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The inhibitory effect of curcumin on voltage-dependent K^+ channels in rabbit coronary arterial smooth muscle cells

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ABSTRACT

We investigated the effects of curcumin, the principal active compound of turmeric, on voltage-dependent K^+ (Kv) channels in freshly isolated rabbit coronary arterial smooth muscle cells using the voltage-clamp technique. Curcumin reduced the Kv current in a dose-dependent manner with an apparent K_d value of 1.07 ± 0.03 μM. Although curcumin did not alter the kinetics of Kv current activation, it predominantly accelerated the decay rate of channel inactivation. The association and dissociation rate constants of curcumin were 1.35 ± 0.05 $\mu M^{-1}\,s^{-1}$ and 1.47 ± 0.17 s^{-1}, respectively. Curcumin did not alter the steady-state activation or inactivation curves. Application of train pulses (1 or 2 Hz) increased curcumin-induced blockade of the Kv current, and the recovery time constant also increased in the presence of curcumin suggesting, that the inhibitory action of Kv currents by curcumin was use-dependent. From these results, we concluded that curcumin inhibited vascular Kv current in a state-, time-, and use-dependent manner.

1. Introduction

Curcumin (diferuloylmethane) is a polyphenolic compound isolated from the roots of *Curcuma longa* (turmeric), commonly used as a spice. In addition to its use as a spice, curcumin has many beneficial biological effects including antioxidant, antiviral, antifungal, antibacterial, anti-inflammatory, and anti-cancer activities [1,2]. As a result, curcumin is useful as a therapeutic agent to treat a variety of diseases such as Alzheimer's disease, diabetes, allergies, arthritis, cystic fibrosis, psoriasis, and other chronic illnesses [2–4]. The beneficial effects of cardiovascular protection by curcumin have also been extensively studied. For example, curcumin decreases the development of heart failure [5], myocardial infarction [6], atherosclerosis [7], and cardiotoxicity induced by adriamycin [8]. Despite these beneficial effects, the side effects of curcumin on vascular ion channels have been neglected.

Several types of K^+ channels, including ATP-sensitive K^+ (K_{ATP}), big conductance Ca^{2+}-activated K^+ (BK_{Ca}), inward rectifier K^+ (Kir), and voltage-dependent K^+ (Kv) channels have been identified in vascular smooth muscle [9]. Among these, Kv channels are regarded as among the important channels for regulating resting membrane potential and thereby resting tone [10]. Inhibition of Kv channels by inhibitors such as 4-aminopyridine induces membrane depolarization and constriction in many arteries [11]. Additionally, alteration of Kv channels in vascular smooth muscle closely related to circulatory and metabolic diseases such as hypertension, hypoxia, and diabetes [12].

Considering that curcumin shows multiple beneficial effects and has clinical relevance, it is essential to investigate the unexpected effects of curcumin on vascular Kv channels to elucidate the cardiovascular toxic effects.

In the present study, we clearly demonstrated the unexpected effect of curcumin on freshly isolated coronary arterial smooth muscle cells using the whole-cell patch clamp technique. Our major findings were that curcumin inhibited Kv channel in a state-, time-, and use-dependent manners.

2. Materials and methods

2.1. Single cell isolation

New Zealand White rabbits (2.0–2.5 kg) of male were anaesthetized by simultaneous intramuscular injection of Zoletil (15 mg/kg), Rompun (0.5 mg/kg) and heparin (100 U/kg). The procedure was conducted in accordance with the guidelines of the Committee for Animal Experiments of Kangwon National University. The left descending coronary arteries were isolated and cleaned of surrounding tissues in normal Tyrode solution under stereomicroscope. The single smooth muscle cells were obtained by two step enzyme treatment with papain (1.0 mg/ml) and collagenase

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(2.8 mg/ml) in Ca^{2+}-free normal Tyrode solution as described previously [13]. The isolated cells were stored at 4 °C under Kraft-Brühe (KB) solution and used within 10 h.

