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Dexmedetomidine Increases the Cocaine Seizure Threshold in Rats

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Background: **Central α adrenoceptors have been demonstrated to play an important role in the control of seizure activity; moreover, α_2 adrenoceptors have been linked to electroencephalogram changes associated with cocaine. The purpose of this study was to determine if dexmedetomidine, a highly selective α_2-adrenoceptor agonist, alters the threshold for cocaine-induced seizure activity in rats.**

Methods: **Sprague-Dawley rats received a cocaine infusion ($1.25\ mg \cdot kg^{-1} \cdot min^{-1}$) followed 15 min later by the coinfusion of either dexmedetomidine (20-μg/kg intravenous bolus followed by an infusion of $1\ \mu g \cdot kg^{-1} \cdot min^{-1}$, CD group, n = 8) or an equal volume of saline (CS group, n = 8). Dexmedetomidine or saline were coinfused with cocaine until the onset of cocaine-induced seizures. Dopamine concentrations in the nucleus accumbens were measured by microdialysis paired with chromatography. To determine if changes in extracellular dopamine were related to the seizures, dopamine (1 μM) was continuously delivered to the nucleus accumbens in a separate group (DACD group, n = 6) *via* retrograde microdialysis. These rats then received an intravenous cocaine infusion followed by dexmedetomidine in the same manner as the CD group.**

Results: **Dexmedetomidine significantly increased the dose of cocaine necessary to produce seizures. Seizures occurred at 25.0 ± 7.7 and 49.3 ± 14.8 min in CS and CD, respectively ($P < 0.001$). The ratio of the percent increase in accumbal dopamine to the cocaine dose at the onset of seizure activity was significantly lower in CD, 39.9 ± 16.5, compared to CS, 82.2 ± 46.5 ($P = 0.04$). Intraaccumbal administration of dopamine prevented the effects of dexmedetomidine on the cocaine seizure threshold.**

Conclusions: **These data suggest that dexmedetomidine increases the cocaine-induced seizure threshold possibly *via* a mechanism related to the attenuation of the extracellular dopaminergic neurotransmitter response to cocaine.**

COCAINE abuse remains a major public health concern in the US today. As of 1999, there were an estimated 1.5 million current cocaine users in the US.[1] According to the Drug Abuse Warning Network, which monitors emergency room illicit drug presentations in the US, cocaine remains the most frequently mentioned illicit drug in patients presenting to emergency rooms with drug-related episodes.[2]

Cocaine use can produce a myriad of neurologic sequelae, including seizures and status epilepticus.[3–5] Cocaine-induced seizure activity has been demonstrated to be often resistant to standard anticonvulsant therapies, including benzodiazepines, barbiturates, and phenytoin; moreover, this central nervous system excitotoxicity, if inadequately treated, can lead to respiratory compromise, permanent neurologic damage, and death.[3,6] Indeed, seizure activity has been demonstrated to be a major determinant of lethality associated with the abuse of cocaine.[4]

Most of the drugs utilized in the treatment of cocaine-induced seizures have γ-aminobutyric acid type A receptors, Na^+ channels, or Ca^{2+} channels as their proposed sites of actions.[3] However, given cocaine's ability to block the reuptake of monoamines in the central nervous system, it is quite feasible that other neurotransmitter pathways, particularly central monoaminergic pathways, may play a role in the central nervous system excitotoxicity of cocaine.[7,8] Indeed, there is evidence to suggest a link between cocaine-induced seizures and various monoaminergic neurotransmitters. Investigators have recently implicated central monoamines, such as dopamine, as potential mediators of cocaine-induced convulsant activity.[9] Moreover, central α adrenoceptors have been demonstrated to play an important role in the control of both drug- and electroshock-induced seizure activity.[10,11] Furthermore, α_2 adrenoceptors (α_2-ARs) have been identified in areas of the central nervous system linked to excitatory pathways and have been implicated in mediating cocaine-induced electroencephalogram desynchronization, a process whereby rhythmic electroencephalogram patterns are replaced by irregular low-voltage activity.[12,13]

Dexmedetomidine is a highly selective α_2-AR agonist, recently introduced into anesthetic practice, with clinically relevant sedative and analgesic properties. Compared to clonidine, dexmedetomidine is approximately 7 times more selective for α_2-ARs.[14] Although the precise mechanisms are unclear, recent studies have suggested that α_2-AR agonists have effects not only on noradrenergic systems but on dopaminergic neurotransmitters as well.[15–17] Certain areas of the brain, such as the nucleus accumbens (NAcc), a mesolimbic dopaminergic area, are known to be terminal projection sites for both noradrenergic and dopaminergic neurons. Moreover, the NAcc has been closely associated with some of the locomotor and other neurobehavioral effects of cocaine.[18,19] Given the evidence that α_2-AR–mediated modulation of extracellular dopamine can occur in areas critical to the psy-

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chostimulant effects of cocaine,[16,20] the purpose of this study was to determine whether dexmedetomidine alters the threshold for cocaine-induced seizure activity.

