Early Afterdepolarizations and Triggered Activity Induced by Cocaine
A Possible Mechanism of Cocaine Arrhythmogenesis

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Background. Cocaine may produce life-threatening cardiac arrhythmias, but it is not clear whether this is an indirect effect of coronary vasoconstriction and ischemia or a direct myocardial effect of the substance. Except for its effects on the Na⁺ current as a local anesthetic, little is known about the direct electrophysiological actions on cardiac cells. Therefore, we studied the effects of cocaine on action potentials and membrane currents in isolated feline ventricular myocytes to test the hypothesis that cocaine-induced arrhythmogenesis may be based on cellular and ionic mechanisms.

Methods and Results. Action potentials and membrane currents were recorded using the patch clamp technique. Single cells were isolated from feline left ventricles by enzymatic digestion. Exposure to cocaine (10 or 50 μM) depressed the plateau phase of the action potential and prolonged action potential duration. Action potential duration measured at 90% repolarization (APD₉₀) was increased from 280±12 msec to 325±17 msec (p<0.01) by 5-minute exposure to 10 μmol cocaine, when the cells were stimulated at 1 Hz. During exposure to 50 μmol cocaine, APD₉₀ was markedly increased from 298±13 msec to 437±35 msec (p<0.01) in seven of 16 cells, and early afterdepolarizations (EADs) developed in these cells. The take-off potential and the amplitude of EADs were −28.3±2.3 mV and 16.8±1.2 mV, respectively. Triggered activity arising from EADs was induced in four of the seven cells. Addition of 1 nmol isoproterenol augmented EADs and induced sustained triggered activity, whereas they were suppressed by exposure to 2 μM verapamil. Whole-cell voltage clamp experiments revealed that cocaine (50 μM) reduced the peak L-type Ca²⁺ current from 1.03±0.13 nA to 0.79±0.11 nA (23% reduction, p<0.05). Cocaine also reduced the peak delayed rectifier K⁺ current from 362±51 pA to 113±32 pA (69% reduction, p<0.01). However, cocaine did not affect activation and inactivation kinetics of these channels. Cocaine had no effect on the inward rectifier K⁺ current.

Conclusions. We conclude that cocaine can prolong action potential duration and induce EADs and triggered activity by blocking the delayed rectifier K⁺ current, and that cocaine-induced abnormalities of repolarization, modulated by its inhibitory effects on catecholamine reuptake, may play a role in the potential of cocaine for induction of acute fatal arrhythmias. (Circulation 1992;85:2227–2235)

Key Words • patch clamp • cell, single ventricular • action potential • delayed rectifier K⁺ current • Ca²⁺ current

Sudden death may result from the use of cocaine.¹⁻³ Although cocaine use may lead to the generation of cardiac arrhythmias,⁴⁻⁶ the underlying mechanisms of cocaine-related sudden death remain poorly defined. Cocaine inhibits the reuptake of norepinephrine by the sympathetic nerve terminals.⁷⁻¹⁰ This effect, combined with central stimulation of sympathetic outflow, elicits intense vasoconstriction in most vascular beds, an increase in heart rate, and increased myocardial contractility. These effects may lead to myocardial ischemia and infarction and indirectly induce contractile dysfunction and cardiac arrhythmias. However, it has also been proposed that cocaine-related deaths of cardiac origin may occur in the absence of myocardial infarction, presumably because of direct adverse effects on cardiac electrophysiology.¹¹⁻¹⁵