2.2. Solutions and chemicals

The normal Tyrode solution contained (in mM): NaCl, 135; KCl, 5.4; NaH_2PO_4, 0.33; $CaCl_2$, 1.8; $MgCl_2$, 0.5; HEPES, 5; glucose, 16.6; adjusted with NaOH to pH 7.4. The intracellular recording solution (pipette solution) for Kv channels contained (in mM): K-aspartate, 110; KCl, 25; NaCl, 5; $MgCl_2$, 1; Mg-ATP, 4; EGTA, 10; HEPES, 10; adjusted to pH 7.25 with KOH. The KB solution contained (in mM): KOH, 70; L-glutamate, 50; KH_2PO_4, 20; KCl, 55; taurine, 20; $MgCl_2$, 3; glucose, 20; HEPES, 10; EGTA, 0.5; adjusted to pH 7.3 with KOH. Curcumin was purchased from Sigma Chemical Co. (St. Louis, MO, USA.) and dissolved in dimethyl sulfoxide (DMSO).

2.3. Electrophysiology and data analysis

Whole cell Kv currents were recorded with a digital interface, NI-DAQ-7 (National Instruments, Union, CA, USA) and EPC-8 amplifier (Medical System Corp., Darmstadt, Germany). Patch pipettes were pulled from thin-walled borosilicate glass (Clark Electromedical Instruments, Pangboune, UK) using a PP-830 vertical puller (Narishige Scientific Instrument Laboratory, Tokyo, Japan). The resistance of patch pipettes was maintained at 3–4 MΩ when filled with the pipette solution. Data acquisition was performed at a sampling rate of 1–3 kHz.

Data analysis was performed with Origin 7.0 software (Microcal Software, Inc., Northampton, MA, USA). A first-order blocking scheme was used to express the drug-channel interaction kinetics, as described previously [14,15]. The apparent affinity constant (K_d) and Hill coefficient (n) were calculated by fitting concentration-dependent data to the following Hill equation:

$$f = 1/\{1 + (K_d/[D])^n\},$$

where f is the fractional block ($f = 1 - I_{drug}/I_{control}$) at the test potential, and $[D]$ is drug concentration.

Activation kinetics were fitted with a single exponential function, which was considered the dominant time constant of activation [16]. The inactivation time courses of the current were fitted to a single (control) or double (presence of curcumin) exponential function. The apparent association (k_{+1}) and dissociation (k_{-1}) rate constants were obtained from the following equation:

$$1/\tau_D = k_{+1}[D] + k_{-1},$$

$$K_d = k_{-1}/k_{+1},$$

where τ_D is the time constant for the drug-induced block.

The experimental points were calculated as:

