Effect of Propofol on Hypotonic Swelling–induced Membrane Depolarization in Human Coronary Artery Smooth Muscle Cells

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Background: Stretch (mechanical stress)–induced membrane depolarization of smooth muscle may contribute to basal vascular tone and myogenic control. Propofol induces vasodilation and inhibits myogenic control. Hypotonic swelling was used as a model of mechanical stress. The authors investigated the effects of propofol and 5-nitro-2-(3-phenylpropylamino)benzoic acid or propofol.

Methods: A voltage-sensitive fluorescent dye, bis-(1,3-diethylthiobarbiturate)trimethine oxonol, was used to assess relative changes in membrane potential semiquantitatively. The cells were continuously perfused with Earle’s balanced salt solution containing 200 nM bis-(1,3-diethylthiobarbiturate)trimethine oxonol and exposed sequentially to isotonic and hypotonic medium. In a second series of experiments, the cells were exposed to hypotonic media in the presence and absence of 5-nitro-2-(3-phenylpropylamino)benzoic acid or propofol.

Results: The relative fluorescence values at 10, 20, and 30% hypotonicity were 147 ± 29, 214 ± 74, and 335 ± 102% of baseline, respectively. The changes were all significantly different from the isotonic time control group. In the presence of 200 µM 5-nitro-2-(3-phenylpropylamino)benzoic acid or 0.1, 1, 10, or 100 µg/mL propofol, the relative fluorescence values at 30% hypotonicity were 87 ± 17, 194 ± 27, 160 ± 18, 130 ± 18, and 84 ± 15%, respectively. These changes were significantly less than the 30% for the hypotonic control (246 ± 23%).

Conclusion: These results suggest that volume-sensitive chloride channels and nonselective cation channels may participate in hypotonicity-induced membrane depolarization and that propofol inhibits hypotonicity-induced membrane depolarization in coronary artery smooth muscle.

STRETCH-INDUCED smooth muscle contraction is important for local regulation of blood flow as well as generation of basal vascular tone.1,2 Many studies have indicated the importance of membrane depolarization as a principle mechanism by which stretch or pressure elicits smooth muscle contraction.3–5 Membrane potential is a key variable that not only regulates Ca2+ influx, but also influences release of Ca2+ from internal stores and Ca2+-sensitivity of the contractile apparatus.5,6 Possible candidates for mechanisms of stretch-induced membrane depolarization are activation of volume-sensitive chloride channels (VSCCs)7 and nonselective cation channels.2,4 These channels are also candidates for mechanisms of swelling-induced membrane depolarization.4,8–11 Hypotonic stress is a convenient, reproducible, reversible, and widely used model of mechanical stimulation.12 We have used hypotonic stress as an in vitro model of mechanical stress.

Propofol, 2,6-diisopropyl phenol, is a potent, short-acting, intravenous anesthetic agent that causes endothelium-independent vasodilatation13,14 as well as attenuation of myogenic responses.15 We hypothesized that propofol may induce its vascular effects by inhibiting the stretch-induced membrane depolarization. Although myogenic tone can be modulated by a variety of endothelial and neurohumoral factors,16 the myogenic response occurs independently of the endothelium and perivascular nerves and is therefore an inherent property of vascular smooth muscle cells.1,5,16 In this study, we investigated the effects of propofol and 5-nitro-2-(3-phenylpropylamino)benzoic acid (NPPB), a chloride channel and nonselective cation channel blocker,4,17 on hypotonic swelling-induced membrane depolarization in cultured human coronary artery smooth muscle cells.

Materials and Methods

Cell Culture

Human coronary artery smooth muscle cells, which were certified to be a virus-free and a pure cell population on the basis of staining patterns for α-actin, were obtained from Cell Application, Inc. (San Diego, CA). The cells were routinely maintained in cell culture medium (Cell Application, Inc.) at 37°C in a humidified atmosphere containing 5% CO2. The third to sixth passage cultures were then seeded onto glass-bottom culture dishes (MatTek Corp., Ashford, MA) and allowed to reach subconfluence in 5–7 days.