Cocaine is a local anesthetic, and its blockade of Na⁺ channels¹⁶,¹⁷ may produce conduction disturbances in the heart. Such conduction disturbances could contribute to the generation of reentrant arrhythmias, and previous investigators have emphasized this concept of cocaine arrhythmogenesis¹¹⁻¹⁵; however, it has also been shown that cocaine prolongs repolarization.¹⁵ In this respect, the effects of cocaine are similar to those of class IA antiarrhythmic drugs, that is, Na⁺ channel block and prolongation of repolarization. Class IA antiarrhythmic drugs, especially quinidine, have been shown to induce triggered activity arising from early afterdepolarizations (EADs),¹₈,¹⁹ which have been proposed as a potential mechanism of arrhythmias in patients with acquired long QT syndrome.²₀⁻²₆ Therefore, we hypothesized that cocaine...
could induce EADs and triggered activity by affecting the ventricular repolarization process. To test this hypothesis, we studied the effects of cocaine on repolarization and the induction of EADs and their effects on transmembrane ionic properties in isolated feline single ventricular myocytes. The data demonstrate that EADs and triggered activity, similar to those generated by class IA antiarrhythmic drugs, is a possible mechanism of cocaine arrhythmogenesis.

**Methods**

**Cell Isolation**

Domestic cats of either sex weighing 2.5-4.0 kg were anesthetized with sodium pentobarbital (30 mg/kg i.p.), and heparin sodium (400 IU/kg) was injected intravenously. The heart was excised and mounted on a Langendorff apparatus and perfused via the aorta with a modified Tyrode’s solution (37°C) containing (in millimoles) NaCl 143, KCl 4, CaCl₂ 1.8, MgCl₂ 0.5, NaHPO₄ 0.33, glucose 5.5, and HEPES 5.5 (pH 7.4 with NaOH) and gassed with 100% O₂. After a 5-minute equilibration period, the preparation was perfused with Ca²⁺-free Tyrode’s solution (otherwise identical to above) for 5 minutes followed by perfusion with 2 mg/ml (300 units/ml) collagenase (type II, Worthington Biochemical Co., Freehold, N.J.) and 0.3 mg/ml protease (type XIV, Sigma Chemical, St. Louis, Mo.) dissolved in Tyrode’s solution with 50 μM Ca²⁺. Exposure to the enzyme was continued until the solution flowed freely (12-14 minutes), after which the collagenase was washed out with a solution containing (in millimoles) KOH 70, KCl 40, glutamic acid 50, taurine 20, KH₂PO₄ 10, MgCl₂ 0.5, glucose 11, EGTA 0.5, and HEPES 10 (pH 7.4 with KOH). Small pieces of left ventricular tissue were dissected from the endocardial layer with fine scissors. After the tissues had been minced, single cells were separated from tissue pieces by passing them through nylon mesh (150 μm). We used ventricular myocytes only. Purkinje cells were differentiated by their unique action potential configuration and were excluded from the present study.

**Electrical Stimulation and Recording**

Isolated cells were introduced into a superfusion chamber (1-ml volume) on the stage of an inverted microscope and superfused with Tyrode’s solution (37°C) at a rate of 3 ml/min. Voltage and current clamp studies were performed using low-resistance (2-4 MΩ) suction pipettes in the whole-cell recording mode. The pipettes were forged by a micropipette puller (model P-87, The Sutter Instrument Co., Novato, Calif.) and heat-polished before use. The electrode potential was adjusted to give zero current between the pipette solution and bath solution immediately before each cell was attached. After a gigaseal (>5 GΩ) was formed by gentle suction, the cell membrane under the electrode tip was broken by further application of negative pressure.

Action potentials were recorded in the current clamp mode. The pipette solution contained 140 mM KCl, 4 mM MgCl₂, 4 mM K₂ATP, and 10 mM HEPES (pH 7.2 with KOH). The cells were stimulated by passing depolarizing currents (1-msec pulse width, twice diastolic threshold) through the pipette at a rate of 1 Hz. After a 10-minute equilibration period, cells were superfused with Tyrode’s solution containing 10 or 50 μM cocaine hydrochloride (Sigma Chemical Co.) for 15 minutes.

