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Block of a Ca^{2+}-activated Potassium Channel by Cocaine

L.S. Premkumar
Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, IL-62702, USA

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Abstract. The primary target for cocaine is believed to be monoamine transporters because of cocaine's high-affinity binding that prevents re-uptake of released neurotransmitter. However, direct interaction with ion channels has been shown to be important for certain pharmacological/toxicological effects of cocaine. Here I show that cocaine selectively blocks a calcium-dependent K^+ channel in hippocampal neurons grown in culture (IC_{50} = ~30 μM). Single-channel recordings show that in the presence of cocaine, the channel openings are interrupted with brief closures (flicker block). As the concentration of cocaine is increased the open-time is reduced, whereas the duration of brief closures is independent of concentration. The association and dissociation rate constants of cocaine for the neuronal Ca^{2+}-activated K^+ channels are 261 ± 37 $\mu M^{-1}s^{-1}$ and 11451 ± 1467 s^{-1}. The equilibrium dissociation constant (K_B) for cocaine, determined from single-channel parameters, is 43 μM. The lack of voltage dependence of block suggests that cocaine probably binds to a site at the mouth of the pore. Block of Ca^{2+}-dependent K^+ channels by cocaine may be involved in functions that include broadening of the action potential, which would facilitate transmitter release, enhancement of smooth muscle contraction particularly in blood vessels, and modulation of repetitive neuronal firing by altering the repolarization and afterhyperpolarization phases of the action potential.

Key words: Cocaine — K^+ channels — Calcium

Introduction

The use of cocaine poses a major health problem because of its high addictive property. Chronic abuse of cocaine induces cellular adaptive changes in the nervous system and in toxic doses induces seizures and life-threatening cardiac arrythmias. Pharmacological actions of cocaine are believed to result from interactions with monoamine transporters (Goeders & Smith, 1986; Wise & Bozarth, 1987). However, dopamine and 5-hydroxytryptamine (5-HT) transporter knock-out mice exhibit continued drug-seeking behavior, suggesting involvement of additional molecular targets for cocaine action (Giros et al., 1996; Rocha et al., 1998; Sora et al., 1998).

Cocaine can potentiate both the synaptically released and exogenously applied 5-HT response (Bobker & Williams, 1991). Similar responses to cocaine have been reported in the hippocampus (Dunwiddie, Proctor & Tyma, 1988) and in the nucleus accumbens (Uchimura & North, 1990). In dorsal raphe nucleus and other monoamine-releasing areas, cocaine has been shown to induce a hyperpolarizing response (Pitts & Marwah, 1988; Pan & Williams, 1989; Cunningham & Lakoski, 1990; Lacey, Mercuri & North, 1990). Using specific dopamine-receptor blockers, it has been shown that dopamine hyperpolarized via D_1 and depolarized via D_2 receptors, whereas 5-HT only depolarized these neurons (Uchimura & North, 1990). Conductance changes caused by DA and 5-HT were potentiated by cocaine (Lacey et al., 1990). Chronic cocaine treatment has been shown to alter voltage-gated Na^+ and Ca^{2+} channel activity via the production of cAMP by D_1 receptor stimulation (Zhang, Hu & White 1998; Zhang, Cooper & White, 2002). Recently, GABA transmission in the nucleus accumbens has been shown to be modulated after cocaine withdrawal (Xi et al., 2003). These studies indicate that cocaine induces conductance changes by modulating neurotransmitter receptors and voltage-gated channels.

Direct modulation of ion channels has been shown to be responsible for certain actions of cocaine. Cocaine blocks voltage-dependent Na^+ channels (Post et al., 1981; Reith, 1988; Crumb & Clarkson, 1990). In concentrations achieved during