Solutions

Earle’s balanced salt solution (measured osmolality, 285 ± 1 mOsm/kg H2O) was used. The composition of Earle’s balanced salt solution was as follows: 116.4 mM
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NaCl, 5.37 mM KCl, 1.8 mM CaCl₂, 0.81 mM MgSO₄, 26.2 mM NaHCO₃, 1.02 mM NaH₂PO₄, and 5.55 mM D-glucose. The pH of the Earle’s balanced salt solution was adjusted to 7.3 by bubbling the solution with 5% CO₂ and 95% O₂. Hypsometric solutions were obtained by diluting the Earle’s balanced salt solutions by 10, 20, or 30% with distilled water. The measured osmolalities of the diluted solutions were 257 ± 2, 229 ± 3, and 201 ± 3 mOsm/kg H₂O, respectively. The pH of the medium diluted by 30% with distilled water was approximately 7.4–7.45. Osmolality was measured by means of the freezing point technique (Osmostat OM-6040; Kyoto Diichi Kagaku, Kyoto, Japan). NPPB, propofol, and a voltage-sensitive fluorescent dye, bis(1,3-diethylthiobarbiturate)trimethine oxonol (bis-oxonol), were dissolved in solutions from stock solutions in dimethyl sulfoxide (final solvent concentration, 0.001–0.1%).

Cell Perfusion System

A cell perfusion system was designed to measure cell fluorescence in response to rapid solution changes. The system uses an inverted epifluorescence microscope (Eclipse TS100; Nikon, Tokyo, Japan). Solutions were infused and aspirated through stainless steel tubing into the glass bottom of a culture dish. The exchange volume of the glass bottom was approximately 150 μl. Cell perfusion solutions were maintained at constant temperature by means of enclosure of the perfusion tubing in a circulating water jacket.

Measurement of Membrane Potential

We used bis-oxonol to assess relative changes in membrane potential of single (subconfluent) cells semiquantitatively. This dye has been used previously to determine membrane potential of various cell types, including smooth muscle cells. When the cell membrane is depolarized, the dye partitions into the membrane, leading to an increase in the measured fluorescence. The cells were continuously superfused with Earle’s balanced salt solution containing 200 mM bis-oxonol at 36–37°C. Excitation of bis-oxonol was obtained from a Xenon lamp (50 W; Nikon) filtered at 450–490 nm and reflected to the microscope objective (×10, CFI Plan Fluor ELWD 10 × C; Nikon) by a dichroic mirror centered at 505 nm. Photobleaching was minimized using a ×10 microscope objective and neutral density filters (2.5–3.5 optical density). Cell fluorescence was collected by the objective, passed to a 520-nm-long path filter, and directed to a cooled digital black-and-white charge-coupled device camera (ORCA; Hamamatsu Photonics, Hamamatsu, Japan). Fluorescence images were acquired at 60-s intervals by means of a computer-controlled shutter (Filter Exchanger; Hamamatsu Photonics) and an image-processing system (AQUACOSMOS; Hamamatsu Photonics). Fluorescence images were analyzed for average pixel intensities of regions of interest. Each region of interest contained one to three cells. The regions of interest were selected manually with a maximum of six regions of interest per field. The responses of all selected cells were averaged to yield a response per dish. Background values (windows of identical area placed beside the cells) were always subtracted. When bis-oxonol fluorescence attained equilibrium (approximately 30 min), the effects of the pharmacologic agents and tonicity on membrane potential were determined. Bis-oxonol fluorescence was measured relative to the value at approximately 30 min after initiation of superfusion (baseline; in percent).

Experimental Protocol

To investigate the effects of hypotonicity on membrane potential, 12 dishes were randomly assigned to two different experimental protocols: superfusion with isotonic solution throughout the experiment and sequential exposure to 10, 20, and 30% hypotonic and isotonic medium (n = 6/group). To investigate the effects of propofol and NPPB on hypotonicity-induced membrane depolarization, 36 dishes treated with 30% hypotonicity were randomly assigned to five different propofol concentrations ranging from 0 to 100 μg/ml and 200 μM NPPB (n = 6/group).