Membrane currents were recorded in the whole-cell voltage clamp mode. For measurement of the slow inward Ca²⁺ current (I_{Ca}), the pipette solution contained 120 mM CsCl, 4 mM ATP, 4 mM MgCl₂, 2 mM EGTA, and 5 mM HEPES (pH 7.2 with CsOH). The sodium current was inactivated by holding the membrane at −40 mV. Potassium currents were minimized by substitution of 120 mM CsCl for KCl in the pipette solution and by addition of 2 mM aminopyridine to the external Tyrode’s solution. The Ca²⁺ current was activated by clamping the membrane voltage for 500 msec to test voltages ranging from −30 mV to 40 mV from a holding potential of −40 mV; the clamp step was induced every 2 seconds. The amplitude of I_{Ca} was measured as the difference between the peak of the inward current and the holding current level. Because I_{Ca} runs down over time, we examined the change in I_{Ca} during superfusion with Tyrode’s solution containing no cocaine as a control.

For measuring the delayed rectifier K⁺ (I_K) current, the pipette solution contained 140 mM KCl, 5 mM MgCl₂, 5 mM K₂ATP, 5 mM EGTA, and 5 mM HEPES (pH 7.2 with KOH). The sodium current was inactivated by holding the membrane potential at −40 mV. The Ca²⁺ current was blocked by addition of 2 mM CaCl₂ to the Tyrode’s solution. EGTA was included in the pipette solution to buffer the intracellular Ca²⁺ transient and thus minimize the influence of intracellular Ca²⁺ concentration on the magnitude of I_{K}. The contribution of Na⁺–Ca²⁺ exchange. I_K was activated by 5-second depolarizing pulses ranging from −20 mV to 50 mV from a holding potential of −40 mV at 0.2 Hz. I_K activated slowly and did not reach a steady-state level even at the end of a 5-second depolarizing pulse. However, we used depolarizing pulses of 5 seconds because long depolarizing pulses are harmful to single cells, often breaking the tight seal between the membrane and the pipette. The current amplitude of I_K and I_{K1} tail (the current elicited upon repolarization from test potentials to the holding potential) was measured from the baseline current level.

For measurement of the background inward rectifier K⁺ (I_{K1}) current, the bath and pipette solutions were the same as those used for the measurement of I_{K}. I_{K1} was studied with 5-second hyperpolarizing and depolarizing voltage steps (ranging from −100 to −20 mV) from a holding potential of −80 mV at 0.2 Hz. Voltage steps positive to −20 mV were not used because such steps activate current flow through both I_K and I_{K1} channels.

**Data Acquisition and Analysis**

The whole-cell membrane currents and potentials were measured by an Axopatch-1D patch clamp system (Axon Instruments, Inc., Burlingame, Calif.) or a Dagan 8900 patch clamp amplifier (Dagan Co., Minneapolis, Minn.). The pipette capacitance and series resistance were compensated. Voltage and current data were displayed on an oscilloscope (Tektronix, Beaverton, Ore.). Analog waveforms for voltage clamp command pulses and data acquisition and analysis were obtained with a software program (PCLAMP, Axon Instruments) using a 12-bit resolution Labmaster A-D converter (Tecmar Inc., Cleveland, Ohio) and an IBM-AT com-
computer. Current traces elicited by voltage steps were filtered at 10 kHz and stored on a hard disk for later analysis.

Data are presented as mean±SEM. Statistical significance was evaluated by ANOVA with repeated measurements or Student’s paired and unpaired t test where appropriate. Differences with a value of p<0.05 were considered significant.