Correspondence to: L.S. Premkumar; email: lpremkumar@siumed.edu

recreational use (1–2 μM), cocaine selectively potentiates current through L-type Ca^{2+} channels in cardiac myocytes. At these concentrations cocaine had no effect on voltage-gated Na^+, K^+ or ligand-gated (GABA and NMDA) channels (Premkumar, 1999). However, at higher concentrations, cocaine blocks voltage-dependent Ca^{2+} channels (Stewart, Rubin & Thomas, 1993; Renard, Pelaville & Thomas, 1994; Zhang et al., 2002). In dorsal root ganglion neurons cocaine has been shown to inhibit Ca^{2+}-dependent K^+ channels (Grossie, 1993). Other ion channels modified by cocaine include K^+ channels activated by acetylcholine and adenosine (Xiao & Morgan, 1997), ether-a-go-go (HERG) K^+ channels (O'Leary 2001; 2002), delayed rectifier K^+ channels (Kimura et al., 1992) and the ryanodine receptor channels (Tsushima, Kelly & Wasserstrom, 1996).

This study was undertaken to determine the effect of cocaine on K^+ channels and to identify the molecular mechanism(s) of action from the analyses of single-channel currents. Here, I show that cocaine causes a 'flicker' block of a Ca^{2+}-activated potassium channel in hippocampal neurons.

Materials and Methods

Primary cultures from the hippocampus of new-born rats were grown according to standard methods. The cells were used from 1 to 4 weeks after plating to record whole-cell and single-channel currents (inside-out/outside-out patches). The extracellular solution had the following composition (in mM): NaCl 140; KCl 2.5; $CaCl_2$ 2; HEPES 5; TTX 0.0005–0.001; pH was adjusted to 7.3 with NaOH. Patch electrodes were made from thick-walled borosilicate glass tubes (Clark Electormedical), and filled with a solution containing (in mM): K-gluconate, 140; KC1 10; $MgCl_2$ 0.5; HEPES 10, $CaCl_2$ 0.01; ATP 2; GTP 0.25 and pH was adjusted to 7.3 with KOH. Electrodes had a resistance of 5 to 10 MΩ. All experiments were performed at room temperature (22–25°C). Agar-bridge electrodes were used to avoid changes injunction potentials.

Whole-cell currents were recorded with a current-to-voltage converter (Axopatch 200A, Axon Instruments, Foster City, CA), filtered at 10 kHz and digitized at 5 kHz using Lab View-based programs (National Instruments, Austin, TX). The capacitative currents were carefully canceled, and the series resistance compensation was set at 70–80%. Single-channel current recordings were digitized at 94 kHz (VR-10B; Instrutech Corp., Great Neck, NY) and stored on videotape. For amplitude histograms the data were filtered at 2.5 kHz (-3db frequency with an 8-pole low-pass Bassel filter; Frequency Devices, Haverhill, MA) and digitized at 5 kHz. For kinetic analysis the recordings were filtered at 10 kHz and sampled at 100 kHz. Cells under voltage clamp were perfused continuously with the control solution from a 300 μM barrel positioned 50–100 μm away from the cell under study.

Single-channel current amplitude was estimated from all-point amplitude histograms (Channel 2 software written by Michael Smith, Australian National University, Canberra) and fitted to Gaussian densities (Microcal Origin, Northampton, MA). Patches that apparently had a single channel (as judged from the lack of overlapping events, when the channel-open probability P_o was > 0.7) were used for dwell-time analysis. Single-channel currents were idealized using a modified Viterbi algorithm (QUB software, www.qub.buffalo.edu). Dwell-time distributions were fitted with mixtures of exponential densities using a method of maximum likelihood. Additional exponential components were incorporated only if the maximum log likelihood increased more than 2 units (Qin, Auerback & Sachs, 1996; Premkumar, Quin & Auerbach, 1997). A dead time (τ_d) of 25/50 μs was retrospectively imposed, in that events shorter than 25/50 μs were ignored.

Drugs

All the drugs were purchased from Sigma Aldrich, St. Louis, MO.

