Propofol increases the Ca\textsuperscript{2+} sensitivity of BK\textsubscript{Ca} in the cerebral arterial smooth muscle cells of mice

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Aim: Propofol has the side effect of hypotension especially in the elderly and patients with hypertension. Previous studies suggest propofol-caused hypotension results from activation of large conductance Ca\textsuperscript{2+}-sensitive K channels (BKCa). In this study, the effects of propofol on the Ca\textsuperscript{2+} sensitivity of BKCa were investigated in mice cerebral arterial smooth muscle cells.

Methods: Single smooth muscle cells were prepared from the cerebral arteries of mice. Perforated whole-cell recording was conducted to investigate the whole-cell BKCa current and spontaneous transient outward K\textsuperscript{+} current (STOC). Inside-out patch configuration was used to record the single channel current and to study the Ca\textsuperscript{2+} - and voltage-dependence of BKCa.

Results: Propofol (56 and 112 \textmu mol/L) increased the macroscopic BKCa and STOC currents in a concentration-dependent manner. It markedly increased the total open probability (NPo) of single BKCa channel with an EC\textsubscript{50} value of 76 \textmu mol/L. Furthermore, propofol significantly decreased the equilibrium dissociation constant (K\textsubscript{D}) of Ca\textsuperscript{2+} for BKCa channel. The K\textsubscript{D} value of Ca\textsuperscript{2+} was 0.881 \textmu mol/L in control, and decreased to 0.694, 0.599, and 0.177 \textmu mol/L, respectively, in the presence of propofol 28, 56, and 112 \textmu mol/L. An analysis of the channel kinetics revealed that propofol (112 \textmu mol/L) significantly increased the open dwell time and decreased the closed dwell time, which stabilized BKCa channel in the open state.

Conclusion: Propofol increases the Ca\textsuperscript{2+} sensitivity of BKCa channels, thus lowering the Ca\textsuperscript{2+} threshold of the channel activation in arterial smooth muscle cells, which causes greater vasodilating effects.

Keywords: propofol; BK\textsubscript{Ca}; cerebral arterial vascular smooth muscle; hypotension; vasodilation

Introduction

Propofol, an intravenous anesthetic, has been widely used for sedation in general anesthesia and in intensive care unit (ICU) because of its increasing agonist efficacy at the GABA\textsubscript{A} receptor\textsuperscript{[1, 2]}. However, propofol has the potential side effect of hypotension, which especially affects elderly patients\textsuperscript{[3]} and hypertensive rats\textsuperscript{[4, 5]}. The wide variability of sensitivity to propofol may lead to circulatory instability among patients, the underlying mechanisms of which are complicated. The relaxation of vascular smooth muscle is the main mechanism of propofol-mediated vasodilation\textsuperscript{[6]}. Some reports have shown that the modulation of ionic channels contributes to this effect through various modes of action, such as the inhibition of L-type voltage-dependent calcium channels (VDCCs) on vascular smooth muscle cells (SMCs), the activation of large conductance calcium- and voltage-activated potassium channels (BK\textsubscript{Ca}), ATP-sensitive K\textsuperscript{+} channels (K\textsubscript{ATP}) and an increase in the calcium sensitivity of SMCs\textsuperscript{[7–9]}

BK\textsubscript{Ca} are expressed broadly on SMCs and play a critical role in the regulation of vascular tone, which is activated by both membrane depolarization and intracellular calcium\textsuperscript{[10–12]}. The activation of BK\textsubscript{Ca} leads to cell membrane hyperpolarization, which causes the closure of L-type VDCC, resulting in the block of the influx of extracellular Ca\textsuperscript{2+} \textsuperscript{[12–14]}. The activation of BK\textsubscript{Ca} may be one of the mechanisms affecting vasodilation and hypotension in many antihypertensive agents, such as the drug-mediated vasodilation of the endothelium-derived relaxing factors (EDRFs), which includes nitric oxide (NO)\textsuperscript{[15, 16]}. Ketamine, an anesthetic associated with increases in arterial blood pressure, inhibits the activity of BK\textsubscript{Ca}\textsuperscript{[17]}. Structurally, BK\textsubscript{Ca} are comprised of four pore-forming \alpha subunits and four accessory \beta subunits in the arterial smooth muscle. The function of the \beta subunits is to enhance channel Ca\textsuperscript{2+} affinity and voltage sensitivity. Local [Ca\textsuperscript{2+}]\textsubscript{free} transients (Ca\textsuperscript{2+} sparks) have been widely studied in arterial smooth muscle cells\textsuperscript{[13, 18]}. 