Results
Effect of Cocaine on Action Potentials in Ventricular Myocytes

Action potential parameters were stable for at least up to 30 minutes, when the cells were superfused with drug-free Tyrode’s solution. Action potentials recorded before and 5 minutes after exposure to 10 and 50 μM cocaine are superimposed in Figure 1. The cells were stimulated at a frequency of 1 Hz. The onset of effect was very rapid, with action potential duration (APD) measured at 90% repolarization (APD90) beginning to prolong 1 minute after exposure to cocaine. At the same time, the plateau phase of the action potential was depressed. During superfusion with 10 μM cocaine, the magnitude of APD prolongation was relatively uniform among the cells studied. Exposure to 50 μM cocaine, however, produced a bimodal response pattern. In nine of 16 cells, the magnitude of APD prolongation was similar to that observed during superfusion with 10 μmol cocaine (Figure 1, B1). These cells did not develop EADs. In the other seven cells, marked APD prolongation occurred (Figure 1, B2), and EADs were induced. The effects of 5-minute superfusion with cocaine on action potential characteristics are summarized in Table 1; the response to 50 μM cocaine is provided separately for the cells with and without EADs. Prolongation of APD90 reached a maximum at 5 minutes, and thereafter APD90 remained stable or began to shorten, with further depression of the plateau phase. Resting membrane potential and action potential amplitude were little affected by cocaine at concentrations of 10 or 50 μM.

Induction of EADs by Cocaine

During 20-minute superfusion with Tyrode’s solution containing 10 μM cocaine, EADs were not induced in any of eight cells studied. However, as noted above, during exposure to 50 μM cocaine, EADs were induced in the seven cells in which APD90 was markedly prolonged.

Figure 2 shows a representative experiment demonstrating the generation of EADs in association with marked prolongation of APD as early as 5 minutes after exposure to 50 μmol cocaine. Subsequently, triggered activity was generated from EADs (Figure 2, 6 minutes). The take-off potential of the EAD (the most negative voltage reached before the depolarization of the EAD) was -28±2.3 mV (mean±SEM, n=7, range, -23 to -38 mV). The mean amplitude of the EADs was 17.8±2.2 mV (range, 14–30 mV). EADs were induced within 5 minutes after starting superfusion with cocaine in five of the seven cells and at approximately 15 minutes in the other two cells. Triggered activity arising from EADs developed spontaneously (without any further intervention) in four of the seven cells.

Effect of Isoproterenol and Verapamil on Cocaine-Induced EADs

The effect of the β-adrenergic agonist isoproterenol and the Ca2+ channel blocker verapamil on cocaine-induced EADs is shown in Figure 3. In three cells in which EADs developed during superfusion with 50 μM
cocaine but no spontaneous triggered activity occurred, the addition of 1 nM isoproterenol to the superfusate immediately induced sustained triggered activity (Figure 3A). Figure 3B shows another experiment demonstrating that verapamil (2 μM) suppressed cocaine-induced EADs. Similar effects were observed in three cells tested with verapamil.

**Effect of Cocaine on Ca\(^{2+}\) Current**

To explore the ionic mechanisms by which cocaine prolongs APD, we examined its effects on membrane currents. First, we studied the effects of cocaine on the L-type Ca\(^{2+}\) current (I\(_{\text{Ca}}\)), because I\(_{\text{Ca}}\) plays an important role in the maintenance of APD at the plateau level.

Figure 4A shows a representative experiment demonstrating the effect of 5-minute exposure to 50 μM cocaine on peak I\(_{\text{Ca}}\) elicited by 500-msec depolarizing pulses from a holding potential of −40 mV to a test potential of 0 mV. Figure 4B shows the averaged current–voltage relation of I\(_{\text{Ca}}\) before and after exposure to cocaine (n=8). At a concentration of 50 μmol, cocaine reduced the peak I\(_{\text{Ca}}\) at test potentials of −10 to +10 mV without affecting the current–voltage relation. At a test potential of 0 mV, the peak I\(_{\text{Ca}}\) was reduced from 1.03±0.13 nA to 0.79±0.11 nA (−23% reduction, p<0.01). Because I\(_{\text{Ca}}\) runs down over time, we examined the change in I\(_{\text{Ca}}\) during superfusion with Tyrode’s solution containing no cocaine as a control. There was a significant difference between the extent of reduction of I\(_{\text{Ca}}\) induced by cocaine and cocaine-free solution (−16.4±4.1% versus −4.2±2.9% at 5 minutes after exposure to cocaine, n=6, p<0.05).

