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Clinically Relevant Concentrations of Propofol Have No Effect on Adenosine Triphosphate–sensitive Potassium Channels in Rat Ventricular Myocytes

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Background: **Activation of adenosine triphosphate–sensitive potassium (K_{ATP}) channels produces cardioprotective effects during ischemia. Because propofol is often used in patients who have coronary artery disease undergoing a wide variety of surgical procedures, it is important to evaluate the direct effects of propofol on K_{ATP} channel activities in ventricular myocardium during ischemia.**

Methods: **The effects of propofol (0.4–60.1 μg/ml) on both sarcolemmal and mitochondrial K_{ATP} channel activities were investigated in single, quiescent rat ventricular myocytes. Membrane currents were recorded using cell-attached and inside-out patch clamp configurations. Flavoprotein fluorescence was measured to evaluate mitochondrial oxidation mediated by mitochondrial K_{ATP} channels.**

Results: **In the cell-attached configuration, open probability of K_{ATP} channels was reduced by propofol in a concentration-dependent manner (EC_{50} = 14.2 μg/ml). In the inside-out configurations, propofol inhibited K_{ATP} channel activities without changing the single-channel conductance (EC_{50} = 11.4 μg/ml). Propofol reduced mitochondrial oxidation in a concentration-dependent manner with an EC_{50} of 14.6 μg/ml.**

Conclusions: **Propofol had no effect on the sarcolemmal K_{ATP} channel activities in patch clamp configurations and the mitochondrial flavoprotein fluorescence induced by diazoxide at clinically relevant concentrations (< 2 μM), whereas it significantly inhibited both K_{ATP} channel activities at very high, nonclinical concentrations (> 5.6 μg/ml; 31 μM).**

PROPOFOL is widely used in cardiac surgery and intensive care units. Coetzee[1] reported that propofol failed to provide a functional benefit in reperfused pig myocardium, whereas accumulating evidence suggests that propofol provides cardioprotection against ischemia–reperfusion injury. It has been shown that propofol acts as an antioxidant by reacting with free radicals,[2] attenuates lipid peroxidation,[3] and inhibits whole cell L-type Ca^{2+} currents.[4,5] In addition, Park *et al.*[6] showed that propofol has a direct endothelium-dependent vasodilatory effect in rat distal coronary arteries. Mathur *et al.*[7] also showed that propofol attenuates the onset and magnitude of ischemic contracture in isolated rat hearts.

Cardiac myocytes have adenosine triphosphate–sensitive potassium (K_{ATP}) channels both in the sarcolemmal and inner mitochondrial membranes.[8,9] The activation of K_{ATP} channels may be an endogenous mechanism that protects against cardiac damage during myocardial ischemia. In the experiments of Park *et al.*[6] and Mathur *et al.*,[7] glibenclamide[10] had no effect on the cardioprotective effects of propofol. These results suggest that K_{ATP} channels might not be involved in the cardioprotection by propofol. However, we are unaware of any reported study investigating the direct effects of propofol on K_{ATP} channel activity in isolated ventricular myocardium during simulated ischemia. We measured both sarcolemmal K_{ATP} currents and mitochondrial oxidation mediated by mitochondrial K_{ATP} channels in isolated rat ventricular myocytes.

Materials and Methods

Preparation of Cardiac Ventricular Myocytes

This study was approved by the Animal Investigation Committee of Tokushima University (Tokushima, Japan) and was conducted according to the animal use guidelines of the American Physiologic Society (Bethesda, MD).

Details of the experimental design were similar to those of our previous studies.[10,11] Sixty-five male Wistar rats (weight, 250–300 g) were anesthetized with ether, and 1.0 IU/g heparin was injected intraperitoneally 30 min before surgery. Myocytes were obtained enzymatically (0.2 mg/ml collagenase and 0.05 mg/ml pronase) with a Langendorff apparatus. All cells used in this experiment were rod-shaped and striated.