Results

Block of Whole-Cell Ca^{2+}-activated K^+ Currents by Cocaine in Cultured Hippocampal Neurons

Whole-cell currents were recorded from one-to three-weeks old hippocampal neurons grown in culture. Outward potassium currents were elicited by depolarizing voltage steps (10 or 20 mV for 50 ms) from a holding potential of -120 mV. Na^+ currents were eliminated by the addition of 0.5 to 1 μM TTX in the extracellular solution. The outward current consisted of an inactivating (A-current) and a non-inactivating (delayed rectifier and Ca^{2+}-activated K^+ current) components (Fig. 1*a*). The steady-state outward current reversed (−100 mV) close to the calculated reversal potential for potassium ions (−106 mV). The current-voltage relationship was nonlinear at potentials more positive than −30 mV and the linearity could be restored when extracellular Ca^{2+} was eliminated or in the presence of cadmium (Fig. 1*b*), indicating the contribution of Ca^{2+}-activated potassium channels to the outward current. Application of cadmium (50 μM) blocked a significant percentage of the late phase of the outward current (47 ± 3%, mean ± SEM ($n = 7$). Higher concentrations of cadmium did not block the late phase of the current, further suggesting complete block of the Ca^{2+}-dependent K^+ channel component.

The effect of cocaine was investigated on the outward potassium current. Cocaine induced a dose-dependent block of the outward current; 10 μM cocaine blocked 27 ± 6% ($n = 4$, $P < 0.001$) of the current; 20 μM blocked 44 ± 4% ($n = 9$, $P < 0.001$) of the current. A simple one-site binding model is not appropriate because there is a constant residual current even at higher concentrations of cocaine. The residual current comes from two sources: 1) cocaine induces a flicker block that does not block the channel completely; 2) cadmium-insensitive potassium channels. Therefore, an equation of the following forms was used to fit the data:

$$g = \Delta g/1 + [\text{cocaine}]/K_m) + g_{inf}$$

where g = conductance and g_{jnf} = infinite concentration of cocaine. The cocaine block follows a

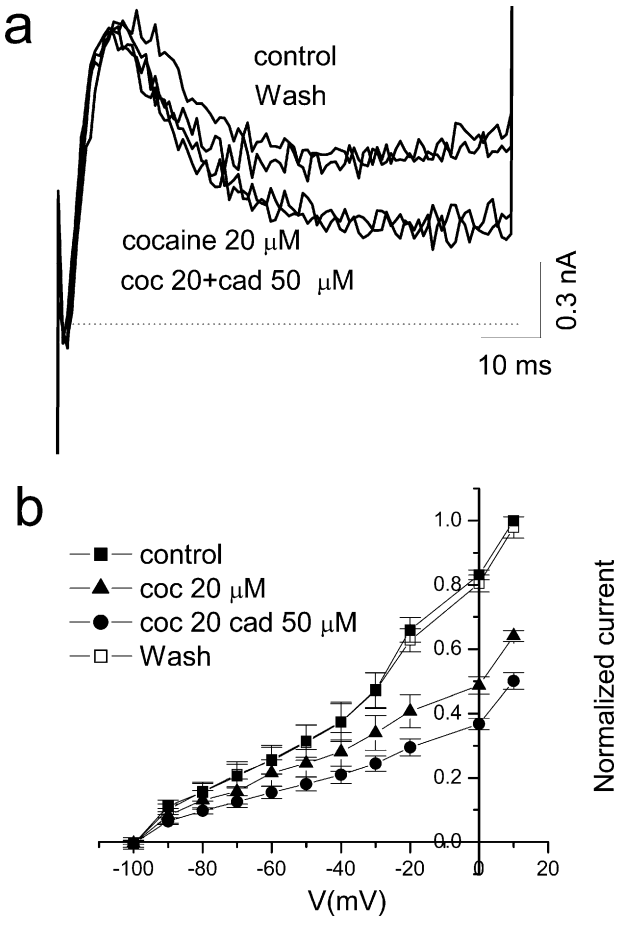

Fig. 1. Effect of cocaine on whole-cell K^+ currents recorded from hippocampal neurons in culture. (*a*) Cadmium-sensitive late phase of the K^+ current activated in response to a step depolarization from −100 to 0 mV is blocked by cocaine. (*b*) Current-voltage relationships of the outward potassium current in the presence of cocaine, and cocaine plus cadmium.