Although cocaine reduced peak I\(_{\text{Ca}}\), it did not change the time course of inactivation of I\(_{\text{Ca}}\) (Figure 4A). The time course of inactivation of I\(_{\text{Ca}}\) elicited by 500-msec depolarizing pulses from −40 mV to 0 mV was fitted to a two-exponential function. The time constants of the fast and slow components were 9.5±2.4 msec and 56.4±4.7 msec in controls and 10.5±2.1 msec and 59.2±5.2 msec after 5-minute exposure to 50 μM cocaine.

**Effect of Cocaine on Delayed Rectifier K\(^{+}\) Current**

The results in the previous section indicate that the depression of the plateau phase of the action potential by cocaine is partly due to a reduction in I\(_{\text{Ca}}\). However, exposure to cocaine did not change the time course of inactivation of I\(_{\text{Ca}}\); this indicates that other currents are involved in the prolongation of APD. Because the delayed rectifier K\(^{+}\) current (I\(_{\text{K}}\)) activates slowly and may play a major role in the late phase of the cardiac action potential,29 we tested the hypothesis that cocaine reduces I\(_{\text{K}}\) resulting in prolongation of APD\(_{50}\).

Figure 5A shows a representative experiment demonstrating the effect of 50 μM cocaine on I\(_{\text{K}}\) elicited by 5-second depolarizing pulses from a holding potential of −40 mV to a test potential of +50 mV. Both the activating current and tail current of I\(_{\text{K}}\) were markedly
decreased by 5-minute exposure to 50 µmol cocaine. Because I_K developed slowly and did not reach a steady-state level even after 5-second depolarizing pulses, the tail current was measured. Figure 5B shows the current–voltage relation of the I_K tail current elicited by repolarization from test potentials ranging from −20 to 50 mV to the holding potential of −40 mV (n=8). At a test potential of 50 mV, the I_K tail current was reduced from 362±51 pA to 113±32 pA (69% reduction, p<0.01) by exposure to 50 µmol cocaine.

To further investigate the mechanisms of action of cocaine on I_K, we determined the effect of cocaine on the voltage dependency of I_K. Figure 6 shows activation curves of I_K, which were constructed from the amplitude of the tail current in the absence and presence of 50 µmol cocaine. The relative activation values at various membrane potentials were obtained by normalizing the amplitude of the I_K tail by the value at 60 mV. The data points (means of eight experiments) were fitted to a Boltzmann distribution equation

\[ \text{Relative activation value} = \frac{1}{1 + \exp[(V_h - V_m) / K]} \]

where \(V_h\) is the half-activation potential and \(K\) is the slope factor. The activation curve was not changed by cocaine; \(V_h\) and \(K\) were −2 mV and 10 mV in the absence of cocaine and −1.5 mV and 11 mV in the presence of cocaine.

We also examined the effect of cocaine on the kinetics of I_K. Figure 7 shows the time course of activation of I_K before (panel A) and after (panel B)
exposure to 50 \( \mu \)M cocaine. Because \( I_K \) developed slowly, the current level at the end of a 5-second depolarizing pulse was taken as a steady-state level. The activation time course of \( I_K \) was fitted to a two-exponential function. Neither the fast nor the slow component was changed by cocaine. The time constants of the fast component were 223 msec and 214 msec, and the time constants of the slow component were 1,520 msec and 1,593 msec before and after exposure to cocaine, respectively. Similarly, the time course of deactivation of \( I_K \) was fitted to a two-exponential function, and neither the fast nor the slow time constant was changed by cocaine (data not shown).