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The Ca²⁺-dependent relaxation of the SMCs, which is called Ca²⁺-induced Ca²⁺ release (CICR), can be mediated by local Ca²⁺ releases through ryanodine receptor channels from the sarcoplasmic reticulum (SR). Higher local Ca²⁺ concentrations increase the activation of BKCa by more than 10³ times and produce BKCa currents, which are called strong spontaneous transient outward K⁺ currents (STOCs). Thus, STOCs have been noted as a singular type of BKCa current and represent the calcium sensitivity of BKCa. Studies have demonstrated the downregulated expression of the β₁ subunit of BKCa and the abnormal coupling of Ca²⁺ spark/STOCs in spontaneously hypertensive rats (SHR). Studies have also noted abnormal coupling and downregulated Ca²⁺ sensitivity with hypertension in the β₁-subunit knockout mouse. Ion channels, receptors, etc. can be downregulated or upregulated, but the channel calcium sensitivity either increases or decreases.

Klockgether-Radke et al reported that the activation of BKCa may contribute to the propofol-mediated relaxation of porcine coronary artery rings. Nagakawa et al showed that propofol-mediated hyperpolarization can be attributed to the activation of BKCa in the mesenteric vascular smooth muscle tissue of rats by measuring the membrane potential. Stadnicka et al reported that the activation of BKCa was involved in the membrane hyperpolarization and in the propofol-mediated dilatation of mesenteric SMCs in rats, and that the effect of propofol on BKCa was significantly greater in Dahl salt-sensitive rats when using patch clamp techniques. In elderly or hypertensive rats, the effect of propofol on BKCa was more serious. Vascular calcium overload occurred in the vascular SMCs during hypertension. It has also been shown that the calcium sensitivity of BKCa is downregulated in patients with hypertension. These reports suggest that the change in calcium sensitivity in BKCa may be linked to the differential effects of propofol among patients.

Previous research has demonstrated that BKCa are crucially involved in propofol-induced vasodilation, especially in the setting of hypertension. In our study, we hypothesized that the variable effect of propofol among patients was due in part to its effect on the calcium sensitivity of BKCa. To learn more about the mechanisms of these processes, we studied the interaction of propofol with the vascular smooth muscle BKCa by analyzing the macroscopic and single channel currents recorded on the cerebral arterial SMCs of mice.

**Materials and methods**

**Single cell isolation**

The Ethics Committee of Luzhou Medical College approved this study. The mice were obtained from the animal care center of Luzhou Medical College. The animals were deeply anesthetized with pentobarbital sodium (60 mg/kg ip). The brain was dissected out and placed in an ice-cold normal physiological saline solution (PSS). The cerebral arteries were carefully dissected out from the brain and then exposed to low Ca²⁺ PSS (0.1 mmol/L CaCl₂). The arteries were enzymatically dissociated for 9.5 min in a low Ca²⁺ PSS containing (in g/L) 0.3 papain and 0.2 dithioerythritol (DTT). The arteries were then treated for another 9.5 min in a low Ca²⁺ PSS containing (in g/L) 0.8 collagenase F, 1.0 collagenase II and 1.0 dithioerythritol (DTT) at 37°C. The single cerebral arterial smooth muscle cells were obtained by gently triturating the digested tissues in culture dishes filled with PSS containing 1 g/L albumin. The cells were then stored at 4°C until the subsequent electrophysiological experiments were performed.

All measurements were obtained at room temperature (23±2°C).