monotonic function and the IC_{50} was determined to be 26.6 μM. Change in the current amplitude could result from altered voltage dependency for channel activation. Plots of I/I_{max} do not indicate a shift in the voltage axis, suggesting cocaine does not alter the voltage dependency of the channel. In order to determine whether cadmium and cocaine blocked different K^+ channels, cadmium and cocaine were applied simultaneously. Cadmium (50 μM) plus cocaine (20 μM) blocked 49 ± 3% of the current ($n = 6$), which is not significantly different from that blocked either by cadmium (47%) or cocaine alone (44%), indicating that both cadmium and cocaine blocked the same population of channels. Figure 1*a* shows that in the presence of 20 μM cocaine a substantial portion of the late phase of the current (cadmium-sensitive component) was abolished without affecting the early inactivating phase of the current. The current-voltage relationship (Fig. 1*b*) shows that cocaine blocks the outward current at potentials

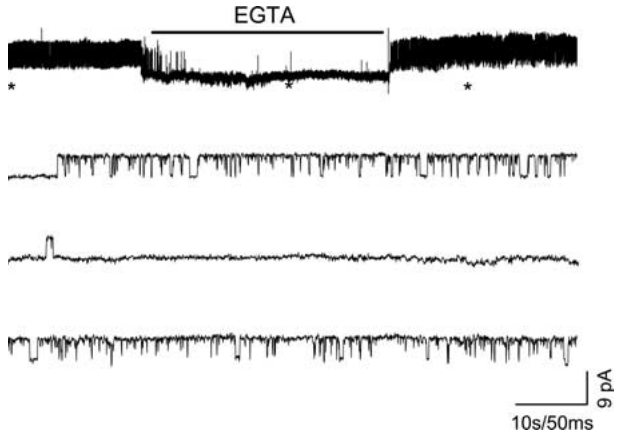

Fig. 2. Single-channel Ca^{2+}-activated K^+ currents in hippocampal neurons. Exposure of the cytoplasmic surface of an inside-out membrane patch to EGTA (5 mM) abolished single-channel activity. The asterisks denote the regions that are shown at a higher time resolution below.

more positive than –40 mV, potentials at which Ca^{2+} entry occurs via the voltage-gated Ca^{2+} channels. These results suggest that cocaine selectively blocks the Ca^{2+}-dependent potassium current.

Block of Single-Channel Ca^{2+}-Dependent Potassium Currents by Cocaine

In order to study the cocaine-induced block of K^+ channels in detail, we recorded single-channel currents. A variety of single-channel currents were activated in response to step depolarizations from −100 to 0 mV. However, I could consistently record a non-inactivating steady-state single-channel current activity, which was sensitive to calcium chelator. When the intracellular surface of the membrane was exposed to a solution containing EGTA (5–10 mM), the channel-open probability decreased, leading to a complete loss of channel activity and the effect could be reversed readily (Fig. 2). These currents were unaffected whether the intracellular solution contained Kgluconate or KCl and reversed close to K^+ equilibrium potential, indicating that the current was mainly carried by K^+. The single-channel current has a slope conductance of ~65 pS and a mean open-time of ~2.5 ms. These observations suggest the presence of a Ca^{2+}-activated K^+ channel of an intermediate conductance in these cells.

Single-channel currents were first idealized as described in the Methods section. The open- and closed-time histograms were best fitted by a model having one open and four or five closed states using the method of likelihood maximization. Patches that had a channel-open probability P_o of greater than 0.7 were used for kinetic analysis, which eliminated long closures between bursts of openings. In these patches dwell-time distribution could be best fitted with two

