</th>
<th>Cocaine + Dexmedetomidine 1 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>92 ± 2</td>
<td>100 ± 2*</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>62 ± 2</td>
<td>75 ± 4*</td>
<td>65 ± 4†</td>
</tr>
<tr>
<td>Skin SNA, total activity/min, %</td>
<td>100</td>
<td>246 ± 94§</td>
<td>29 ± 15†</td>
</tr>
<tr>
<td>bursts/min</td>
<td>17 ± 2</td>
<td>29 ± 3§</td>
<td>6 ± 3†</td>
</tr>
<tr>
<td>Skin blood flow, perfusion units</td>
<td>8.05 ± 2.22</td>
<td>4.43 ± 1.25*</td>
<td>8.73 ± 1.91†</td>
</tr>
<tr>
<td>Skin vascular resistance, bursts/min</td>
<td>18.31 ± 3.03</td>
<td>30.43 ± 2.93*</td>
<td>16.59 ± 2.77‡</td>
</tr>
<tr>
<td>OAAS scale</td>
<td>5.00 ± 0.00</td>
<td>5.00 ± 0.00</td>
<td>3.83 ± 0.46§</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SE. *p <0.01 vs. baseline, †p <0.05 vs. saline, §p <0.05 vs. baseline.

SNA = sympathetic nerve activity.
Figure S3.

Baseline

Dex 0.1 mcg/kg bolus over 1 min

10 min

BP, HR, skin blood flow, SNA, [NE]

Dex 0.2 mcg/kg bolus over 1 min

10 min

BP, HR, skin blood flow, SNA, [NE]

Dex 0.3 mcg/kg bolus over 1 min

10 min

BP, HR, skin blood flow, SNA, [NE]

Figure S4.

Rest

Dex 1 mcg/kg bolus over 10 min

LBNP

10 min

BP, HR

3 min

BP, HR

Rest

10 min

BP, HR

LBNP

3 min

BP, HR

Figure S5.

Baseline

Intranasal cocaine 3 mg/kg

10 min

BP, HR, skin blood flow, skin SNA

30 min

Time 0

Dex 0.4 mcg/kg vs

Dex 1.0 mcg/kg vs

saline

10 min

BP, HR, skin blood flow, skin SNA

10 min

BP, HR, skin blood flow, skin SNA
Baseline plasma [NE] was higher in cocaine-addicted cases vs. cocaine-naïve controls (*p<0.05). Dexmedetomidine in a 0.1-0.6 µg/kg dose range caused similar dose-dependent decreases in muscle SNA and plasma [NE].