**Electrophysiological methods**

Electrophysiological recordings were performed as previously described. Macroscopic BKCa currents were recorded using stepwise 10-mV depolarizing pulses (400-ms duration, 1-s interval) from a constant holding potential of -60 mV in cells or a ramp pulse at 0.375 V/s from -80 to +70 mV. The bathing solution contained the following (in mmol/L): NaCl 137, KCl 1.2, CaCl₂ 1.8, glucose 10 and HEPES 10 (pH 7.4). The pipette solution contained the following (in mmol/L): KCl 128, NaCl 12, MgCl₂ 4, HEPES 10 and EGTA 0.05 (pH 7.2), with 0.2 g/L amphotericin B. STOCs were recorded at steady-state membrane potentials between -50 mV and 0 mV.

Single channel currents were recorded 20–30 min after a membrane patch formation and more than 5 min after each drug application. During the inside-out patch experiments, the pipette solution consisted of the following (in mmol/L): K-aspartate (K-Asp) 40, KCl 100, HEPES-K 10 (pH 7.2) and EGTA 2. The bath solution consisted of the following (in mmol/L): K-Asp 100, KCl 40, HEPES-K 10 (pH 7.4) and EGTA 1. The free Ca²⁺ concentration in the bath solution ([Ca²⁺]ₗₒₒ) was calculated according to the following equation,

\[
[Ca^{2+}]_{\text{free}} = \frac{(1+K')(\text{EGTA})+[Ca^{2+}]_{\text{free}}}{1+[Ca^{2+}]_{\text{free}}\times K'}
\]

where \([Ca^{2+}]_{\text{add}}\) is the concentration of CaCl₂, \([Ca^{2+}]_{\text{free}}\) is the concentration of free calcium ion, [EGTA] is the concentration of EGTA, and \(K'\) is the association constant of calcium with EGTA, where \(K'=10^{7.1}(\text{pH}=7.2, 22°C)\). To prepare \([Ca^{2+}]_{\text{free}}\) of 0, 0.01, 0.1, 0.5, 1, or 10 μmol/L, the CaCl₂ concentration was changed to 0, 0.11, 0.55, 0.86, 0.92, or 1 mmol/L, respectively. The membrane potential (\(V_m\)) was expressed as the potential at the intracellular side minus the potential at the extracellular side.

**Drug and chemicals**

Propofol was purchased from AstraZeneca Co, England (production lot number: GF357). The drug was dissolved in DMSO to obtain a 100 mmol/L stock solution and was added to the bath solution to obtain the desired concentration. K-aspartate, HEPES, EGTA, and enzymes were obtained from Sigma (USA).

**Statistical analysis**

Whole-cell macroscopic currents were analyzed using pClamp software 10.0 (Axon, USA) and the STOCs were analyzed...
using MiniAnalysis program (Synaptosoft Software, Leonia, NJ). The total open probability (NPo), the amplitude and the kinetic characteristics of the channels were analyzed by pClamp software 10.0 and by QUB software (www.qub.buffalo.edu). Data are expressed as the mean±SEM. Student’s t-test was used for paired data, and the independent test was used for statistical analysis. A value of P<0.05 was considered to be statistically significant, and “a” (P>0.05), “b” (P<0.05) and “c” (P<0.01) are indicated in the figures. The relationship between the drug concentration and the normalized NPo was integrated into the Hill equation,

\[ y = \frac{x^b}{(c^b + x^b)} \]

(Eq 2)

where x is the concentration of propofol or calcium, c is the half maximal effective concentration (EC50) of propofol or equilibrium dissociation constant (Kd) of calcium and b is the slope factor (Hill coefficient, nH).