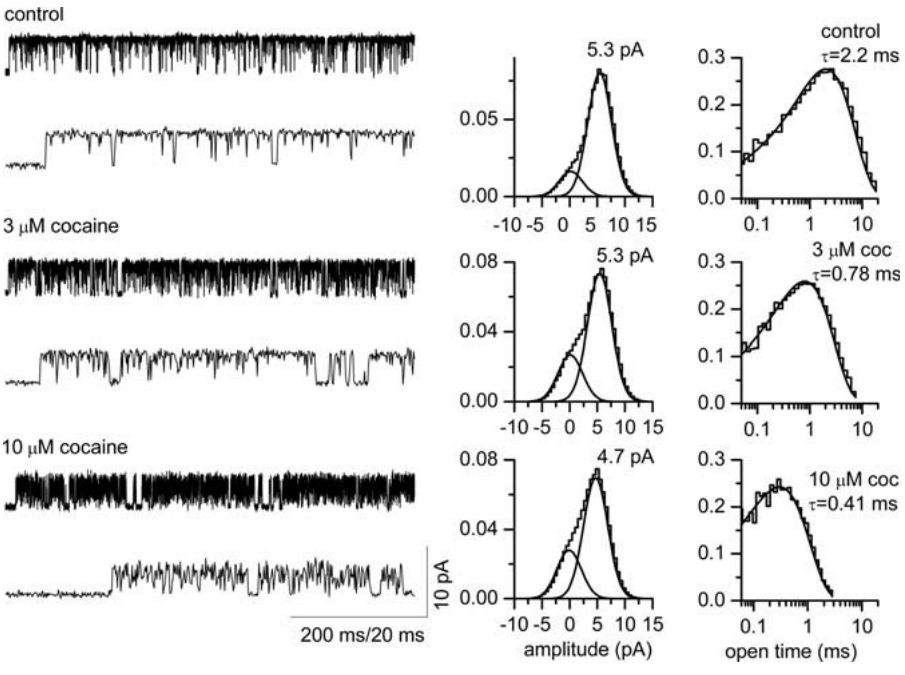

Fig. 3. Effect of cocaine on the single-channel Ca^{2+}-activated K^+ currents recorded from hippocampal neurons. *Left column*: Single-channel current traces show the concentration dependent increase in the number of brief closures induced by cocaine. *Middle column*: All-point amplitude histograms show an apparent reduction in the current amplitude at higher concentrations of cocaine. *Right column*: Single-exponential fit to open-time distribution.

closed and one open state. Addition of cocaine caused brief closures (flickers) and an additional closed (block) state was needed for kinetic description of the data. Extensive analysis carried out by this method showed consistency in dwell-time distributions in segments of data within a patch as well as between patches.

Cocaine induced a flicker block of single-channel currents. At lower concentrations (0.3 μM), discrete closures were readily observed; as the concentration was increased (Fig. 3, left column) the number of these closures increased and a slight reduction in the single-channel current amplitude was seen (Fig. 3, middle column). In control conditions the single-channel amplitude was 5.3 pA; 3 μM cocaine reduced the amplitude to 5.2 pA and 30 μM to 4.7 pA. The apparent reduction in single-channel amplitude is due to rapid transition between blocked and unblocked states that are beyond the resolution of the recording system.

In order to quantify the change in the kinetics induced by cocaine, open (τ_O) and closed (τ_C) time constants were estimated by fitting exponential functions to open and closed-time histograms. The open-time histogram is well fitted with single-exponential components (Fig. 3, right column) and the closed-time histograms could be fitted with 2 or 3 exponential components (*data not shown*). The mean open-time decreased with increasing concentrations of cocaine: control, 2.04 ± 0.19 ms, $n = 4$; 3 μM, 0.72 ± 0.04 ms, $n = 3$; 30 μM, 0.29 ± 0.03 ms, $n = 3$, Mean ± SD) (Table 1). These findings are consistent with the open-channel block of the scheme:

$$C \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} O \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B$$

where C and O are closed and open state of the channel; in the presence of cocaine an additional block state (B) is introduced. β, α, k_+, and k_- are opening, closing, association and dissociation rate constants, respectively.

In such a scheme the open (τ_O) and blocked (τ_B) time constants are given by the following:

$$\tau_o = (\alpha + k_+[\text{cocaine concentration}])^{-1} \quad (1)$$

$$\tau_B = (k_-)^{-1} \quad (2)$$

$$K_B = k_-/k_+ \quad (3)$$

where, τ_O and τ_B are open and blocked time constants, and K_B is the equilibrium dissociation constant for the blocker.