Propofol Delivery and Determination of Concentrations

Because propofol is highly lipophilic and might be absorbed to plastic syringe and vinyl chloride tubing, we measured actual propofol concentrations in the superfusate. Propofol, dissolved in dimethyl sulfoxide (final concentration < 0.1%), was diluted in superfusate to final five concentrations (1, 3, 10, 30, and 100 μg/ml) and directly applied to myocytes in the glass-bottom plastic cell bath (2-ml volume) at a rate of 2–2.5 ml/min using a plastic syringe (50-ml volume), vinyl chloride tubing (0.8-mm ID; 50-cm length), and syringe pump (Terumo

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STC-525; Tokyo, Japan); preliminary studies showed that dimethyl sulfoxide had no significant effects on electrophysiologic and flavoprotein fluorescence measurements. At the end of each measurement (mostly 3 min after the start of each concentration of propofol), 2-ml samples of superfusate in the cell bath were collected for determination of propofol concentrations by high-performance liquid chromatography (EICOM, Kyoto, Japan) with electrochemical detector.

Electrophysiologic Measurements

Cell-attached and inside-out patch configurations were applied to record the current through single channels *via* patch clamp amplifier, as described by Hamill *et al.*[12] In cell-attached configurations, the bathing solution was composed of the following: 140 mM KCl, 10 mM HEPES, 5.5 mM dextrose, and 0.5 mM EGTA. The pipette solution contained 140 mM KCl, 10 mM HEPES, and 5.5 mM dextrose. For inside-out configurations, the bathing solution (intracellular solution) contained 140 mM KCl, 10 mM HEPES, 5.5 mM dextrose, 1 mM $MgCl_2$, and 0.5 mM EGTA. The pipette solution (extracellular medium) was of the same composition as that used in cell-attached experiments. The pH of all solutions was adjusted to 7.3–7.4 with KOH. Patch pipettes were pulled with an electrode puller (PP-830; Narishige, Tokyo, Japan) and coated with Sylgard. The resistance of pipettes filled with internal solution and immersed in the Tyrode solution was 3–4 MΩ. Experiments were conducted with solution temperatures of 36 ± 0.5°C. Channel currents were recorded with a patch clamp amplifier (CEZ 2200; Nihon Kohden, Tokyo, Japan) and stored in a personal computer (Aptiva; International Business Machine Corporation, Armonk, NY) with an analog-to-digital converter (DigiData 1200; Axon Instruments, Foster, CA). Sampling frequency of single-channel data was 5 KHz with a low-pass filter (1 KHz). pClamp version 7 software (Axon Instruments) was used for data acquisition and analysis. The open probability (NPo) was determined from current amplitude histograms and was calculated as follows:

$$NP_0 = \sum_{n=0}^{N} (n \cdot Pn)$$

where N is the number of channels in the patch and Pn is the integrated channel opening. The NPo of the K_{ATP} channels was determined from recordings lasting longer than 60 s and normalized to the NPo value obtained with 25 μM of 2,4-dinitrophenol[10] alone (relative channel activity) in the cell-attached configuration. In the inside-out configuration, the NPo of the K_{ATP} channels was normalized to the baseline NPo value obtained before propofol at bathing solution without ATP (relative channel activity). Data points obtained were plotted as actual propofol concentrations compared with relative channel activity. The actual propofol concentration needed to induce 50% inhibition of 2,4-dinitrophenol–induced K_{ATP} channel activity (EC_{50}) was calculated as described in our previous study.[11] The Hill coefficient was calculated as described by Ko *et al.*[13]