$$\text{Normalized} I = (I - I_c)/(I_{max} - I_c),$$

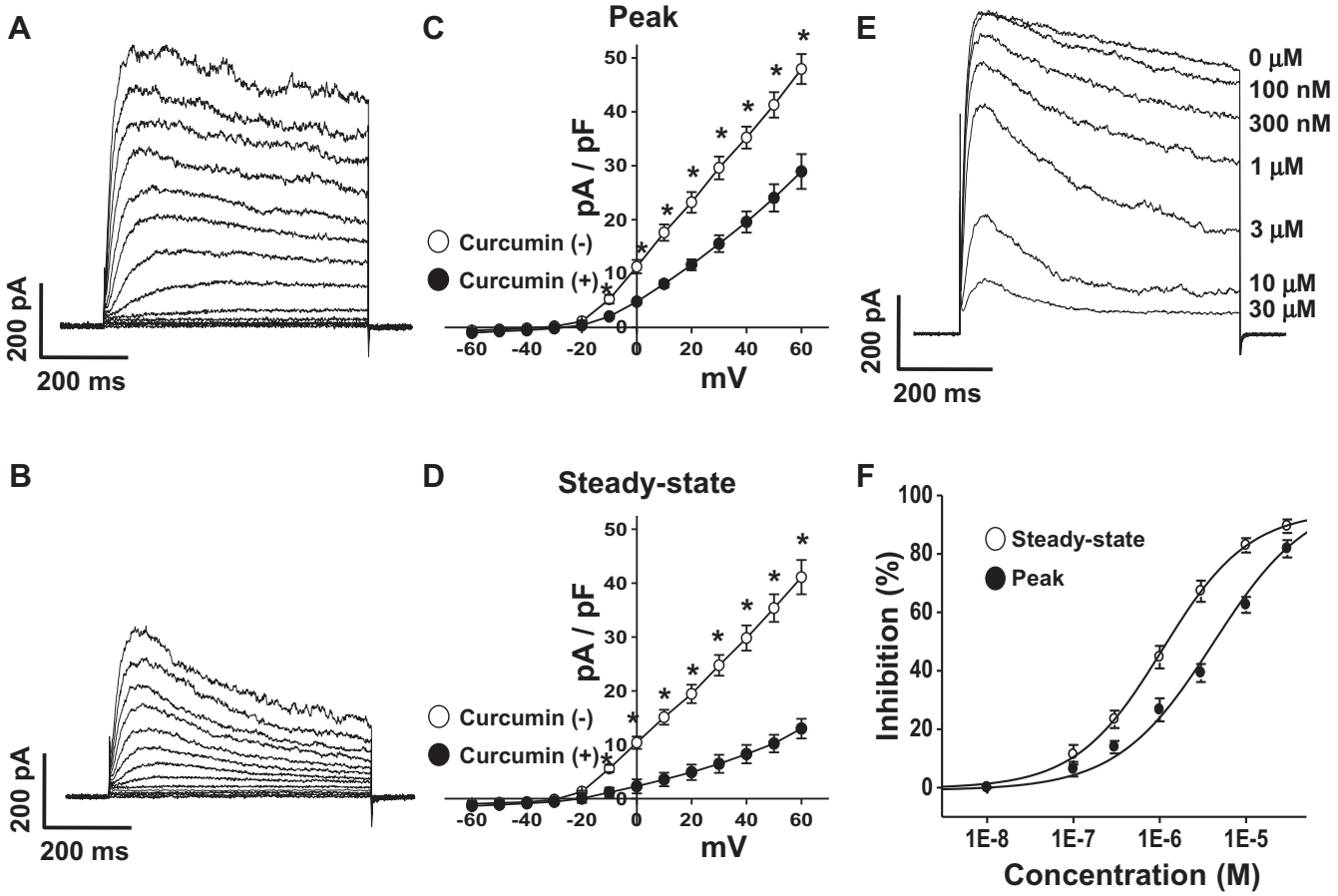

Fig. 1. Effect of curcumin on voltage-dependent K^+ (kV) current in rabbit coronary arterial smooth muscle cells. The superimposed kV current was elicited by 600 ms step depolarizing pulses from −60 to +60 in steps of 10 mV at a holding potential of −60 mV under control (A) and in the presence of 3 μM curcumin (B), respectively. (C) The current–voltage (I–V) relationship at peak kV current in the absence (○) and presence (●) of 3 μM curcumin. $n = 6$. $^*P < 0.05$. (D) I–V relationship at steady-state kV current in the absence (○) and presence (●) of 3 μM curcumin. Steady-state kV currents were measured at the end of 600 ms pulses. $n = 6$. $^*P < 0.05$. (E) Concentration-dependent curves for the inhibition of kV current by curcumin. representative current traces obtained in the absence and presence of 0.1, 0.3, 1, 3, 10, and 30 μM curcumin. (F) Curcumin-induced inhibition was measured at peak (●) and steady-state (○), and normalized to the current amplitude in the absence of curcumin. kV currents were elicited by 600 ms depolarizing pulses from a holding potential of −60 mV to +60 mV. All $n = 7$.

where I_{max} is the measured maximal current, and I_c represents the nonzero residual current. We eliminated this nonzero residual current from the actual values.