Materials and Methods

Materials

Dexmedetomidine HCl was a gift from Orion Pharmaceuticals Farmos (Espoo, Finland). Cocaine HCl was donated by the National Institute on Drug Abuse (Bethesda, MD). The artificial cerebrospinal fluid (CSF) solution for microdialysis probe perfusion was purchased from Harvard Apparatus (Holliston, MA) and had the following ionic composition: 150 mM Na^+, 3.0 mM K^+, 1.4 mM Ca^{2+}, 0.8 mM Mg^{2+}, 1 mM PO_4^{3-}, 155 mM Cl^-. Ethylenediamine-tetraacetic acid was purchased from Sigma (St. Louis, MO), and perchloric acid, orthophosphoric acid, and 1-octanesulfonic acid (sodium salt monohydrate) were purchased from Fluka Chemie AG (Milwaukee, WI). Citric acid monohydrate, NaOH, and methanol were purchased from Fisher (Fair Lawn, NJ). Deuterated cocaine was purchased from Sigma Chemical Company.

Animals

The protocol was approved by the Columbia University Animal Care and Use Committee (New York, New York) in accordance with National Institutes of Health guidelines. Male Sprague-Dawley rats, weighing 275–300 g, were purchased from a commercial breeder (Charles River Laboratories, Wilmington, MA) and were individually housed in a temperature-controlled room at 22°C. All animals were on a 12/12 h light/dark cycle, had access to food and water *ad libitum*, and underwent an acclimatization period for a minimum of 24 h. The rats were divided into several groups: group CD (n = 8) received a continuous infusion of cocaine followed 15 min later by the coinfusion of dexmedetomidine, whereas the control group CS (n = 8) received the same cocaine infusion and an equal volume of saline in lieu of dexmedetomidine. Cerebral microdialysis was performed in the NAcc of CD and CS rats in order to measure changes in extracellular dopamine concentrations during drug administration. In order to determine if changes in extracellular accumbal dopamine were related to alterations in the cocaine-induced seizure threshold, a dopamine solution (1 μM) was continuously delivered to the NAcc of a separate group of rats (DACD group, n = 6) *via* retrograde microdialysis. Fifteen minutes after the start of accumbal dopamine delivery, the rats received an intravenous infusion of cocaine followed by dexmedetomidine in the same manner as the CD group.

Surgical Preparation

One week prior to the study, the rats were anesthetized with a ketamine (35 mg/kg intraperitoneal) and pentobarbital (35 mg/kg intraperitoneal) mixture and had a microdialysis guide cannula (CMA/12; CMA, North Chelmsford, MA) stereotaxically placed in the NAcc using the following coordinates, according to the atlas of Paxinos and Watson[21]: 1.7 mm anterior to the bregma, 1.4 mm lateral to the midline, 6.0 mm from the top of the skull. Then, a bipolar electroencephalogram recording electrode (MS303/1-A; Plastics One, Roanoke, VA) was placed in the cortex using the following coordinates, according to the atlas of Paxinos and Watson[21]: 1.1 mm anterior to the lambda, 1.4 mm to the midline, 3.0 mm from the top of the skull. Following a 48- to 72-h recovery period, the animals underwent a second survival surgery under similar anesthesia, and catheters constructed of polyethylene tubing (Intramedic PE-50; Becton Dickinson, Sparks, MD) were inserted in the internal jugular and femoral vein as well as the carotid artery.

Experimental Procedure

The experimental procedure was performed 24–48 h following the catheterization surgery. On the day of the study, a CMA/12 cerebral microdialysis probe (2 mm length, 0.5 mm OD) was gently placed in the NAcc of the awake rat, and the probe was continuously perfused with the artificial CSF solution at a rate of 2 μl/min. The rat was then placed in a transparent study cage (BeeKeeper; BAS Inc., West Lafayette, IN) that was equipped with a rotating swivel and platform (Raturn; BAS Inc.), which allowed the catheterized rat to move about freely so that gross behavioral observations could be made. Once in the transparent cage, the arterial line and the electroencephalogram recording electrode were connected to a computerized data acquisition system (MP100; Biopac Systems, Santa Barbara, CA) running polygraph recording software (Acknowledge®; Biopac Systems), and arterial blood pressure as well as heart rate were continuously monitored and recorded. The cortical bioelectric signals were amplified and filtered using an amplifier (EEG 100; Biopac Systems), and the electroencephalogram signals were then stored on the same computer running the Acknowledge® software.