Results

Properties of BK Ca currents in cerebral arterial smooth muscle cells

We confirmed that BKCa in the cerebral arterial SMCs of mice possess the characteristic properties found in other tissues. A typical recording of whole-cell macroscopic BK Ca currents is shown in Figure 1A. The STOCs are superimposed stochastically onto the whole-cell currents, and both currents were significantly suppressed by the external application of 200 nmol/L IbTX, a specific blocker of BKCa. The amplitude and frequency of the STOCs increased, as did the membrane depolarization. These effects can also be blocked with 200 nmol/L IbTX (Figure 1B). Figure 1C shows representative records of single BKCa currents under the inside-out configuration at different voltages with the symmetrical 140 mmol/L K+ ([Ca2+]0=0.5 μmol/L). The activity of BKCa increased with membrane depolarization. The intracellular calcium also activated BKCa (Figure 1D). The single channel conductance of BKCa, measured with symmetrical K+ concentration (140 mmol/L) on both sides of the membrane, was 205±44 pS (n=25). With the use of different salt compositions (substituting Na+ for K+ in the bath and pipette solution), the data indicated that the channels are K+ selective (data not shown). The currents were blocked by 200 nmol/L IbTX applied to the bath through the outside-out patches (Figure 1E). These properties of BKCa are consistent with those previously reported[16, 30].

The effects of propofol on BKCa in the whole-cell configuration

Figure 2 shows the effects of propofol on the BKCa macroscopic currents using step depolarizations (A) or a ramp voltage (B). Propofol 56 and 112 μmol/L markedly increased the macroscopic current density. The external application of 200 nmol/L IbTX inhibited the STOCs completely and the macroscopic current partially (Figure 2B). At +60 mV membrane potential, propofol 56 and 112 μmol/L increased the macroscopic current density 1.4-fold.

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Figure 1. Properties of BKCa in mouse cerebral artery smooth muscle cells. (A) A typical recording of macroscopic currents of BKCa. STOCs superimposed stochastically onto whole-cell currents, and both currents were significantly suppressed by 200 nmol/L IbTX, a specific blocker of BKCa. (B) The properties of STOCs. The amplitude and frequency of STOCs increased as the membrane depolarization, which can also be blocked by 200 nmol/L IbTX. (C) A typical recording of single channel currents in an inside-out membrane patch configuration. The upward deflection indicates outward currents. (D) An example of testing Ca2+ dependence of BKCa (inside-out patch, at +40 mV membrane potential). (E) An example of testing IbTX blockage of BKCa (outside-out patch, at +40 mV membrane potential).
(12.7±1.1 pA/pF vs 8.8±0.5 pA/pF, P<0.01, n=15) and 2.4-fold (18.9±1.8 pA/pF vs 8.8±0.5 pA/pF, P<0.01, n=12), respectively (Figure 2D).

The STOCs were recorded at -30 mV membrane potential. As shown in Figure 3, propofol 56 and 112 μmol/L increased the amplitude of the STOCs 1.5-fold and 1.6-fold, respectively, from 18.5±0.8 pA to 28.0±1.1 pA (P<0.01, n=5) and to 30.1±5.7 pA (P<0.01, n=4), respectively. The frequency of the STOCs increased 1.7-fold and 2.7-fold from 3.6±1.4 Hz to 6.0±2.2 Hz (P<0.05, n=5) and to 9.5±3.4 Hz (P<0.01, n=4), respectively. Propofol 112 μmol/L increased the frequency of the STOCs more than the 56 μmol/L concentration (P<0.05). The results strongly suggest that the enhancement of the frequency and amplitude of the STOCs by propofol is one of the major causes

Figure 2. Effect of propofol on the macroscopic currents of BK_α. (A) The typical recording of the effect of 56 and 112 μmol/L propofol on BK_α by step pulse. (B) The typical recording of the effect of 56 and 112 propofol on BK_α by ramp pulse. The effect of propofol can be blocked by 200 nmol/L IbTX. (C) The I-V relation curve of the macro-currents. Propofol 56 and 112 μmol/L shifted the curve at various membrane voltages. (D) The histogram of the effect of 56 and 112 μmol/L propofol on the BKα currents density at V_m=+60 mV. bP<0.05, cP<0.01 vs control group; dP<0.05, eP<0.01 vs 56 μmol/L propofol.