The activation curve was obtained from tail currents elicited by the return potential to −40 mV after depolarizing voltage from −60 to + 60 mV. Activation curves were fitted with the Boltzmann equation:

$$y = 1/\{1 + \exp(-(V - V_{1/2})/k)\},$$

where V is the test potential, $V_{1/2}$ is the voltage at half-maximal conductance, and k is the slope factor.

Steady-state inactivation curves were obtained using a two-pulse voltage protocol; currents were measured with a test potential to +40 mV during 600 ms, and 7 s preconditioning pulses were varied from −80 to + 30 mV (10 mV increments) in the absence and presence of drugs. The steady-state inactivation data were fitted with another Boltzmann equation as below:

$$y = 1/\{1 + \exp((V - V_{1/2})/k)\},$$

where V is the test potential, $V_{1/2}$ is the potential at the half-inactivation point, and k represents the slope factor.

The results are expressed as the mean ± standard error. Student's t-test was applied to identify significant differences. A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Inhibition of the Kv channel by curcumin

We examined the effect of curcumin on Kv channels in rabbit coronary arterial smooth muscle cells. Activation of other K^+ channels was effectively excluded by inclusion of a high concentration of EGTA and ATP in the pipette solution to block the Ca^{2+}-activated K^+ and ATP-sensitive K^+ channels, respectively (see Section 2). The Kv current, which was recorded by step depolarizing pulses from −60 to +60 mV with a holding potential of −60 mV, rapidly reached a peak and then rather slowly and partially inactivated due to intrinsic inactivation [10,17]. Exposure to 3 μM curcumin rapidly (within 2 min) inhibited the Kv current throughout the entire voltage range of channel activation (Fig. 1A and B). Fig. 1C and D shows the current–voltage (I–V) relationships of peak and steady-state currents in the absence and presence of curcumin, respectively. The I–V relationships revealed that the inhibition of Kv current by curcumin was more predominant in steady-state current (Fig. 1D) than in peak current (Fig. 1C).

Fig. 1E and F illustrates the concentration-dependent inhibition of the Kv current by various curcumin concentrations. Superimposed traces of the Kv current in the presence of 0.1, 0.3, 1, 3, 10, and 30 μM curcumin are presented in Fig. 1E. Fig. 1F summarizes curcumin-induced inhibition of Kv current at various curcumin concentrations measured at peak and steady-state and normalized by the current in the absence of curcumin. A nonlinear least-squares fit of the Hill equation to the concentration–response data at +60 mV yielded a K_d value of 1.07 ± 0.03 μM and a Hill coefficient of 0.87 ± 0.02 for steady-state inhibition (Fig. 1F).

3.2. Time course of Kv channel inhibition

The rising phase of each current trace was fitted with a single exponential function to evaluate the kinetics of Kv channel inhibition by curcumin. The dominant time constants for activation of the kV current elicited by a 600 ms depolarizing pulse from a holding potential of −60 to +60 mV were 12.67 ± 0.36 ms (n = 7) and 13.02 ± 0.44 ms (n = 7) in the absence and presence of curcumin, respectively. These results suggest that the activation process was not significantly modified by curcumin.

In contrast to the activation process, the decay of Kv current was accelerated by curcumin in a concentration-dependent manner (Fig. 1E). Therefore, we applied double exponential function to obtain two different time constants using Origin 7.0 software (Microcal Software, Inc., Northampton, MA, USA). As described in previous studies, the faster time constant represents the development of a drug-induced blockade of the Kv current (τ_D), and a slower time constant reflects the intrinsic inactivation process in vascular smooth muscle cells [13,18,19]. Fig. 2 shows τ_D at +60 mV plotted against curcumin concentration. The straight line represents the least-squares fit of $1/\tau_D = k_{+1}[D] + k_{-1}$. From this fit, we calculated the association constant (k_{+1}) and dissociation constant (k_{-1}) as 1.35 ± 0.05 $\mu M^{-1}\ s^{-1}$ and 1.47 ± 0.17 s^{-1}, respectively. We derived the theoretical K_d value based on a first-order reaction between the drug and channel as 1.09 μM, which was very close to the K_d value calculated by concentration-dependent curve (Fig. 1F).