Dilution with distilled water produces various changes. To clarify the effects of pH change on hypotonicity-induced membrane depolarization, we performed another study (n = 6) by keeping the pH at 7.35 throughout the study by bubbling the solutions with 5% CO₂ and 95% O₂. To clarify the effects of 30% low potassium concentration on hypotonicity-induced membrane depolarization, we performed an additional study (n = 6) by reducing osmolality but maintaining a normal potassium concentration and by keeping the pH at 7.35 throughout the study. To clarify the effects of 30% low sodium concentration itself on membrane potential, we performed an additional study (n = 6) by reducing the sodium concentration but maintaining a normal osmolality by means of addition of sucrose and by keeping pH at 7.35 throughout the study. The sequence of measurement was altered.

The results of the second series of experiments suggested that propofol and NPPB have different mechanisms of action on hypotonicity-induced membrane depolarization. To investigate the interaction of propofol and NPPB on hypotonicity-induced membrane depolarization, we performed an additional study. Twenty-four dishes treated with 30% hypotonicity were assigned to four different experimental protocols of drug administration: hypotonic control, 50 μM NPPB, 1 μg/ml propofol, and 50 μM NPPB plus 1 μg/ml propofol (n = 6/group). All studies were performed by reducing osmolality but maintaining a normal K⁺ concentration and by keeping pH at 7.35 throughout the study.
Biological phenomenon 1

Biological phenomenon 2

Biological phenomenon 3

Biological phenomenon 4

Biological phenomenon 5

Biological phenomenon 6

Biological phenomenon 7

Biological phenomenon 8

Biological phenomenon 9

Biological phenomenon 10
were evaluated. \( \bullet \) = hypotonicity, \( \circ \) = isotonic time control.  

FIG. 2. Effects of tonicity on change in relative bis-oxonol fluorescence in human coronary artery smooth muscle cells.  

Effects of Propofol on Membrane Potential  
Results obtained from representative cells are illustrated in figure 4A. In the presence of 0.1, 1, 10, or 100 \( \mu \)g/ml propofol, relative bis-oxonol fluorescence values at 30% hypotonicity were 194 \( \pm \) 27, 160 \( \pm \) 18, 130 \( \pm \) 18, and 84 \( \pm \) 15% respectively. These changes were significantly less than the 30% hypotonic control \( (P < 0.05; \text{fig. 4B}) \). Therefore, hypotonicity-induced membrane depolarization was significantly inhibited by propofol in a dose-dependent manner. Cessation of 100-\( \mu \)g/ml propofol infusion resulted in an increase in fluorescence, suggesting the partial reversibility of the suppression. When the tonicity returned to baseline, the fluorescence intensity also returned to baseline.

Effects of pH Change on Hypotonicity-induced Membrane Depolarization  
Relative bis-oxonol fluorescence at 30% hypotonicity in the additional study (229 \( \pm \) 33%) was not significantly different from the percent change in second study (246 \( \pm \) 23%).

Effects of Low Potassium Concentration on Hypotonicity-induced Membrane Depolarization  
Relative bis-oxonol fluorescence at 30% hypotonicity in the normal potassium concentration group (240 \( \pm \) 41%) was not significantly different from the percent change in the 30% low potassium concentration group (229 \( \pm \) 33%).

Effects of Low Sodium Concentration Itself on Membrane Potential  
Results obtained from representative cells are illustrated in figure 5A. Relative bis-oxonol fluorescence in the 30% low sodium concentration group (87 \( \pm \) 5%) was significantly lower than that in the normal sodium concentration group (100%) \( (P < 0.05; \text{fig. 5B}) \).