Two hours after probe insertion, microdialysate samples were collected at 15-min intervals in vials containing 5 μl $HClO_4$, 0.1 M, in order to minimize dopamine degradation, and dialysate dopamine concentrations were subsequently measured *via* high-performance liquid chromatography with electrochemical detection. Once a stable baseline was obtained (3 to 4 samples with $< 10\%$ variation from their respective average), the study drugs were administered. Each rat received a continuous infusion of cocaine (1.25 $mg \cdot kg^{-1} \cdot min^{-1}$) throughout the study. Fifteen minutes after the start of the cocaine infusion, either dexmedetomidine (20-μg/kg intravenous bolus over 2 min followed by a continuous infusion of dexmedetomidine at a rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, CD group, n = 8) or an equal volume of saline (CS group, n = 8) was coinfused with cocaine

until the onset of cocaine-induced seizure activity. The dosing regimen for dexmedetomidine was based on dose ranges used in previously described experiments in rats[22,23] and our own pilot studies. The onset of seizure activity was associated with burst epileptiform activity on the electroencephalogram (fig. 1) and tonic–clonic convulsions. An arterial blood sample was obtained at the onset of seizures in CD and CS for the measurement of the plasma cocaine concentration. In order to ensure the collection of a microdialysate sample that accurately corresponded to the extracellular dopamine milieu at the start of seizure activity, the infusions were continued until the end of the 15-min sampling interval following the onset of seizures. This point was deemed the end of the study.

In the DACD rats, the microdialysis probes were used for the intraaccumbal administration of dopamine; hence, extracellular dopamine was only measured until a stable baseline was established. At that point, the artificial CSF perfusion used hitherto was changed to an artificial CSF solution containing 1 μM dopamine. This concentration of dopamine was selected in order to achieve extracellular dopamine concentrations approximately 10 times the baseline values, which was in the range of extracellular accumbal dopamine concentrations measured in CS and CD during cocaine infusion. Fifteen minutes after the initiation of dopamine delivery, a continuous, intravenous infusion of cocaine, 1.25 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}, was administered followed 15 min later by the simultaneous infusion of dexmedetomidine (20-μg/kg intravenous bolus over 2 min followed by an infusion of dexmedetomidine at a rate of 1 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}). The rats were then observed for the onset of cocaine-induced seizure activity. At the end of the study, all animals were immediately euthanized with an overdose of pentobarbital.

Analytical Methods

Dopamine concentrations in microdialysate samples were measured *via* high-performance liquid chromatography with electrochemical detection using a method that we have previously described.[20] Briefly, a mobile phase consisting of an ion-pairing phosphate–citrate buffer and methanol was delivered through a Princeton SPHER C18 reversed phase column (100 $\times$ 2 mm ID, 5 μm particle size; Princeton Chromatography Inc., Cranbury, NJ) maintained at 30°C. A 10-μl injection was performed using a Rheodyne PEEK injector (9725i; Rheodyne, Cotati, CA) with a 20-μl loop. Quantitation of dopamine was achieved with an amperometric detector (INTRO; Antec, Leyden, The Netherlands) fitted with a VT-03 flow cell with a glassy carbon working electrode, a 25-μm spacer, and a salt bridge Ag/AgCl reference electrode.

The analysis of plasma cocaine concentrations was performed *via* gas chromatography–mass spectrometry using a deuterated internal standard, positive chemical ionization, and simultaneous ion monitoring. We have previously described this method in detail.[24] Briefly, the deuterated internal standard for cocaine was added to the rat plasma prior to sample processing. The electron impact mass spectra of cocaine showed fragmentation patterns with appropriate mass unit shifts for the deuterated internal standard. The intraday and interday coefficients of variation for these compounds were less than 6% across the entire range. Quality control samples at low, medium, and high concentrations were analyzed with each analytic run, and the limit of quantitation was 0.5 ng/ml.