3.3. Effect of curcumin on steady-state activation and inactivation of Kv channels

We found that the inhibitory effect of curcumin was due to a shift in the activation and inactivation curves. The activation curve was constructed using the tail current elicited by returning the potential to −40 mV in the absence and presence of curcumin, and the data were fitted to the Boltzmann function. As shown in Fig. 3A, application of 3 μM curcumin did not alter the steady-state activation curve. The half-maximal activation potential ($V_{1/2}$) and slope value (k) were −11.64 ± 0.66 mV and 8.71 ± 0.44, respectively, under control conditions and −11.71 ± 0.58 mV and 9.07 ± 0.43, respectively, in the presence of curcumin.

The steady-state inactivation of Kv current was also tested in the absence and presence of curcumin using the two-pulse protocol. The inactivation curve was fitted to another Boltzmann function. As shown in Fig. 3B, the steady-state inactivation curve was not affected by curcumin. The half-maximal activation potential ($V_{1/2}$) and slope value (k) were −33.53 ± 0.72 mV and 5.60 ± 0.34, respectively, under control conditions and −35.08 ± 0.61 mV and

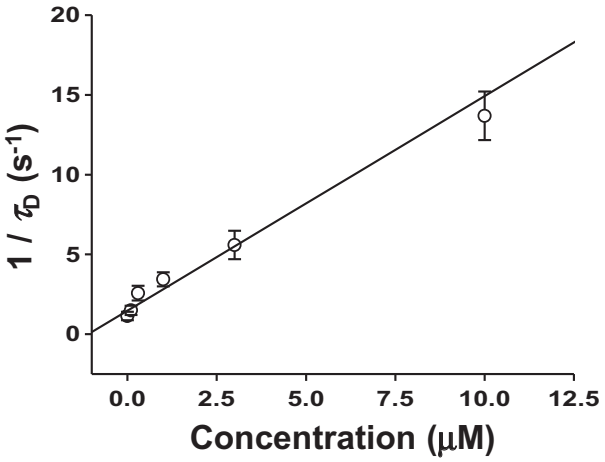

Fig. 2. Time constant of inhibition as a function of various drug concentrations. The apparent decay time constants (τ_D) were estimated by single (control) or double (in the presence of curcumin) exponential functions using falling current traces in Fig. 1E. The reciprocals of τ_D obtained were plotted against various curcumin concentration at +60 mV (n = 4). The straight line represents a least-squares fit of the data to the relationship: $1/\tau_D = k_{+1}[D] + k_{-1}$. k_{+1} and k_{-1} values were calculated by the slope and intercept value of the fitted line.