Flavoprotein Fluorescence Measurements

The mitochondrial redox state was monitored by recording the fluorescence of flavin adenine nucleotide-linked enzymes in mitochondria and served as an index of mitochondrial K_{ATP} channel activity. Myocytes were superfused with bath solution containing 140 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM HEPES (pH adjusted to 7.3–7.4 with NaOH). Experiments were conducted with solution temperature of 27 ± 1°C. Fluorescence was monitored microscopically (Eclipse TS100; Nikon, Tokyo, Japan) with a digital CCD camera (ORCA; Hamamatsu Photonics, Hamamatsu, Japan) from one cell at a time by focusing on individual myocytes. Fluorescence of single cells was excited for 100 ms every 10 s. Excitation of flavoprotein was produced by Xenon arc lamp filtered at 450–490 nm, and reflected to the objective lens (×40) of the microscope by a dichroic mirror centered at 505 nm. Emitted fluorescence passed through the dichroic mirror to a 520-nm path filter was recorded and stored in a computer. The redox signal images were analyzed for average pixel intensities of regions of interest per myocyte by means of an image processing system (Aquacosmos; Hamamatsu Photonics). We assessed the effects of diazoxide[11] alone and in combination with propofol on flavoprotein fluorescence. The change in fluorescence was normalized to the baseline flavoprotein fluorescence value obtained after exposure to 5 μM of 2,4-dinitrophenol at the end of experiments. In each cell, flavoprotein fluorescence was recorded before (diazoxide alone) and with propofol at five different concentrations. The six data points obtained for each cell were plotted as actual propofol concentrations relative to the normalized flavoprotein fluorescence values. The actual propofol concentration needed to induce 50% inhibition of diazoxide-induced flavoprotein oxidation (EC_{50}) was calculated in each cell as described in our previous study.[11] The Hill coefficient was calculated as described by Ko *et al.*[13]

Drugs

Collagenase (Yakult Co., Tokyo, Japan) and pronase (Sigma Chemical Co., St. Louis, MO) were used for enzymatic dissociation. Propofol (2,6-diisopropylphenol; Aldrich Chemical Co., Milwaukee, WI) and diazoxide (Sigma) were dissolved in dimethyl sulfoxide (final concentration < 0.1%) and prepared as stock solutions. 5-Hydroxydecanoic acid[11] was purchased from Biomol Research Laboratories (Plymouth Meeting, PA); 2,4-dinitrophenol (Sigma) and glibenclamide (Sigma) were prepared as stock solutions. All other solutions were made freshly each day.

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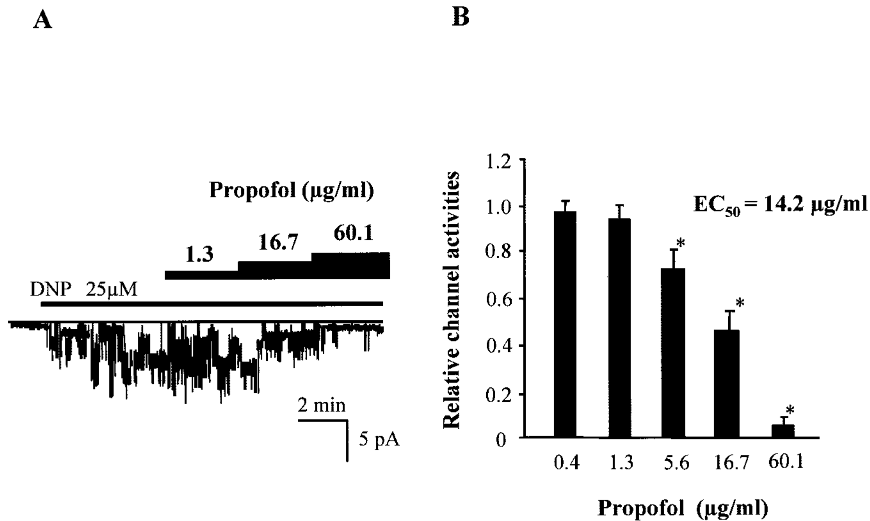