Histology

At the end of the experiment, the rats were euthanized with an overdose of pentobarbital (100 mg/kg intravenous). The brain was immediately harvested and preserved in a 10% formalin and 15% sucrose solution. Coronal sections were obtained (50 μm), and the probe placement was verified using the atlas of Paxinos and Watson.[21] Data were analyzed only from animals in which proper probe placement was verified.

Statistical Analysis

The data are reported as mean $\pm$ SD. Within-group comparisons to baseline and between-group (CS *vs.* CD) comparisons were performed by means of an unpaired *t* test with the Welch correction applied as indicated. Comparisons among all three groups (CD,CS, and DACD) were performed using one-way analysis of variance followed by a Bonferroni multiple comparisons *post hoc* test as indicated. InStat® statistical analysis software (GraphPad Software, Inc., San Diego, CA) was used to perform all statistical analyses. A value of $P < 0.05$ was deemed statistically significant.

Results

Baseline mean arterial pressure and heart rate during the sampling intervals were similar in CS and CD: 102 $\pm$ 8 mmHg and 404 $\pm$ 56 beats/min in CS and 101 $\pm$ 10 mmHg and 393 $\pm$ 44 beats/min in CD. Compared to baseline, there was a trend toward an increase in mean arterial pressure and a decrease in heart rate during the study; however, these changes were mainly statistically significant in CD (fig. 2). In CD, the maximum mean arterial pressure, 135 $\pm$ 15 mmHg, occurred 15 min into the cocaine infusion, and the maximum decrease in heart rate occurred 45 min into the cocaine infusion, 298 $\pm$ 29 beast/min (fig. 2). Of note, there was no significant difference in mean arterial pressure and heart rate between CD and CS throughout the study.

Figure 1 shows representative electroencephalograms in the rats at various, randomly chosen times during the