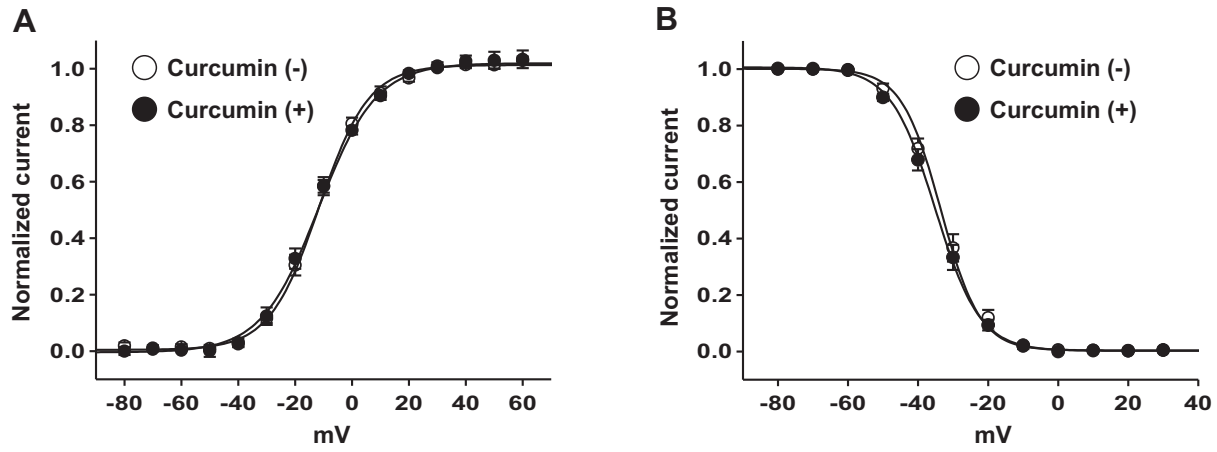

Fig. 3. Influence of curcumin on the steady-state activation and inactivation curves. (A) Steady-state activation curve in the absence (○) and presence (●) of curcumin. $n = 5$. (B) Steady-state inactivation curve in the absence (○) and presence (●) of curcumin. $n = 6$. Curves were fitted to the Boltzmann equation and represented as smooth lines.

6.36 ± 0.24, respectively, in the presence of curcumin. The lack of an effect of curcumin on the steady-state activation and inactivation curves suggests that it interacts with the Kv channel in an open state rather than an inactivated state.

3.4. Use-dependent inhibition of Kv channels by curcumin

To evaluate the use-dependent inhibition of Kv channels by curcumin, we applied train pulses to the Kv current at frequencies of 1