Fig. 1. Effects of propofol on the adenosine triphosphate–sensitive potassium (K_{ATP}) channel activities in the cell-attached configuration. Membrane potentials were clamped at −50 mV. Propofol concentrations presented are the actual concentrations measured in the current study. (*A*) Representative example of the effects of 25 μM 2,4-dinitrophenol (DNP) alone or in combination with propofol on K_{ATP} currents. The periods of drug treatment are marked with horizontal bars. Propofol attenuated 2,4-dinitrophenol–induced K_{ATP} currents in a concentration-dependent manner. (*B*) Concentration-dependent effects of propofol on 2,4-dinitrophenol–induced K_{ATP} channel activities. Each vertical bar constitutes measurements from 15–20 patches (mean ± SD). *$P < 0.05$ *versus* baseline (2,4-dinitrophenol alone).

Statistical Analysis

Data are expressed as mean ± SD. Differences between data sets were evaluated by analysis of variance followed by Scheffé test. $P < 0.05$ was considered significant, and all *P* values were two-tailed.

Results

Propofol Concentrations

Actual propofol concentrations in the superfusate were 0.4 ± 0.1, 1.3 ± 0.2, 5.6 ± 0.4, 16.7 ± 0.6, and 60.1 ± 3.6 μg/ml at 1, 3, 10, 30, and 100 μg/ml, respectively (n = 6).

Effects of Propofol on Adenosine Triphosphate-sensitive Potassium Channels in the Cell-attached Configuration

We studied whether propofol could block K_{ATP} channels from the outside of ventricular myocytes. As shown in figure 1A, K_{ATP} channel activity was inhibited by propofol in a concentration-dependent manner (n = 26). The relations between relative K_{ATP} channel activity and concentrations of propofol is shown in figure 1B. Propofol inhibited K_{ATP} channel activity significantly at actual concentrations of 5.6 μg/ml or greater in the cell-attached configuration. The EC_{50} value was 14.2 μg/ml, and the Hill coefficient was 1.2. A decreased NPo of K_{ATP} channel activity induced by propofol returned toward baseline values almost completely after propofol washout.

Effects of Propofol on Sarcolemmal Adenosine Triphosphate-sensitive Potassium Channels in the Inside-out Configuration

We also studied whether propofol could block K_{ATP} channels directly from the cytosolic side of ventricular myocytes. Because K_{ATP} channels are inhibited by intracellular ATP, we studied the activities of these channels in the absence of ATP. When inside-out patches were performed, the channel activities were observed at a holding potential of −50 mV (fig. 2A). These channel activities were blocked by 3 mM of ATP (fig. 3 in reference 10) and 10 μM of glibenclamide. The inhibitory