**Effect of Cocaine on Inward Rectifier \( K^+ \) Current**

Because the inward rectifier current (\( I_{K1} \)) may also contribute to the repolarization phase of the action potential, we studied the effect of 50 \( \mu \)mol cocaine on \( I_K \). Figure 8A shows current tracings of \( I_{K1} \) elicited by 5-second hyperpolarizing (−90 mV) and depolarizing (−60 mV) pulses from a holding potential of −80 mV before and after exposure to cocaine. The current—voltage relation of \( I_{K1} \) obtained from six cells is shown in Figure 8B. There was inward rectification with a negative slope region from −60 to −30 mV. \( I_{K1} \) was little affected by 5-minute exposure to 50 \( \mu \)mol cocaine.

**Discussion**

The major findings of the present study are 1) cocaine depresses the plateau phase and prolongs the late repolarization phase of the action potential recorded from isolated feline ventricular myocytes; 2) EADs and triggered activity are induced in association with lengthening of APD, an effect enhanced by isoproterenol and suppressed by verapamil; 3) cocaine reduces the \( L \)-type \( Ca^{2+} \) current and the delayed rectifier \( K^+ \) current without affecting their kinetic properties; and 4) it does not affect the inward rectifier \( K^+ \) current.

Previous investigators also have shown that cocaine prolongs the APD and the refractory period in rabbit atrial and right ventricular papillary tissues. However, they found neither marked action potential prolongation nor EADs. A possible explanation for this discrepancy is that single cells is entirely surrounded by bathing solution containing cocaine, whereas the surface membrane of the cells is exposed to the drug in multicellular preparations, resulting in the differential degree of response to the drug; for example, more drastic and rapid effects are seen in single cells exposed to autonomic agonists (Kimura et al, unpublished observations).
It has been long recognized that cocaine has local anesthetic properties. In the heart, it depresses the upstroke of action potentials recorded from the atrial, ventricular, and Purkinje fibers.15,16 Recently, Crumb and Clarkson,17 using the patch clamp technique, have directly demonstrated that cocaine (10–50 μmol) reduces the Na+ current in isolated guinea pig ventricular myocytes. The present study demonstrates that in addition to these classical local anesthetic effects on the fast Na+ current, cocaine has direct actions on other membrane currents. Reduction of L-type Ca2+ current and delayed rectifier K+ current by cocaine can explain the action potential changes described in the present report. The inactivation process of ICa was not affected by cocaine; therefore, the depression of the plateau of the action potential is probably due, at least in part, to a reduction in peak ICa, although blockade of the Na+ window current may also be involved.30 The marked suppression of IK probably contributes to the action potential prolongation; IK is a major outward current in cardiac cells that plays an important role in the late phase of repolarization.29 We cannot rule out a possible effect of cocaine on transient outward current, which may also control the APD, although we found little effect of the drug on phase 1 repolarization (data not shown).

The mechanism by which cocaine reduces IK is not certain. The magnitude of IK is sensitive to intracellular Ca2+, and a decrease in intracellular Ca2+ reduces IK in guinea pig ventricular cells.28 In the present study, cocaine reduced ICa, and thereby it is conceivable that the reduced IK is an indirect effect of the change in intracellular Ca2+ concentration. However, we included EGTA (5 mM) in the pipette solution to minimize the influence of changes in intracellular Ca2+ concentration on the measurement of IK, supporting a direct action on IK, although this conclusion cannot be certain in the absence of measurement of intracellular Ca2+ concentration. Cocaine did not affect the time constants of any components of activation and deactivation of IK at the potential examined. The absence of changes in kinetics or voltage dependency suggest that cocaine may reduce the number and/or the open probability of functional IK channels. Studies at the single-channel level are required to test this possibility.