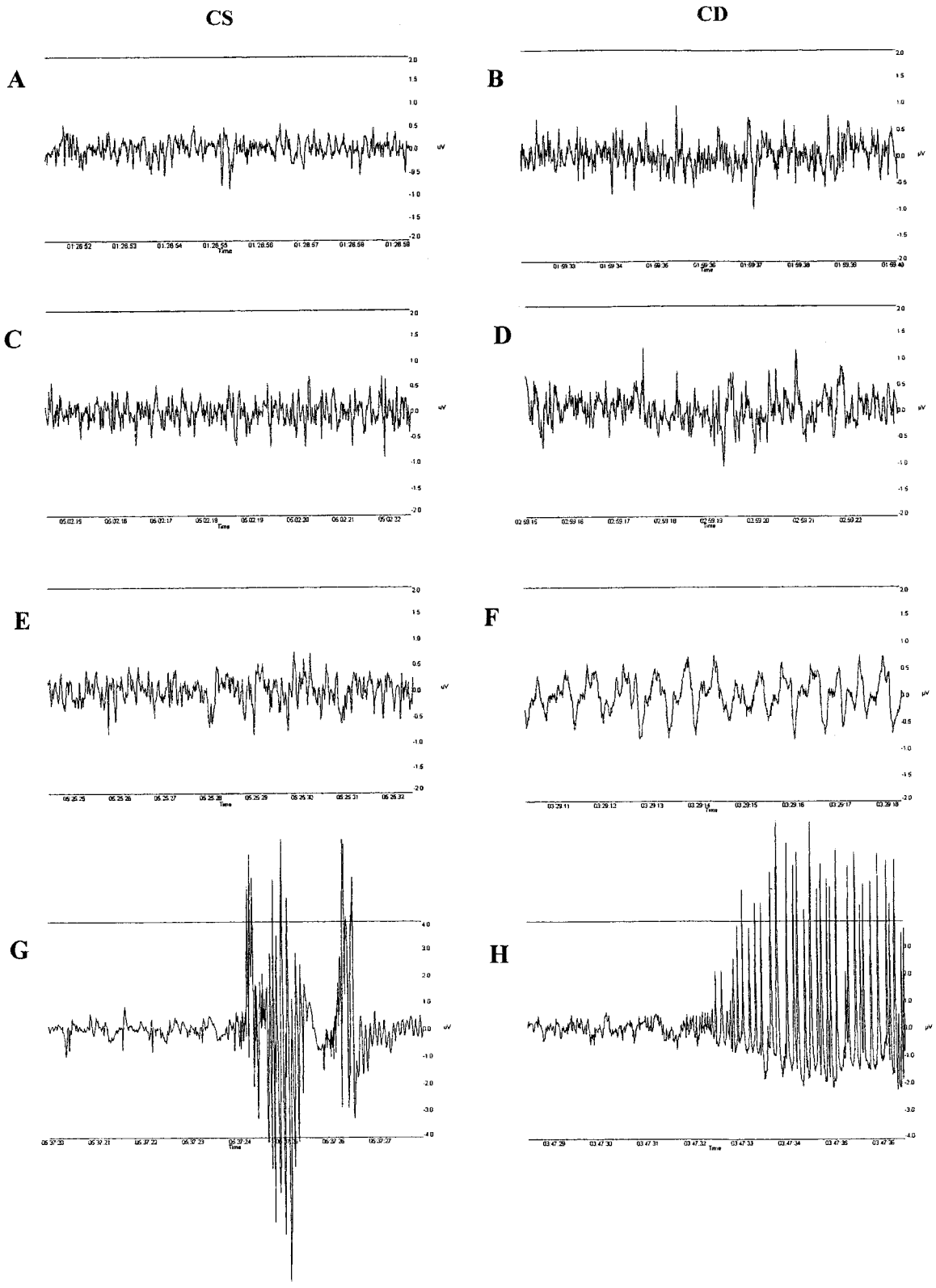

Fig. 1. Representative electroencephalogram recordings for CS (*A*, *C*, *E*, *G*) and CD (*B*, *D*, *F*, *H*) at baseline (*A*, *B*) as well as at various, comparable time points: within 15 min of the start of cocaine (*C*, *D*), within 15 min of the start of saline (*E*) or dexmedetomidine (*F*), and at the onset of generalized seizure activity (*G*, *H*). Each electroencephalogram tracing is from a rat that received the infusion of cocaine (1.25 mg · kg^{-1} · min^{-1}) followed 15 min later by the coinfusion of either dexmedetomidine (CD, n = 8) or saline (CS, n = 8). The infusion of dexmedetomidine produced significant electroencephalogram slowing in the presence of cocaine (*F*). Cocaine typically produced burst epileptiform activity that corresponded to generalized seizure activity in the rats (*G*, *H*).

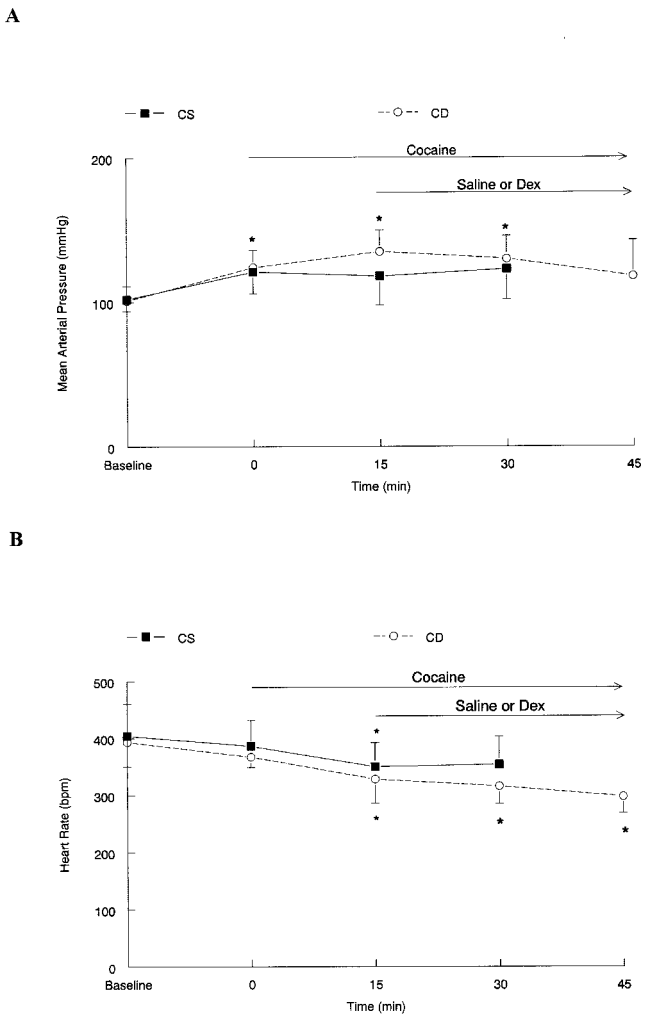

Fig. 2. Mean arterial pressure (*A*) and heart rate (*B*) of rats at baseline and during the intravenous infusion of cocaine (1.25 mg · kg^{-1} · min^{-1}) followed 15 min later by the coinfusion of either dexmedetomidine (20-μg/kg intravenous bolus over 2 min followed by a continuous infusion of dexmedetomidine at a rate of 1 μg · kg^{-1} · min^{-1}, CD, n = 8) or an equal volume of saline (CS, n = 8). The cocaine infusion was started at time = 0 min and continued until the end of the study. Dexmedetomidine and saline infusions were started at time = 15 min and continued until the end of the study. Data are expressed as mean ± SD. *P < 0.05 compared to each group's respective baseline value. Each point on the abscissa represents the start time of a sampling interval (0 = 0–15 min interval), and each point on the ordinate represents the average value during a 15-min sampling interval.