The association rate constant was determined by fitting the data points to Eq. 1. The duration of the blocking events did not change significantly with the concentration of cocaine. There is an inherent closed-time exponential component at 78 ± 2 μs ($n = 4$). In the presence of cocaine, a closed-time component appeared (89 ± 12 μs, $n = 8$), the area of which increased with increasing concentrations of cocaine (Table 1). Therefore, the time constant was taken as the τ_B. The equilibrium dissociation constant for the

Table 1. Kinetic analysis of cocaine-induced block

Cocaine (μM)	*n*	Open time (ms)	Closed time (ms) τ_1	τ_2	τ_3
Control	4	2.04 ± 0.19	0.078 ± 0.002	1.09 ± 0.2	225 ± 370
		(1)	(0.78 ± 0.02)	(0.18 ± 0.04)	(0.017 ± 0.02)
3	3	0.72 ± 0.07	0.089 ± 0.017	1.08 ± 0.16	62.2 ± 55.1
		(1)	(0.90 ± 0.01)	(0.08 ± 0.02)	(0.001 ± 0.001)
10	2	0.38	0.085	0.875	5.75
		(1)	(0.93)	(0.049)	(0.0007)
30	3	0.29 ± 0.03	0.09 ± 0.005	0.726 ± 0.53	2.58 ± 0.077
		(1)	(0.95 ± 0.01)	(0.03 ± 0.008)	(0.007 ± 0.004)

Values are mean ± SD; the area of the component is given in parentheses.

blocker (K_B) was determined (Eq. 3) to be 43 μM (Fig. 4).

Typically channel blockers also exhibit voltage dependence and the relationship between k_+ and transmembrane voltage has the form

$$k_{v+} = k_{0+}e^{(-z\delta FV/KT)} \quad (4)$$

where k_{v+} is the association rate constant at a given voltage; k_{0+}, the association rate constant at zero voltage; z, valence; δ, fractional electrical distance to the blocking site; V, transmembrane voltage; F, R and T have their usual meaning. Figure 5 shows that there is no voltage dependency of the channel block induced by cocaine. The nature of the block observed is due to an interaction of the cocaine molecule with the channel pore, which briefly occludes the current flow. Although the cocaine-induced block appears to be a typical channel block, it differs in that cocaine blocks the outward potassium current, probably by binding to a site at the mouth of the pore and interrupting the flow of K^+. This prediction is further supported by the lack of voltage dependence of the block. Since at physiological pH cocaine is positively charged and its protonated form does not cross the membrane, it could bind to a negative residue around the extracellular surface of the pore.

The block of potassium channel induced by cocaine is specific to Ca^{2+}-dependent potassium channels. We used higher concentrations (up to 100 μM) on other channels to investigate the specificity of cocaine action. Cocaine did not block other potassium channels even at higher concentrations. Experiments were carried out to investigate the effect of cocaine on ligand-gated channels. Neither the amplitude nor the time course of the whole-cell currents induced by GABA (100 μM) or NMDA (100 μM) were altered by cocaine (50 μM). All these experiments strongly suggest that cocaine selectively blocks Ca^{2+}-activated potassium channels.

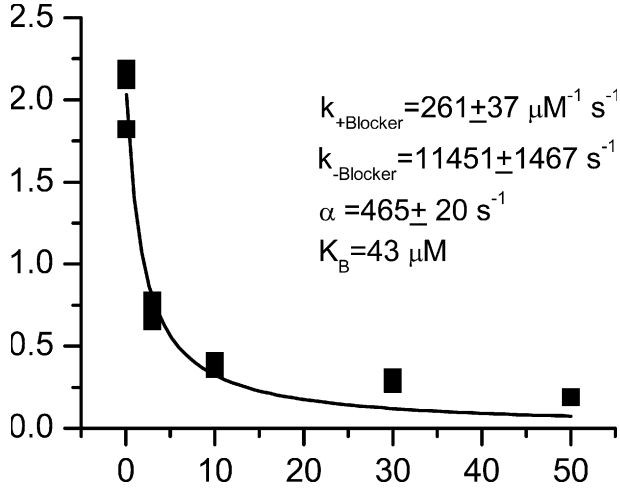

Fig. 4. Kinetic analysis of the block of single-channel currents induced by cocaine. Association and closing rate constants are determined by plotting the relationship between cocaine concentration and the open-time and fitting the data points to Eq. 1. The dissociation rate constant (k_-) is $1/\tau_B$.