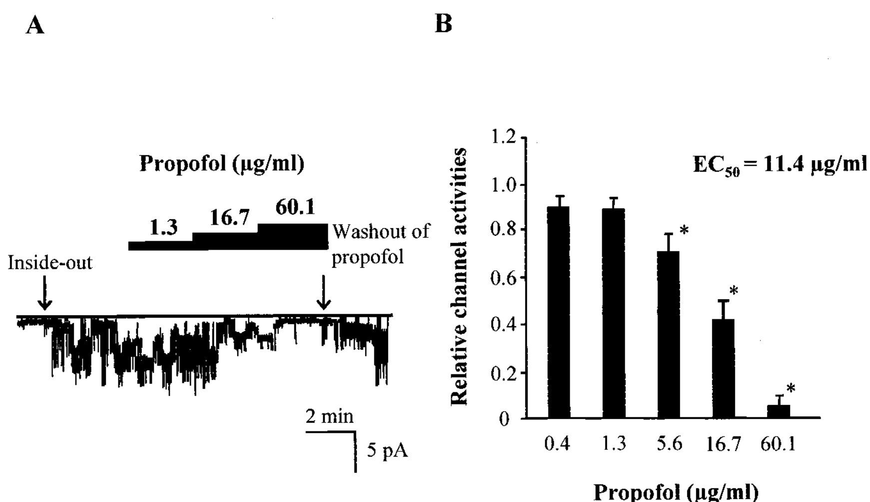

Fig. 2. Effects of propofol on the adenosine triphosphate–sensitive potassium (K_{ATP}) channel activities in the inside-out configuration. Membrane potentials were clamped at −50 mV. Propofol concentrations presented are the actual concentrations measured in the current study. (*A*) Representative example of the K_{ATP} currents obtained before (baseline) and after the application of propofol. The periods of drug treatment are marked with horizontal bars. Propofol attenuated K_{ATP} currents in a concentration-dependent manner. (*B*) Concentration-dependent effects of propofol on K_{ATP} channel activities. Each vertical bar constitutes measurements from 14–20 patches (mean ± SD). *$P < 0.05$ *versus* baseline (before propofol).

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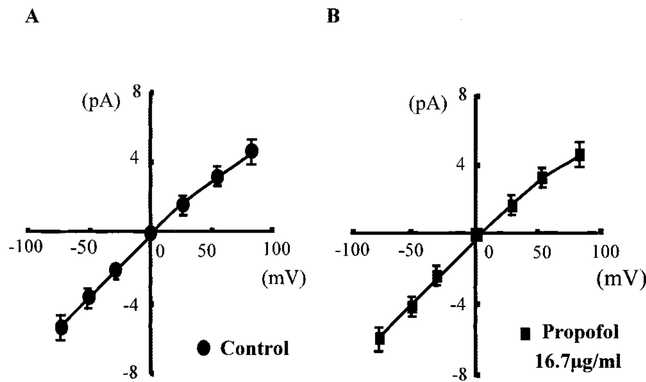

Fig. 3. The current–voltage relation for adenosine triphosphate–sensitive potassium channels during (*A*) control conditions and (*B*) after the application of propofol (16.7 µg/ml). The propofol concentration presented is the actual concentration measured in the current study. The curve is linear in the negative membrane potential range but shows rectification with depolarization beyond zero. Each data point (vertical bars) is presented as the mean ± SD.

effect of propofol on K_{ATP} channel activities is shown in figure 2A; channel activities are shown to be reactivated after washout of propofol. The open probabilities were suppressed by increased concentrations of propofol (n = 24). As shown in figure 2B, propofol inhibited relative K_{ATP} channel activity significantly at actual concentrations of 5.6 µg/ml or greater in the inside-out configurations. The EC_{50} value was 11.4 µg/ml, and the Hill coefficient was 1.06. The average recovery of the K_{ATP} channel activity after propofol washout was 93 ± 7% of the NPo obtained before application of propofol.

The current–voltage relation observed from 20 patches before and after application of propofol (16.7 µg/ml) is shown in figure 3. The current–voltage curves before and after the application of propofol were linear in the negative potential range, with single channel conductances of 73 ± 2 and 75 ± 1 pS before and after 16.7 µg/ml propofol, respectively. There was no significant difference between the nontreated and the propofol-treated series, suggesting that propofol does not change the K_{ATP} channel conductances in the inside-out configuration.

Effects of Propofol on Mitochondrial Adenosine Triphosphate-sensitive Potassium Channels

A representative example of the time course of flavoprotein oxidation in cells exposed to diazoxide alone and in combination with propofol is shown in figure 4A. In the presence of 25 µM diazoxide, subsequent exposure to propofol reduced the diazoxide-induced oxidation of the flavoproteins in a concentration-dependent manner (fig. 4A). After washout of propofol, the diazoxide-induced oxidation was reproducible. The relations between propofol concentration and diazoxide-induced flavoprotein oxidation (n = 12), which was normalized to the flavoprotein fluorescence value obtained with 5 µM of 2,4-dinitrophenol at the end of the experiments, is shown in figure 4B. Propofol inhibited flavoprotein oxidation significantly at actual concentrations of 5.6 µg/ml and greater. The EC_{50} value was 14.6 ± 4.7 µg/ml, and the Hill coefficient was 0.28.