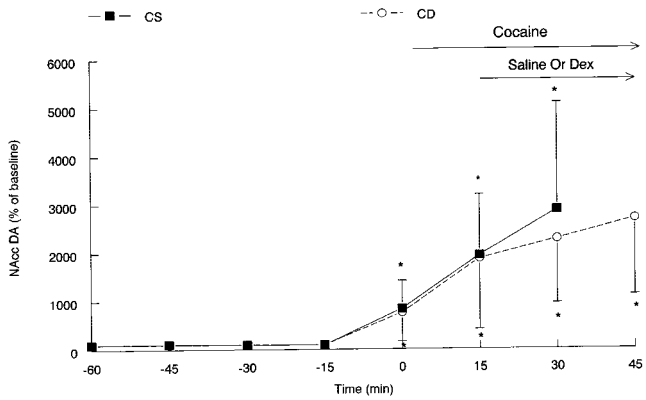

Fig. 3. Extracellular dopamine (DA) concentrations (expressed as a percentage of the baseline concentration) in the nucleus accumbens (NAcc) in rats measured at baseline (−60 to −15 min) and during the intravenous infusion of cocaine (1.25 mg · kg^{-1} · min^{-1}) starting at time = 0 min followed 15 min later by the coinfusion of either dexmedetomidine (CD, n = 8) or an equal volume of saline (CS, n = 8). Data are expressed as mean ± SD. Each point on the abscissa represents the start time of a sampling interval (0 = 0–15 min interval). *P < 0.05 in both CS and CS when compared to their respective baseline extracellular dopamine concentrations.

study intervals, including the following: baseline, 15 min from the start of the cocaine infusion, during the infusion of dexmedetomidine or saline, and during the onset of generalized electroencephalographic seizure activity. Following the administration of cocaine, dexmedetomidine typically produced electroencephalogram slowing (fig. 1F). Seizure activity occurred significantly later in the CD group, 49.3 ± 14.8 min *versus* 25.0 ± 7.7 min in CS ($P < 0.001$). Furthermore, dexmedetomidine significantly increased the cumulative dose of cocaine necessary to induce seizure activity, 61.7 ± 18.6 mg/kg in CD *versus* 31.2 ± 9.6 mg/kg in CS ($P < 0.001$).

The average extracellular dopamine concentrations in the NAcc at baseline were similar in CS and CD: 8.9 ± 1.9 nM and 10.0 ± 1.3 nM, respectively. As expected, the administration of cocaine, a dopaminergic reuptake blocker, produced a progressive increase in extracellular dopamine in CS and CD (fig. 3). At the onset of seizures, extracellular dopamine concentrations in the NAcc, expressed as a percentage of the baseline value (% of baseline), were similar in CS and CD: 2,508 ± 1,911 and 2,431 ± 1,404% of baseline, respectively. However, when these percent increases at the onset of seizure activity were normalized for the corresponding cumulative cocaine dose, the ratio of the extracellular dopamine increase to the cocaine dose was significantly lower in CD (fig. 4A), 39.9 ± 16.5, compared to CS, 82.2 ± 46.5 ($P = 0.04$). The plasma cocaine concentration at the onset of seizures was significantly higher in CD, 16.7 ± 9.3, *versus* 7.20 ± 2.2 mg/ml in CS ($P = 0.03$), consistent with the observation that the animals in CD convulsed later and thus received a larger cocaine dose. Consequently, when the percent increase in extracellular dopamine was normalized for the plasma cocaine concentration at the onset of seizure activity, the ratio was significantly lower in CD, 163.2 ± 83.6 compared to 345.2 ± 176.7 in CS ($P = 0.03$; fig. 4B). Thus, although the rats in CD received a larger dose of cocaine and had a higher plasma cocaine concentration at the onset of seizure activity, the normalized increases in extracellular dopamine were significantly lower in CD.