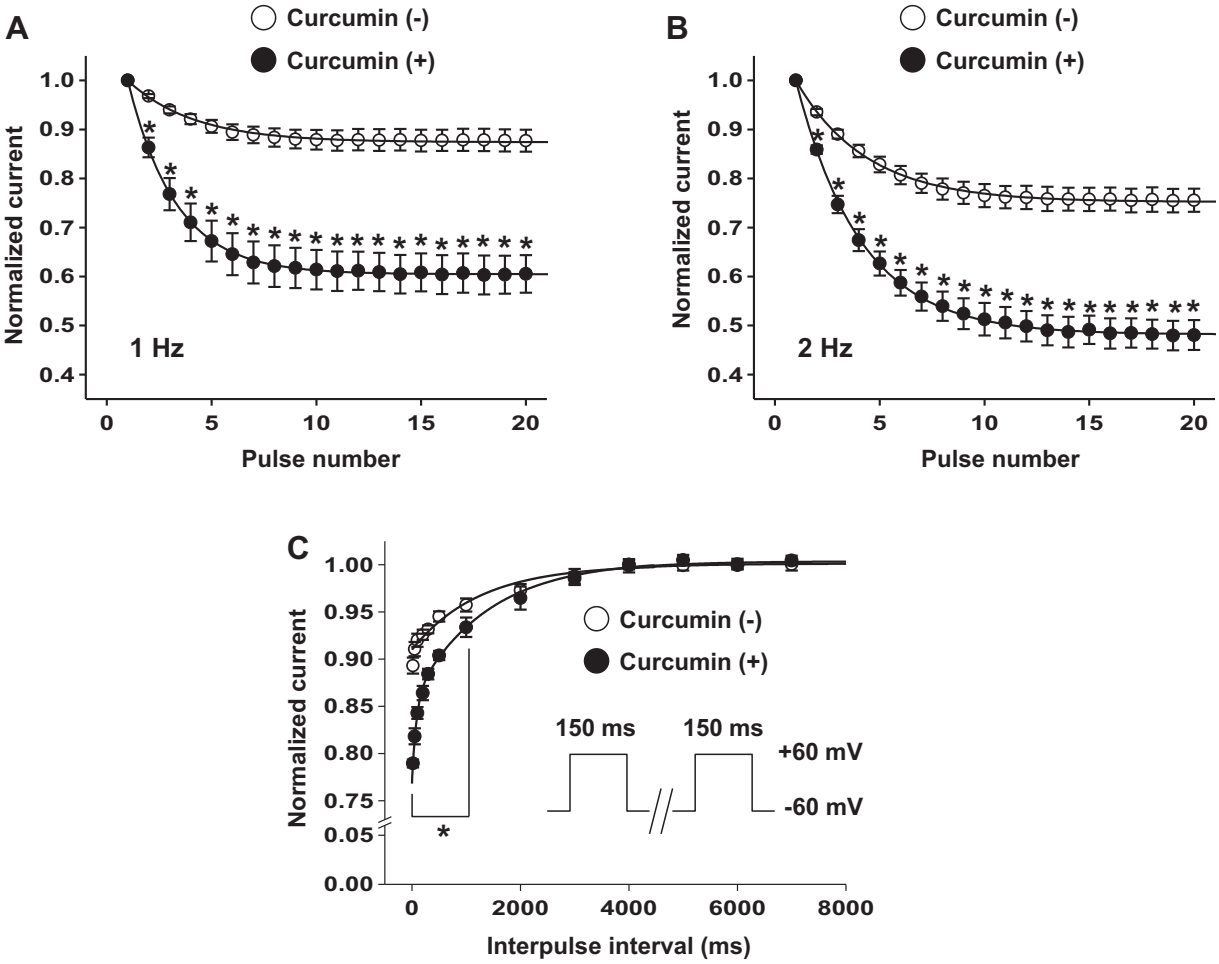

Fig. 4. Use-dependent inhibition of kV currents by curcumin. Twenty repetitive 150 ms +60 mV depolarizing pulses were applied at frequencies of 1 Hz (A) and 2 Hz (B) in the absence (○) and presence (●) of 3 μM curcumin. The peak current amplitude at each pulse was normalized to the peak current amplitude at the first pulse. All $n = 5$. $^*P < 0.05$. (C) Effect of curcumin on recovery kinetics of kV channels from inactivation. The recovery time constant was measured by the double-pulse protocol as described in the inset. The peak current evoked by the second pulse was normalized to the peak current elicited by the identical first pre-pulse and plotted as a function of various pulse intervals from 20 to 7000 ms. The solid line represents the recovery kinetics of kV current obtained in the absence (○) and presence (●) of 3 μM curcumin. $n = 6$. $^*P < 0.05$.

and 2 Hz in the absence and presence of curcumin. Under the control condition, applying 20 repeated depolarizing pulses reduced the Kv current of both 1 Hz (12%) and 2 Hz (25%) stimulation (Fig. 4A and B). However, the peak amplitude of the Kv current decreased gradually by 39% at 1 Hz (Fig. 4A) and 52% at 2 Hz in the presence of curcumin (Fig. 4B). These results strongly suggest that curcumin-induced inhibition of the Kv channel is frequency (use)-dependent.

In agreement with this prediction, we examined the Kv current recovery kinetics in the absence and presence of curcumin. Recovery time from inactivation was measured using a double-pulse protocol as described in Fig. 4C (inset). The interval duration was varied from 20 to 7000 ms. The representative curves for recovery from inactivation in the absence and presence of curcumin fit the single exponential function well. As shown in Fig. 4C, 3 μM curcumin reduced the recovery time, with recovery time constants of 606.51 ± 38.39 ms under control condition and 763.44 ± 25.73 ms in the presence of curcumin. The slower recovery time constant also provided the evidence for the use-dependent blockade of the Kv current by curcumin.

4. Discussion

In the present study, we investigated the effect of curcumin on the Kv channel in rabbit coronary arterial smooth muscle cells. Our major findings were that curcumin inhibited Kv channels in an open state, time- and use-dependent manner. Additionally, the steady-state activation and inactivation curves of the Kv channel were not affected by curcumin.