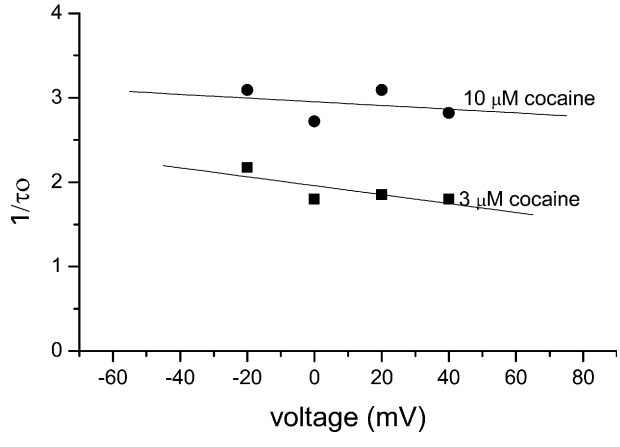

Fig. 5. Lack of voltage dependence of cocaine-induced flicker block of single-channel currents. Current recordings from hippocampal neurons at different voltages were analyzed. The flicker block, which reduced the open-time, showed no voltage dependence.

Discussion

Although the plasma concentrations of cocaine during recreational use range between 1.7 and 3.3 μM, postmortem samples from overdose victims suggest that the plasma levels of cocaine could reach up to 50–70 μM (Van Dyke et al., 1976; Mittleman & Wetli, 1984). Therefore, in chronic cocaine users the plasma levels may be higher and have a potential to induce toxic effects relating to the block of Ca^{2+}-activated potassium channels described in this study. Submicromolar concentrations of cocaine block neurotransmitter transporters (Ritz et al., 1987). However, at higher concentrations cocaine interacts with a variety of targets in a specific and non-specific manner. Cocaine concentrations above 5 μM block voltage-gated Na^+ channels and act as a local anesthetic similar to that of procaine and xylocaine. Cocaine has been shown to block a Ca^{2+}-activated K^+ channel in DRG neurons (Grossie, 1993). In cardiac myocytes, higher concentrations of cocaine block voltage-gated Ca^{2+} and delayed rectifier K^+ channels (Kimura et al., 1992; Stewart et al., 1993; Renard et al., 1994). In cardiac myocytes, lower concentrations (< 3 μM) of cocaine broaden the action potential, whereas higher concentrations (> 30 μM) shorten the action potential. These effects have been attributed to a balanced block of inward and outward currents (Clarkson et al., 1996). The effect of cocaine on other K^+ channels is becoming more apparent when studied individually in expression systems without interference from other channel types. In one such study, cocaine blocked human HERG channels with an IC_{50} of 6 μM (O'Leary, 2001). Cocaine has been shown to the block acetylcholine-activated muscarinic and adenosine-activated purinergic K^+ channel in ferret cardiac myocytes. ACh-induced shortening of the action potential was partly reversed by cocaine (Xiao & Morgan, 1997). In this study, I show that cocaine blocks Ca^{2+}-dependent K^+ channels without affecting the A- or delayed rectifier-type voltage-gated K^+ channels. It is possible that induction of seizures and vasoconstriction, including coronary vasospasm, in higher doses of cocaine could be partly due to its ability to block Ca^{2+}-activated potassium channels described in this study.

Three types of Ca^{2+}-activated K^+ channels have been identified and cloned and are classified according to their single-channel conductance and sensitivities to toxins and blockers, as large-, intermediate-, and small-conductance Ca^{2+}-activated K^+ channels (Sah & Faber, 2002). In cultured hippocampal neurons, most often a 65 pS Ca^{2+}-activated K^+ channel, which was sensitive to cocaine, could be recorded. In neuronal channels the association and dissociation rate constants are 261 ± 37 $\mu M^{-1}s^{-1}$ and 11451 ± 1467 s^{-1}, respectively.