The baseline extracellular dopamine concentration in DACD was 13.9 ± 4.2 nM, and this concentration was not significantly different from the baseline values for

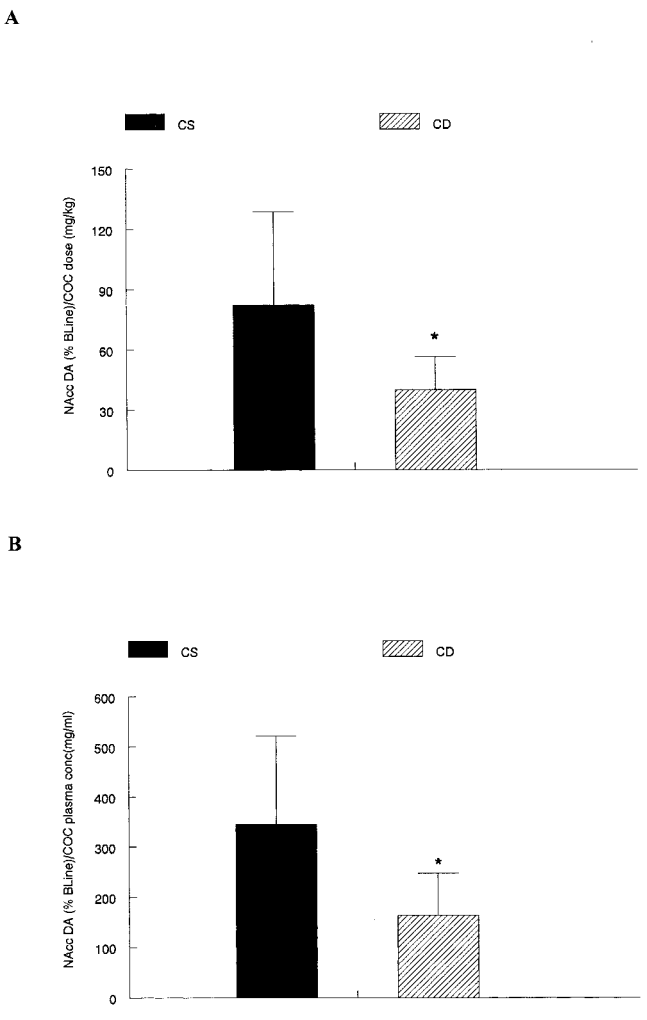

Fig. 4. Extracellular dopamine (DA) concentrations in the nucleus accumbens (NAcc) at the onset of seizure activity, expressed as a percentage of the baseline DA concentration (% BLine) and normalized for the total cocaine (COC) dose in mg/kg (*A*) as well as for the plasma cocaine (COC) concentration in mg/ml (*B*) in rats receiving an infusion of cocaine (1.25 mg · kg^{-1} · min^{-1}) followed by a dexmedetomidine infusion (CD) or saline infusion (CS). Data are expressed as mean ± SD. *$P < 0.05$ compared to the CS group.

dopamine in CD and CS. The delivery of dopamine directly into the NAcc prevented the dexmedetomidine-induced increase in the cocaine seizure threshold observed in CD. Specifically, seizure activity occurred significantly sooner in DACD, 28.2 ± 5.5 min, *versus* 49.3 ± 14.8 min in CD ($P < 0.01$), and at a lower dose in DACD, 35.2 ± 6.9 mg/kg, compared to 61.7 ± 8.6 mg/kg in CD ($P < 0.01$). There was no statistically significant difference between DACD and CS in terms of the onset of and the cocaine dose required to produce seizure activity.

Discussion

The effects of intravenous dexmedetomidine administration on the cocaine seizure threshold were examined in awake rats. In contrast to other studies, the current study not only evaluated the anticonvulsant properties of a highly specific α_2-AR agonist but also examined the modulation of central dopamine concentrations by dexmedetomidine during the development of cocaine-induced seizures. The data demonstrate that systemic dexmedetomidine administration during a proconvulsant infusion of cocaine significantly delays the onset of cocaine-induced seizure activity and consequently increases the cumulative dose of cocaine required to produce this activity. In addition, this increase in the cocaine seizure threshold was closely associated with a significant attenuation in the extracellular dopaminergic response to cocaine in the NAcc. Moreover, the observation that the anticonvulsant effects of dexmedetomidine were prevented by the direct administration of dopamine into the NAcc supports the notion that mesolimbic dopamine may play a role in mediating cocaine-induced seizure activity.