Several lines of evidence suggest that the inhibitory effect of curcumin on the Kv channel is likely due to an interaction with the channel open state. First, the time course of Kv current was accelerated by curcumin in a dose-dependent manner; therefore, curcumin only slightly reduced peak Kv current amplitude rather than steady-state amplitude at the onset of depolarizing pulses (Figs. 1 and 2). Second, curcumin did not shift the steady-state activation and inactivation curves, suggesting that it interacts with the Kv channel in an open state rather than an inactivated state (Fig. 3). Third, the action of curcumin blocking the Kv channel was use-dependent (Fig. 4). Therefore, the inhibitory effect of curcumin was enhanced by higher rates of Kv channel activation (open state). Furthermore, we could not address the detailed binding mechanisms, as the inhibitory effect of curcumin occurred rapidly (within 2 min); thus, curcumin may inhibit Kv current by acting directly on Kv channels.

As described in many studies, curcumin possesses many therapeutic properties including antioxidant, antiviral, antifungal, antibacterial, anti-inflammatory, and anticancer activities. However, recent studies have shown that curcumin affects several K^+ channels. Curcumin inhibits the human ether-a-go-go related gene (hERG) potassium channel stably expressed in HEK293 cells with an IC_{50} value of 5.55 μM [20] and in the infant acute monocytic leukemia cell line with an IC_{50} value of 1–2 μM [21]. Curcumin also inhibits bTREK-1 K^+ channels with an IC_{50} value of 0.93 μM [22] and inhibits the Kv1.4 channels with an IC_{50} value of 4.4 μM [23] expressed in bovine adrenal zona fasciculate cells. Besides K^+ channels, several other ion channels are also affected by curcumin. For example, curcumin inhibits the transient receptor potential vanilloid 1 (TRPV1) expressed in HEK 293 cells, therefore, inhibits TRPV1-mediated pain and thermal sensation [24]. Furthermore, Ca^{2+}-release-activated Ca^{2+} (CRAC) channels in Jurkat-T cells [25], Ca(v)3.2 channels in adrenal zona fasciculate cells [26], and IP_3 receptors in porcine cerebellar microsomes [27] are also inhibited by curcumin. In the present study, we revealed for the first time the inhibitory effect of curcumin on Kv channels recorded from freshly isolated coronary arterial smooth muscle cells. Taken together, these findings indicated that the side effects on ion channels should be considered when using curcumin in functional ion channel studies.

The Kv channel expressed in vascular smooth muscle plays an important role in regulating the resting membrane potential thereby the resting tone in some arteries. Additionally, Kv channels are involved in the regulation of agonist-induced vascular tone by activating or inhibiting protein kinases [10]. Several studies have reported that pathological conditions reduce vascular Kv channel function [12]. Thus, reversed expression of the Kv channel has been recognized as a therapeutic target to overcome vascular diseases. Considering the physiological importance of the Kv channel expressed in arterial smooth muscle, it is essential to elucidate the unexpected actions of curcumin on vascular Kv channels for proper interpretations of experimental data obtained using this substance. In fact, many studies, including our own, have reported that several chemicals affect the vascular Kv channels besides their own function [28]. Therefore, caution is required when using these chemicals, including curcumin to study vascular Kv channels.

During the last half century, intensive studies on the biological effects of curcumin have revealed that curcumin exhibits numerous beneficial effects for various diseases. In a phase one clinical trial of curcumin, amounts up to 8000 mg/day did not show harmful effect to humans. However, the peak serum concentration of curcumin after taking 8000 mg increased to 1.77 μM [29], a value higher than our measured K_d (1.07 μM) for inhibiting vascular Kv current. Therefore, ingesting a higher concentration of curcumin could be harmful to the vascular Kv channel. For this reason, it is good to consume the appropriate of curcumin for its beneficial effects.

In the present study, we found for the first time that curcumin inhibited the Kv channels isolated from rabbit coronary arterial cells in a state-, time-, and use-dependent manner. However, more detailed studies on the mechanism of the interaction between curcumin and Kv channels are required.

Acknowledgments

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