Interaction of Propofol and NPPB on Membrane Potential  
Results obtained from representative cells are illustrated in figure 6A. In the presence of 1 \( \mu \)g/ml propofol, 50 \( \mu \)M NPPB, and 50 \( \mu \)M NPPB plus 1 \( \mu \)g/ml propofol, relative bis-oxonol fluorescence values at 30% hypotonicity were 194 \( \pm \) 27, 160 \( \pm \) 18, 130 \( \pm \) 18, and 84 \( \pm \) 15% respectively. These changes were significantly less than the 30% hypotonic control \( (P < 0.05; \text{fig. 4B}) \). Therefore, hypotonicity-induced membrane depolarization was significantly inhibited by propofol in a dose-dependent manner. Cessation of 100-\( \mu \)g/ml propofol infusion resulted in an increase in fluorescence, suggesting the partial reversibility of the suppression. When the tonicity returned to baseline, the fluorescence intensity also returned to baseline.

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nicity were 169 ± 36, 172 ± 44, and 102 ± 21%, respectively. These changes were significantly less than the 30% hypotonic control (240 ± 41%, P < 0.05; fig. 6B). In the presence of 50 μM NPPB plus 1 μg/ml propofol, relative bis-oxonol fluorescence values at 30% hypotonicity were significantly less than that in the presence of 1 μg/ml propofol (P < 0.05; fig. 6B). Therefore, NPPB potentiates the effect of propofol on hypotonicity-induced membrane depolarization.

Discussion
The major finding of this study was that in human coronary artery smooth muscle cells, hypotonic exposure induced membrane depolarization in a tonicity-dependent manner. The depolarization was blocked with NPPB, suggesting the involvement of VSCCs and nonselective cation channels. More importantly, propofol inhibited the hypotonicity-induced membrane depolarization in a dose-dependent manner.

Hypotonicity-induced membrane depolarization was measured using bis-oxonol in this study. The bis-oxonol system semiquantitatively captures the membrane potential. Calibration of bis-oxonol fluorescence suggests that 30% hypotonicity induced approximately 36 mV depolarization in this study. Lang et al.24,25 reported, using high-resistance microelectrodes, that exposure of the human vascular smooth muscle cells to 25% hypo-

Fig. 4. Effects of propofol on hypotonicity-induced change in relative bis-oxonol fluorescence in human coronary artery smooth muscle cells. (A) Representative variations of fluorescence intensity. Bis-oxonol fluorescence was measured relative to baseline (percent). At the point indicated (arrow), the values were evaluated. ◊ isotonic time control; □ 30% hypotonicity; ○ = 0.1 μg/ml propofol; ▲ = 1 μg/ml propofol; ◯ = 10 μg/ml propofol; ▼ = 100 μg/ml propofol. (B) Propofol significantly attenuated the increase in fluorescence by 30% hypotonicity in a concentration-dependent fashion (n = 6). Values are expressed as mean ± SD. * P < 0.05 versus the value of 30% hypotonicity.
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Fig. 5. Effects of 30% low sodium concentration itself on change in relative bis-oxonol fluorescence in human coronary artery smooth muscle cells. (A) Representative variations of fluorescence intensity. Bis-oxonol fluorescence was measured relative to the normal sodium concentration (percent). At the point indicated (arrow), the values were evaluated. (B) Thirty-percent low sodium concentration itself significantly reduced the fluorescence (n = 6). Values are expressed as mean ± SD.  * P < 0.05 versus the value of 30% hypotonicity.