Discussion

The principal findings of the current study are that propofol has no effect on K_{ATP} channel activities at clinically relevant concentrations (< 2 µM), while it inhibits both sarcolemmal K_{ATP} channel activity without changing the single-channel conductance and diazoxide-induced flavoprotein fluorescence, which correlates with mitochondrial oxidation and depolarization, at very high, nonclinical concentrations (> 5.6 µg/ml; 31 µM).

Propofol is widely used with fentanyl to achieve safe anesthesia in patients who have coronary artery disease and are undergoing a wide variety of surgical procedures. It is also used for sedation in the intensive care units after coronary artery surgery. Coetzee *et al.*[1] reported that propofol (2 or 6 µg/ml; 11 or 34 µM) failed

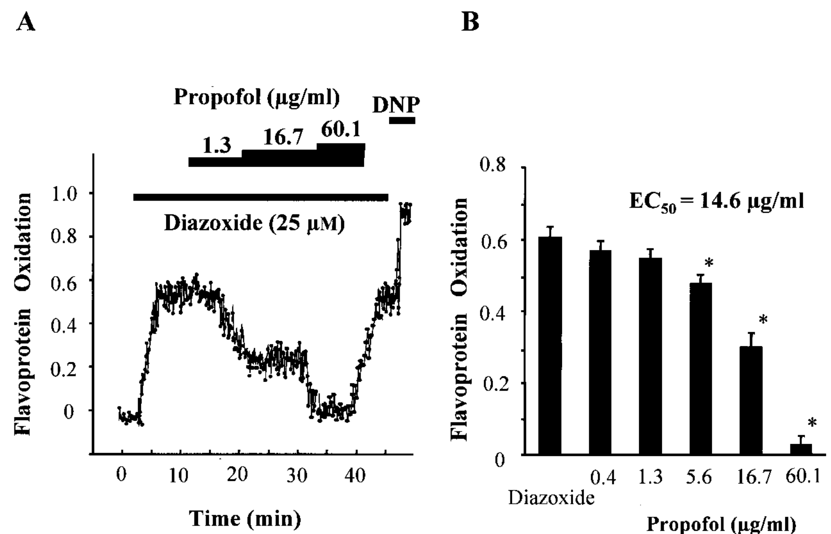

Fig. 4. Effects of propofol on diazoxide (25 µM)-induced flavoprotein oxidation. Propofol concentrations presented are the actual concentrations measured in the current study. (*A*) Representative example of the effects of diazoxide alone or in combination with propofol on flavoprotein fluorescence. The periods of drug treatment are marked with horizontal bars. Propofol attenuated diazoxide-induced flavoprotein oxidation in a concentration-dependent manner. The redox signal was normalized to the fluorescence value obtained with 5 µM of 2,4-dinitrophenol (DNP) at the end of experiments. (*B*) Concentration-dependent effects of propofol on diazoxide-induced flavoprotein oxidation. Each vertical bar constitutes measurements from 12 single ventricular myocytes (mean ± SD). *P < 0.05 *versus* diazoxide alone.

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to provide functional benefit on the reperfused pig myocardium after left anterior descending coronary artery occlusion. However, accumulating evidence suggests that propofol provides cardioprotection in the presence of ischemia–reperfusion injury.[2–7,14–16] It has been revealed that propofol (1–10 μM) acts as an antioxidant by reacting with free radicals.[2] Moreover, there is clinical evidence that propofol in therapeutic doses attenuates ischemia–reperfusion-induced lipid peroxidation in patients undergoing elective peripheral surgery using a tourniquet.[14] Recent study has also demonstrated in isolated rat heart that propofol (25 or 50 μM) attenuates the mechanical derangement and lipid peroxidation induced by exogenously applied hydrogen peroxide and that it preserves ATP content.[3] Propofol (6–560 μM) has also been shown to inhibit L-type Ca^{2+} currents at supratherapeutic concentrations in isolated guinea pig and rat ventricular myocytes[4,5] and decrease transsarcolemmal Ca^{2+} influx at concentrations of 30 μM or greater in isolated ferret ventricular myocytes.[15] These effects are of potential benefit in reducing the severity of the ischemia–reperfusion injury because lipid peroxidation and Ca^{2+} overload are associated with myocardial stunning and ischemic reperfusion injury.[17,18] In addition, 100 or 35 μM propofol has been reported to delay or attenuate the onset and magnitude of ischemic injury in isolated ischemia-reperfused rat hearts.[7,16] Propofol has been shown to have an endothelium-dependent vasodilatory effect on subepicardial coronary arteries in rats.[6]