Cocaine induces a 'flicker' block similar to that observed with a variety of channel blockers, in that when the pore is occupied by the blocking molecule, the permeant ion movement is momentarily occluded, inducing a brief closure. Block of N-methyl-D-aspartate receptor by Mg^{2+} is a typical example for such a channel block. This type of channel block also exhibits strong voltage dependence; at negative potentials the block is more pronounced due to an increase in the occupancy probability of the blocking molecule to its binding site. The rate of block is exponentially related to voltage and the electrical distance of the binding site.

Even though cocaine induces flickers similar to other channel blockers, the difference is that cocaine blocks the outward flow of K^+ probably by binding to an external site at the mouth of the pore. This prediction is further strengthened by the lack of voltage dependence of the blocking kinetics. In an earlier study, Tsushima et al. (1996) have described cocaine-induced block of the ryanodine receptor. The concentration required to induce flicker block was in the millimolar range. Although cocaine-induced block of the ryanodine receptor appears to be similar to that described in this study, the block of ryanodine receptors by cocaine is a typical channel block and has the hallmark of voltage dependence. It is inferred from these findings that cocaine need not be present in the pore, but binding to an external site at the vestibule may be sufficient to interrupt the outward movement of potassium ions. It is possible that cocaine can cross the cell membrane and block; and the protonated form of cocaine at physiological pH, which does not cross the membrane, blocks the channel from the intracellular surface, but the ready reversibility of the block argues against this possibility.

Block of K^+ channels could underlie a variety of effects mediated by cocaine. In the central nervous system block of the K^+ channel can broaden the action potential and increase Ca^{2+} influx at the presynaptic terminal, which may augment neurotransmitter and hormone release. Chronic cocaine users tend to exhibit gynecomastia and premature births; these effects may be associated with increased hormone secretion from the pituitary (Gold, 1993). Increased catecholamine release from adrenal medulla could be partly due to this effect (Elhamdani, Zhou & Artalejo, 1998). In neurons, Ca^{2+}-activated potassium channels are involved in the repolarizing and afterhyperpolarizing phases of the action potential. The magnitude and the duration of the afterhyperpolarization determine the rate of neuronal firing. Block of Ca^{2+}-activated K^+ channels may facilitate repetitive neuronal firing that may enhance the propensity to induce seizures during cocaine over-dose. At higher concentrations, block of Na^+ and Ca^{2+}

channels would also play a predominant role in the modulation of neuronal functions.

In vascular smooth muscle cells, contraction may be enhanced by increasing the amount of Ca^{2+} entry due to broadening of the action potential. This action may partly contribute to the acute increase in blood pressure after ingestion of cocaine. Ca^{2+}-activated potassium channels have been shown to be involved in maintaining basal vascular tone (Sobey, 2001). In cardiomyocytes, broadening of the action potential in lower concentrations could be explained by the augmentation of Ca^{2+} currents caused by cocaine (Premkumar, 1999) and the block of HERG and delayed rectifier K^+ channels (O'Leary, 2001; 2002). However, the mechanism(s) underlying the shortening of the action potential is not clearly understood, but has been suggested to be due to an altered balance between Na^+ and K^+ currents (Clarkson et al., 1996) and block of Ca^{2+} currents at higher concentrations (Renard et al., 1994). In this context, there is a danger of ignoring the cardiac actions of cocaine in patients who have been admitted for overdose; because of these opposing actions, the action potential waveform and the EKG may appear normal. Cocaine causes prolongation of the QRS duration and this is consistent with the prolongation of the action potential that can be brought about by either enhancing Ca^{2+} current or blocking potassium current. Mutations in the HERG channel and the class III antiarrhythmic drugs prolong the action potential duration by reducing the conductance through the HERG channel. These effects may increase the likelihood of sudden cardiac death by prolonging the QT interval and precipitating *torsades de pointes* in susceptible individuals (Bauman & DiDomenico, 2002). In the emergency rooms, a variety of treatment options have been considered for cocaine toxicity. It is believed that K^+ channel block may prolong the depolarization and may generate early afterdepolarization (Chakko, 2002). Toxic levels of cocaine also cause hyperkalemia (Baraban & Schwartzkroin, 1997); both hyperkalemia and K^+-channel block can lead to membrane depolarization and increase the membrane excitability, which could lead to deleterious consequences.

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