Hypotonic extracellular fluids led to a rapid depolarization of 13 mV. The reason for the differences in magnitude of membrane depolarization is not clear. However, experimental conditions and the method of measurement may affect the results. Welsh et al. reported that a hypotonic exposure elicited a functional response that was similar to a myogenic control. Therefore, hypotonic exposure can induce both swelling- and stretch-induced channel activation. Hypotonic exposure was used as a model of in vivo stretch applied to isolated cells in this study. Wu and Davis reported that longitudinal stretch to 130% of cell length induced a 17-mV membrane depolarization from a resting potential near −60 mV in coronary smooth muscle cells. Increase of transmural pressure from 0 to 100 mmHg induced 16- and 36-mV membrane depolarizations in cat middle cerebral artery and rat posterior cerebral artery, respectively. The resting membrane potential in vascular smooth muscle without tone (approximately −50 to −75 mV) is more negative than when the muscle has tone (approximately −40 to −55 mV), either from vasoconstrictors or from spontaneous tone. Therefore, 30% hypotonicity induces a mechanical stress that is relevant to mechanical stress that occur in vivo. The influence of cell swelling on cell membrane potential depends on the ion channels preferentially activated or inactivated and on the potential difference before cell swelling. Activation of anion or nonselective cation channels and a highly negative initial cell membrane potential as smooth muscle cells have (approximately −50 to −75 mV) favor depolarization. The effect of tonicity on membrane depolarization was almost completely inhibited by 200 μM NPPB in this study. The concentration of NPPB was selected to block the VSCCs completely. NPPB does not inhibit VSCCs selectively at this concentration. NPPB blocks VSCCs, Ca2+-activated Cl− channels, nonselective cation channels, L-type calcium channels, and swelling-activated K+ channels. Some studies performed at room temperature have suggested that VSCCs do not account for the stretch-induced membrane depolarization. Doughty and Langton also reported that at room temperature (18–21°C), a small, pressure-independent Cl− efflux was measured. However, at the same time, they reported that on warming to 37°C, arteries developed pressure-dependent myogenic tone, and this was associated with a pressure-dependent increase in Cl− efflux. We performed experiments at 36–37°C in this study. The Cl− channels involved in the myogenic response were insensitive to Ca2+-activated Cl− channel blockers. Ca2+-channel blockers inhibited myogenic tone but was without effect on Cl− flux. Nelson et al. reported that pressure-induced depolarization of cerebral arteries occurs in the presence of Ca2+-channel blockers, which reduce intracellular Ca2+ concentrations to less than that required for Ca2+-activated chloride channel activity. Therefore, Ca2+-activated Cl− channels do not account for the membrane depolarization. Effects on calcium channels also do not account for the membrane depolarization because current flow through these channels is probably too small to account for stretch-induced depolarization, which persists in the presence of Ca channel blockade. Opening of K+ channels may provide a negative feedback mechanism for stretch-induced smooth muscle depolarization. Therefore, K+ channels do not account for the effect of NPPB observed in this study. Hence, VSCCs and nonselective cation channels are candidates for mechanisms of the swelling- and stretch-induced membrane depolarization. It seems that NPPB induced the decrease of basal bis-oxonol fluorescence in this study. It is possible that VSCCs and nonselective cation channels are open at basal isotonic conditions. Therefore, NPPB may induce the hyperpolarization of the basal membrane potential by inhibiting VSCCs and/or nonselective cation channels.

Propofol inhibited the hypotonicity-induced membrane depolarization in a dose-dependent manner in this study. This finding suggests that propofol inhibits the swelling- and stretch-induced membrane depolarization. In addition, our previous study using a chloride-sensitive dye suggests that propofol inhibits VSCCs in human coronary artery smooth muscle cells, and many VSCC-
blocking reagents inhibit nonselective cation channels. Propofol inhibits phospholipase C. Phospholipase C is critically important in the genesis of pressure-induced membrane depolarization. Although Jarajapu and Knot suggest the inhibition of K channel, phospholipase C activates nonselective cation channels and VSCCs also in smooth muscle cells. Propofol induces changes in the cytoskeletal organization and actin polymerization. Actin cytoskeleton disruption induces pressure-induced membrane depolarization. Therefore, propofol-induced actin polymerization might participate in the action of propofol. The effect propofol on hypotonicity-induced membrane depolarization persisted after washout in this study. The reasons for this persistence are not clear. However, effects of propofol on actin cytoskeleton or cell signaling system may participate in the persistence of the effects. NPPB potentiated the effect of propofol on hypotonicity-induced membrane depolarization in this study. This result suggests that propofol and NPPB exert their main effects via different mode of inhibition. A possible explanation for the result is that NPPB operates directly on VSCCs and/or nonselective cation channels, whereas propofol may inhibit signaling cascades involved in the activation of these channels. Propofol has been shown to relax vascular smooth muscle in an endothelium-independent manner, which has been ascribed to inhibition of free cytosolic Ca\(^{2+}\) mobilization and blockade of volt-
age-gated Ca\(^{2+}\) influx.\(^{13,14}\) However, based on our findings, propofol may also induce vascular effects by inhibition of membrane depolarization.\(^{25}\)