In the heart, K_{ATP} channels open to induce several protective responses during ischemia and reperfusion.[8] It has been thought that activation of sarcolemmal K_{ATP} channels protects the ischemic myocardium by shortening the action potential duration.[19] As another possible mechanism of cardioprotective action of K_{ATP} channels, it was recently suggested that mitochondrial rather than sarcolemmal K_{ATP} channels might play an important role in the protection of myocardium during ischemia.[20–22] However, the importance of sarcolemmal *versus* mitochondrial K_{ATP} channel opening during myocardial ischemia is still a matter of controversy. Thus, in the current study, we evaluated and compared the effects of propofol on sarcolemmal and mitochondrial K_{ATP} channel activities. In the experiments of Park *et al.*[6] and Mathur *et al.*,[7] demonstrating the cardioprotective effects of propofol, 1 or 10 μM glibenclamide had no effect on the cardioprotection associated with propofol treatment. These results suggest that K_{ATP} channels are not involved in the cardioprotective effects of propofol. In the current study, propofol inhibited sarcolemmal K_{ATP} currents and reduced diazoxide-induced flavoprotein fluorescence significantly at greater than 5.6 μg/ml (31 μM). Plasma concentrations of propofol necessary to prevent autonomic responses in humans are 4 μg/ml (22 μM) for major surgery and 3 μg/ml (17 μM) for nonmajor surgery.[23] In another report, the propofol blood concentrations at which 50% of patients do not respond to verbal command and to skin incision are 3.3 μg/ml (18 μM) and 15.2 μg/ml (85 μM), respectively.[24] After an intravenous induction dose, the peak plasma concentration of propofol is as high as 44 μM, whereas plasma concentrations typically range from 10 to 20 μM for maintenance of anesthesia.[16] In addition, because protein binding of propofol exceeds 95%, free fractions of propofol are less than 2 μM.[16] Thus, the concentrations of propofol that significantly inhibited K_{ATP} channel activities in the current study are very high, nonclinical concentrations, suggesting that propofol has no effect on K_{ATP} channels at clinically relevant concentrations (< 2 μM).

Our study had several limitations. First, in our cell-attached configurations, we used 2,4-dinitrophenol to simulate ischemia. Because 2,4-dinitrophenol inhibits mitochondrial ATP synthesis, we were able to observe marked opening of K_{ATP} channels. However, activation of K_{ATP} channels by 2,4-dinitrophenol may differ from activation by ischemia or hypoxia.[13] Second, the high extracellular potassium concentration (140 mM) and resulting membrane depolarization in the patch clamp experiment might have altered the behavior of the channel and the sensitivity of propofol.[13] Third, we studied the effects of propofol in isolated rat ventricular myocytes. The effects of propofol on rat myocardium may be different from those on human myocardium. Therefore, we should be careful in extending the current results to the human heart.

In summary, propofol had no effect on the sarcolemmal K_{ATP} channel activities in patch clamp configurations and the mitochondrial flavoprotein fluorescence induced by diazoxide at clinically relevant concentrations (< 2 μM), whereas it significantly inhibited both K_{ATP} channel activities at very high, nonclinical concentrations (> 5.6 μg/ml; 31 μM).

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