Figure 3. Effect of propofol on STOCs in mouse cerebral arterial SMCs. (A) A typical recording of STOCs. Propofol 56 and 112 μmol/L activates the STOCs. (B) The histogram shows that 56 and 112 μmol/L propofol increased frequency of STOCs. (C) The histogram shows the effect of 56 and 112 μmol/L propofol on the amplitude of STOCs. bP<0.05, cP<0.01 vs control group. dP>0.05, eP<0.05 vs 56 μmol/L propofol.
of propofol-induced vasodilation.

The effects of propofol on single BKCa channel activity
To investigate the mechanisms of propofol that increase the frequency and amplitude of the STOCs, we studied the effect of propofol on single channel activities. We examined the effect of propofol (0–224 μmol/L) on activity at [Ca^{2+}]_{free}=0.1 μmol/L when propofol was applied to the cytoplasmic side of a single BKCa using the inside-out patch configuration. Figure 4A shows examples of the records at $V_m=+40$ mV with different propofol concentrations. Propofol increased the activity of BKCa in a concentration-dependent manner. Propofol 56 and 112 μmol/L increased the NPo 52-fold and 193-fold, respectively, in comparison with the control group (0.23±0.09, 0.85±0.10 vs 0.004±0.001, n=5). The propofol dose-response curve is presented in Figure 4B. This figure shows that the values of NPo were normalized to the NPo value at a propofol concentration of 224 μmol/L. The data were integrated through the use of the Hill equation (Eq 2) with an EC50 of 76±8 μmol/L and an $n_H$ of 3.62.

Propofol increases the calcium and voltage dependence of BKCa
We further investigated the effect of propofol on the calcium sensitivity of BKCa directly with the inside-out patches. The Ca^{2+} sensitivity of NPo increased when propofol was present in the bathing solution (Figure 5A). Figure 5B plots the relations of NPo when normalized to their maximum value against [Ca^{2+}]_{free}. These data were integrated into the Hill equation. When the propofol concentration was increased from 0 to 112 μmol/L, the $K_d$ was shifted from 0.881 to 0.694, 0.599 to 0.177 μmol/L, respectively (Figure 5B). However, there was no significant difference in the value of $n_H$. As shown in Figure 5B, BKCa activity was very sensitive to propofol at the [Ca^{2+}]_{free}=0.1 μmol/L. At 0.5 μmol/L [Ca^{2+}]_{free}, the values of normalized NPo at the propofol concentrations of 0, 28, 56, and 112 μmol/L were 0.06±0.01, 0.20±0.01, 0.34±0.03, and 0.94±0.06, respectively. The results were consistent with the effect of propofol on the STOCs. The augmentation of propofol on BKCa increased with higher levels of intracellular calcium.

We also studied the effects of propofol on the voltage dependence of BKCa. The NPo was normalized to the maximum open probability, and the data were integrated into the Boltzmann function ($y=A_2+(A_1-A_2)/(1+exp((x-x_0)/d)))$. As shown in Figures 5E and 5F, the half activation voltage ($V_{1/2}$) was decreased by the 56 μmol/L propofol concentration from 78.1±1.2 mV (control) to 52.8±1.5 mV at 0.5 μmol/L [Ca^{2+}]_{free} (P<0.05, n=5). These results suggest that propofol lowered the calcium and voltage thresholds for BKCa activation.

The effects of propofol on the kinetics of BKCa
We further investigated the effect of propofol on the kinetics of BKCa at 0.1 μmol/L [Ca^{2+}]_{free}. This investigation included an assessment of the open dwell time, the closed dwell time, the open time constant and the closed time constant (Figure 6). Figure 6A shows the typical current recording for a concentration of 112 μmol/L of propofol on BKCa. The right record suggested that 112 μmol/L of propofol increased the open dwell time of BKCa. Propofol at a concentration of 112 μmol/L increased the open dwell time from 4.9±2.0 to 33.3±2.1 ms (P<0.01, n=5) and reduced the closed dwell time from 4511+604 to 114±47 ms (P<0.01, n=5) (Figure 6B). The histogram in Figure 6C shows the effect of propofol on the open and closed time constant. Propofol 112 μmol/L decreased the open time constant (0.9±0.24 vs 3.10±1.11 ms, P<0.05, n=5) and increased the closed time constant (1.48±0.15 vs 0.55±0.13 ms, P<0.01, n=5) of BKCa. A propofol 112 μmol/L sped up the transition from the closed to the open state and slowed down the transition from the open to the closed state. These findings indicate that propofol not only accelerates BKCa transition time from the closed to the open state, but also that propofol maintains the channel in the open state.