During clinical anesthesia, total and free plasma propofol concentrations differ significantly. The free plasma concentration of propofol is 0.6 μg/ml (3.4 μM) or less,\(^{44}\) because 97–99% of propofol is bound to plasma proteins.\(^{45}\) Park et al.\(^{44}\) estimated that total propofol blood concentration ranges from 1 to 20 μg/ml during clinical anesthesia. Therefore, in our study, propofol significantly inhibited VSCTs and nonselective cation channels at a clinically relevant concentration (0.1 μg/ml).

Some limitations should be noted. Dilution of the Earle’s balanced salt solutions by 30% with distilled water increased the pH by 0.1–0.15 in this study. Extracellular alkalization induces membrane depolarization of vascular smooth muscle cells.\(^{46}\) Dietrich and Dacey\(^{46}\) reported that extracellular alkalization from a pH of 7.3 to 7.65 depolarized the cell membrane potential by 6.4 mV at 37°C with 65 mmHg intraluminal pressure. Tight control of pH studied in an additional study did not significantly alter the relative bis-oxonol fluorescence at 30% hypotonicity in this study. Therefore, the effects of alkalization of the superfusion medium may be small when compared with the effect of hypotonicity. In addition, extracellular alkalization moderately activates VSCTs and slows VSCC inactivation down.\(^{47}\) Activation of nonselective cation channels might also be a mechanism for alkalization-induced membrane depolarization.\(^{48}\) Therefore, alkalization of the media did not have a major effect on the findings. Dilution of the Earle’s balanced salt solutions by 30% with distilled water decreased the potassium and sodium concentration by 30% in this study. However, additional studies suggest that decreases of these electrolytes did not have a major effect on the findings. Relative bis-oxonol fluorescence at 30% hypotonicity in the first study (335 ± 102%) was different from the percent change in the second study (246 ± 23%). The major difference between the two studies was the experimental protocol, and the reasons for the difference in results are not clear. Dimethyl sulfoxide affects actin polymerization and causes a decrease in membrane tension at high concentration (3%).\(^{49}\) However, the final concentration of dimethyl sulfoxide was less than 0.1% in this study, which does not affect the activity of many channels, including Cl\(^{-}\) currents.\(^{9}\) Clinically available propofol is supplied with intralipid. Propofol was not in intralipid before being placed in dimethyl sulfoxide in this study. Therefore, the effect of intralipid was not evaluated in this study. Effects of propofol on hypotonicity-induced cell swelling were considered to be negligible at steady state.\(^{50}\) The effect of endothelium on stretch (mechanical stress)-induced membrane depolarization of smooth muscle was not evaluated in this study. Endothelium also has nonselective cation channels and VSCTs.\(^{11}\) Nonselective cation channels may represent Ca\(^{2+}\) entry pathways in endothelium.\(^{11}\) The Ca\(^{2+}\) influx through these channels is sufficient to activate K\(_{Ca}\) channels to hyperpolarize the membrane.\(^{11}\) Therefore, nonselective cation channels in endothelial cells may participate in negative feedback mechanism in myogenic response. Propofol may inhibit the endothelium-dependent relaxation\(^{51,52}\) by inhibiting the nonselective cation channels. In contrast, activation of VSCTs induces the depolarization of endothelial cells.\(^{53}\) Petros et al.\(^{53}\) suggested that propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells. Therefore, effects of stretch and propofol on endothelium are complex. In addition, under pathologic conditions, endothelium-dependent vasodilatory function is impaired temporarily without morphologic damage.\(^{55}\) Differences in stretch-induced membrane depolarization may occur in vivo, where endothelium is present.

In conclusion, we showed that propofol inhibits hypotonicity-induced membrane depolarization in a dose-dependent manner in human coronary artery smooth muscle cells. Such an effect in vivo would cause vasodilation and hypotension, and that could explain in part the vascular effects of propofol.

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References

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