In addition to its local anesthetic effects, cocaine has the unique ability to block the central reuptake of various monoaminergic neurotransmitters, particularly dopamine. The increases in extracellular dopamine are primarily due to cocaine's ability to inhibit the plasmalemmal dopamine transporter, and these changes in extracellular dopamine have been specifically linked to several of the drug's psychomotor effects.[7,8] Furthermore, it has been previously suggested that dopamine may play a significant role in mediating the toxicity of cocaine. Several authors have already evaluated the effect of dopamine receptor agonists and antagonists on cocaine-mediated seizures and lethality.[9,25,26] Witkin *et al.*[26] previously established that the administration of dopamine antagonists may significantly decrease the lethality of cocaine, a protective effect specifically linked to the dopamine-1 receptor subtype. Moreover, Ushijima *et al.*[9] recently demonstrated that dopamine-1 agonists enhance cocaine-induced convulsions, and they proposed that dopamine may be a specific mediator of cocaine-induced seizure activity. These authors demonstrated that dopamine appears to play an integral role in mediating the activation of an *N*-methyl-D-aspartate–Ca ionophore complex system, an ion complex whose activation appears to play a vital role in the propagation of cocaine-induced seizure activity, particularly in mesolimbic regions of the central nervous system.

The finding that dexmedetomidine significantly increased the cumulative dose of cocaine required to produce generalized seizure activity is consistent with the findings of others who have demonstrated that drugs with a high affinity for the α_2-AR indeed possess anticonvulsant properties in models of drug-induced epilepsy.[10] Papanicolaou *et al.*,[10] using an α_2-AR agonist of modest selectivity, clonidine, observed that the anticonvulsant effects of α_2-AR agonists appear to be related to the selectivity of the agonist for the α_2-AR. Dexmedetomi-

dine is a α_2-AR that is approximately 7 times more selective for α_2 adrenoceptors than clonidine,[14] and the observed anticonvulsant effect is consistent with the observation that the anticonvulsant effects of these compounds are possibly specifically mediated by the α_2-AR. Similarly, in another model of drug-induced epilepsy, Halonen *et al.*[27] demonstrated that dexmedetomidine suppressed the development of kainic acid–induced convulsions and minimized neuronal damage in the hippocampus. We do acknowledge that there exists the possibility that dexmedetomidine may be producing its anticonvulsant effects *via* imidazoline receptors as, indeed, α_2-AR agonists have been shown to have functional effects at imidazoline receptor sites.[28] Moreover, ligands at the imidazoline receptor have been recently shown to modulate dopamine concentrations in the NAcc of rats.[29]

We also acknowledge the fact that other investigators have previously found dexmedetomidine to be proconvulsant. Mirski *et al.*,[30] in a pentylenetetrazol rat model of generalized epilepsy, observed that an infusion of dexmedetomidine at 100 and 500 μg/kg significantly reduced the pentylenetetrazol electroencephalographic seizure threshold. Similarly, Miyazaki *et al.*,[31] in a cat model, found that a high dose of dexmedetomidine decreased the seizure threshold during enflurane anesthesia. Although the reason for this dissimilarity in the observed effects of dexmedetomidine on seizure activity is unclear, we speculate that the differences may indeed be related to the fact that not all models of generalized epilepsy are equivalent. The particular drug or stimulus inducing the seizure may involve very different neurotransmitter pathways. Furthermore, both Mirski and Miyazaki used relatively high doses of dexmedetomidine in their studies. Although dexmedetomidine is a highly selective α_2-AR agonist, it is quite feasible that at high concentrations the drug may lose some of its selectivity for the α_2-AR, and thus, α_1-AR activation may occur. Indeed, agonist activity at the α_1-AR seems to impart a reversal of the anticonvulsant effects of these α_2-AR agonist compounds.[10,11] Moreover, others have suggested that the effect on the seizure threshold may possibly be receptor subtype specific, and again, it is feasible that this specificity may be lost with higher doses of dexmedetomidine.[31]

The dexmedetomidine-induced attenuation in NAcc dopamine observed in this study is consistent with our recently published observation that the lone administration of dexmedetomidine significantly decreases extracellular dopamine concentrations in the NAcc, a reversible effect that appears to be primarily mediated *via* the α_2-AR.[20] Moreover, the attenuation in accumbal dopamine in this study is consistent with the hypothesis that extracellular reductions in mesolimbic dopamine convey a neuroprotective effect in terms of the excitotoxicity of cocaine. Thus, we speculate that dexmedetomidine may be potentially beneficial in controlling cocaine-induced central nervous system excitotoxicity.

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