Discussion
Propofol, an intravenous general anesthetic, is widely used for the induction and maintenance of general anesthesia because of the rapid onset of the drug and the relatively few side effects. However, there is a marked variability in cardiovascular sensitivity to propofol among patients. This variability may induce the serious side effect of hypotension, especially in elderly and hypertensive patients[5]. There are several mechanisms that are known to cause the hypotensive effects

![Figure 4](https://www.chinaphar.com)
of propofol, such as inhibition of the renin-angiotensin system (RAS)\(^{31,32}\), blocking of the release of noradrenaline from the sympathetic nerve endings\(^{33}\), reduction in cardiac contractility and cardiac output\(^{34,35}\), and direct relaxation of the
The major effect of propofol stems from the relaxation of the peripheral vessels. BKCa play a significant role in the regulation of vascular tone. We have confirmed the presence of propofol-activated BKCa in the mesenteric SMCs of humans in cell-attached and whole cell configurations (37). In our study, propofol activated the macroscopic currents of BKCa, the STOCs and single channel currents in a concentration-dependent manner (Figures 2 and 4). These data indicate that BKCa may contribute to the vasodilating effects of propofol.

The variance in circulatory instability with propofol is marked among patients, especially those with hypertension. The characteristics of BKCa change in hypertension, including changes in calcium sensitivity. With the combination of factors that induce higher levels of intracellular calcium, how do BKCa participate in the variable effects of propofol among different patients?

In our study, 56 μmol/L and 112 μmol/L concentrations of propofol increased the amplitude and frequency of the STOCs, which suggests that an augmentation in calcium sensitivity is involved in the effects of propofol on BKCa. However, there was no significant difference between the effects of 56 μmol/L and 112 μmol/L of propofol on the amplitude of the STOCs (P>0.05), which may be due to the increasing frequency of many of the STOCs with lower amplitudes at 112 μmol/L of propofol. The effect of propofol on calcium sensitivity was also confirmed by the experiments in inside-out configuration. The data indicate that propofol increased the calcium sensitivity by decreasing the Ki from 0.881 to 0.177 μmol/L (Figure 5B). The effect of propofol on channel NPo was particularly evident at 0.1 to 1 μmol/L [Ca2+]free, the concentration that activates the contractile apparatus of the cells (38). This indicates that under such conditions (0.1 to 1 μmol/L [Ca2+]free), propofol causes a significant hyperpolarization of the membrane potential. These results suggest that the augmentation effect of propofol on the calcium sensitivity of BKCa could be attributed to the hypotensive side effects of propofol, which are more extensive in the patients with hypertension. Propofol also shifted the voltage dependency of BKCa (Figure 5E, 5F) to more negative potentials. The effects of propofol on both calcium and voltage sensitivity indicate that the threshold of BKCa activation is lowered and that it may be easily activated in the presence of propofol, especially under higher intracellular levels of calcium.

The analysis of the kinetic properties of single channel currents revealed that propofol increased the open dwell time and decreased the closed dwell time. Propofol maintained and stabilized BKCa in the open state. This indicates that the molecular kinetics also participate in the augmenting action of propofol on BKCa.

In conclusion, this study has revealed the molecular mechanisms of propofol on BKCa. As one of the lipophilic anesthetics, propofol is absorbed by cell membrane lipids and directly alters BKCa properties. Propofol enhances calcium and voltage sensitivity, modulates channel kinetics and thus stabilizes BKCa in the open state. These effects may contribute to the greater vasodilator effects of BKCa activation under conditions that favor cellular Ca2+ overload, such as hypertension.

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