The importance of cardiac effects of cocaine in mortality and morbidity has become increasingly evident.1–6 Cocaine may induce acute myocardial ischemia in subjects with or without preexisting coronary artery disease.3,31–33 Cocaine inhibits the reuptake of norepinephrine by the sympathetic nerve terminals,3,10 which, combined with central stimulation of sympathetic outflow, would be expected to elicit intense vasoconstriction in most vascular beds (reduced coronary blood supply), an increase in heart rate, and increased myocardial contractility (increased O2 demand). Eventually, these effects may lead to myocardial ischemia and indirectly induce contractile dysfunction and cardiac arrhythmias. However, it has also been proposed that cocaine-related deaths of cardiac origin may occur in the absence of myocardial ischemia or infarction, presumably because of direct cardiac electrophysiological changes leading to the generation of lethal arrhythmias.11–15

As described above, cocaine blocks the Na+ current in cardiac cells.16 These effects would be expected to result in slowing of cardiac impulse conduction. Indeed, cocaine infusion increases the QRS interval and the HV interval in experimental animals.13–14 Such conduction disturbances could result in the generation of reentrant arrhythmias12–15 in diseased hearts with nonuniform conduction but is less likely to do so with uniform global reduction in coronary flow caused by generalized vasoconstriction.

The present study introduces another mechanism of cocaine arrhythmogenesis. Our data show that cocaine, at a concentration of 50 μM, lengthens APD and induces EADs and triggered activity, properties that appear similar to those that may be responsible for classic proarrrhythmia caused by local anesthetics used as antiarrhythmia drugs, e.g., quinidine. Quinidine is well known to induce polymorphic ventricular tachycardias preceded by long QT intervals (torsade de pointes), which may result from triggered activity induced by
EADs. A similar phenomenon may occur in the presence of cocaine and cocaine-related cardiac arrest. Furthermore, addition of isoproterenol, which may be analogous to cocaine’s inhibitory effects on reuptake of catecholamine in vivo, enhanced and sustained triggered activity induced by cocaine. It has been shown that an intravenous bolus of cocaine prolongs the QT interval in ECG recordings in intact dogs, which suggests that cocaine induces repolarization abnormalities in vivo. Wettl and Wright reported that plasma cocaine concentrations measured at autopsy were in the range of 0.3–12.8 µg/ml (1–43 µM) in 24 patients who apparently died from acute cocaine overdose. The peak plasma concentration would have been much higher, because cocaine is biotransformed by plasma esterases. Thus, it is quite possible that cocaine-induced lethal arrhythmias result from triggered activity induced by EADs, i.e., proarrhythmic rather than ischemic.

A number of substances are known to induce EADs, including catecholamines, Ca2+ channel agonists, sotalol, cesium, and class IA antiarrhythmic drugs. Also, repolarization of ischemic myocardium may induce EADs. Although the precise mechanisms of development of EADs are not well understood, it has been suggested that EAD induction generally requires an initiation or conditioning phase controlled by the sum of membrane currents present at the action potential plateau (inward depolarizing current and outward repolarizing current). This phase is characterized by lengthening and flattening of the plateau within a voltage range in which recovery from inactivation and reactivation of an inward current could occur, possibly carried by L-type Ca2+ channels. Although the L-type Ca2+ current was slightly reduced by cocaine, the lengthening of APD at around −30 mV by blocking Ikr may result in recovery from inactivation and reactivation of the inward current. Our findings that cocaine-induced EADs and triggered activity were enhanced by isoproterenol and suppressed by verapamil are consistent with this hypothesis.

Finally, it should be noted that, to induce EADs and triggered activity, the cells must have been acutely exposed to high concentrations of cocaine. When 50 µM cocaine was applied to the cells that had been exposed to 10 µM cocaine, no EADs were induced. This suggests a possible protective conditioning effect of lower concentrations of cocaine.

We conclude that cocaine can prolong APD and induce EADs and triggered activity by blocking the delayed rectifier K+ current. Together with its inhibiting action on catecholamine reuptake, cocaine-induced abnormalities of repolarization may play a role in its arrhythmogenic potential.

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