Propofol and thiopental attenuate adenosine triphosphate-sensitive potassium channel relaxation in pulmonary veins

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Roh, Woon-Seok, Xueqin Ding, and Paul A. Murray. Propofol and thiopental attenuate adenosine triphosphate-sensitive potassium channel relaxation in pulmonary veins. Am J Physiol Lung Cell Mol Physiol 291: L636–L643, 2006. First published May 25, 2006; doi:10.1152/ajplung.00063.2006.—Pulmonary veins (PV) make a significant contribution to total pulmonary vascular resistance. We investigated the cellular mechanisms by which the intravenous anesthetics propofol and thiopental alter adenosine triphosphate-sensitive potassium (K_{ATP}) channel relaxation in canine PV. The effects of K_{ATP} channel inhibition (glybenclamide), cyclooxygenase inhibition (indomethacin), nitric oxide synthase inhibition (L-NAME), and L-type voltage-gated Ca^{2+} channel inhibition (nifedipine) on vasorelaxation to levocromakalim (K_{ATP} channel activator) alone and in combination with the anesthetics were assessed. The maximal relaxation response to levocromakalim was attenuated by removing the endothelium and by L-NAME, but not by indomethacin. Propofol (10^{-5}, 3 \times 10^{-5}, and 10^{-4} M) and thiopental (10^{-4} and 3 \times 10^{-4} M) each attenuated levocromakalim relaxation in endothelium-intact (E+) rings, whereas propofol (3 \times 10^{-5} and 10^{-4} M) and thiopental (3 \times 10^{-4} M) attenuated levocromakalim relaxation in endothelium-denuded (E−) rings. In E+ rings, the anesthesia-induced attenuation of levocromakalim relaxation was decreased after pretreatment with L-NAME but not with indomethacin. In E-strips, propofol (10^{-4} M) and thiopental (3 \times 10^{-4} M) inhibited decreases in tension and intracellular Ca^{2+} concentration ([Ca^{2+}]_{i}) in response to levocromakalim, and these changes were abolished by nifedipine. These findings indicate that propofol and thiopental attenuate the endothelium-dependent component of K_{ATP} channel-induced vasorelaxation via an inhibitory effect on the nitric oxide pathway. Both anesthetics also attenuate the PV smooth muscle component of K_{ATP} channel-induced relaxation by reducing the levocromakalim-induced decrease in [Ca^{2+}]_{i} via an inhibitory effect on L-type voltage-gated Ca^{2+} channels.

Ca^{2+} influx; anesthetics

ADENOSINE TRIPHOSPHATE-SENSITIVE potassium (K_{ATP}^{+}) channels play an important role in the regulation of vascular smooth muscle tone (27). Activation of K_{ATP} channels causes an increase in K^{+} efflux, membrane hyperpolarization, inhibition of Ca^{2+} influx through L-type voltage-gated Ca^{2+} channels (VGCCs), and subsequent vascular smooth muscle relaxation. Our laboratory and others (2, 6, 8, 22, 28, 29, 34, 36) have demonstrated that K_{ATP} channel agonists can cause marked pulmonary vasodilatation, which is reversed by glybenclamide, a specific K_{ATP} channel inhibitor. Moreover, endogenous K_{ATP}^{+} channel-induced vasorelaxation is functionally significant, because it has been shown to modulate the pulmonary vasconstrictor responses to hypoxia (23) and systemic hypotension (8).

K_{ATP}^{+} channels are present not only in vascular smooth muscle cells but also have been demonstrated in vascular endothelial cells (13, 14). In endothelial cells, K_{ATP} channel activation results in hyperpolarization, an increase in Ca^{2+} influx (18, 19), and the production of endothelium-derived relaxing factors (17, 20) such as nitric oxide and prostacyclin. We have recently demonstrated that K_{ATP}^{+} channel-induced pulmonary arterial vasorelaxation involves both endothelium-dependent and vascular smooth muscle components (28, 34). However, there is very little information about K_{ATP}^{+} channel-induced vasorelaxation in pulmonary veins (PV). Pulmonary venous resistance is an important component of total pulmonary vascular resistance (1). Recent evidence indicates that there are marked regional differences in reactivity to vasodilators in arterial and venous segments of isolated pulmonary vessels (9, 15, 31).

Propofol and thiopental are widely used intravenous anesthetics for induction and maintenance of cardiac and noncardiac anesthesia. Both anesthetics have some benefits for brain protection (5, 21). The effects of these anesthetics on K_{ATP}^{+} channel-induced vasorelaxation have not been investigated in PV. Moreover, underlying mechanisms responsible for the anesthesia-induced attenuation of the smooth muscle component of K_{ATP}^{+} channel-induced relaxation have not been elucidated. Because propofol and thiopental have been shown to inhibit L-type VGCCs in vascular smooth muscle (12, 37), tracheal smooth muscle cells (38), and myocardial cells (3), it is reasonable to hypothesize that these anesthetics could attenuate the vascular smooth muscle component of K_{ATP}^{+} channel-mediated relaxation via an inhibitory effect on L-type VGCCs. Because PV constriction can increase pulmonary capillary pressure and transvascular fluid flux to cause pulmonary edema, an anesthesia-induced attenuation of a PV vasodilator mechanism could result in an increase in pulmonary capillary pressure, pulmonary edema formation, and congestive heart failure. There has been a suggestion that propofol and thiopental may be associated with pulmonary edema (26, 35).

The overall goal of this in vitro study was to investigate the effects of propofol and thiopental on the PV vasorelaxant response to the K_{ATP}^{+} channel agonist levocromakalim. On the basis of our previous results in pulmonary arteries (28, 34), we tested the hypothesis that these anesthetics would attenuate the endothelium-dependent component of vasorelaxation in response to levocromakalim. We also tested the hypothesis that propofol and thiopental would attenuate the vascular smooth muscle component of levocromakalim-induced vasorelaxation by reducing the agonist-induced decrease in intracellular Ca^{2+}.

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concentration ([Ca\(^{2+}\)]) via an inhibitory effect on L-type VGCCs.

**MATERIALS AND METHODS**

All experimental procedures and protocols were approved by the Institutional Animal Care and Use Committee of The Cleveland Clinic Foundation (Cleveland, OH).

**Preparation of PV rings and strips.** Healthy male mongrel dogs (24–30 kg) were anesthetized with pentobarbital sodium (30 mg/kg, intravenously) and fentanyl citrate (15 μg/kg, intravenously). After tracheal intubation, the dogs were placed on positive-pressure ventilation. After the administration of heparin (6,000 units), a catheter was inserted into the right femoral artery for exsanguination by controlled hemorrhage. A left lateral thoracotomy was performed through the fifth intercostal space, and the heart was arrested with electrically induced ventricular fibrillation. The heart and lungs were removed en bloc. The right and left lower intralobar PV (3rd and 4th generation: segments 4 –5 mm in length, with care taken not to damage the endothelium. For protocols using pulmonary venous strips, first and second generation veins were cut into strips (4 × 8 mm). Larger veins were used for the strip studies compared with the ring studies to accommodate the equipment used for fluorescence measurements (described below). In some rings and all strips, the endothelium was intentionally denuded by gently rubbing the inner surface with a cotton swab. Denudation was verified by >90% attenuation in the relaxation response to bradykinin (10^{-8} M).

**Isometric tension experiments.** PV rings were vertically suspended between two stainless steel hooks in organ chambers filled with 25 ml of modified KRB solution (37°C) gassed with 95% O₂ and 5% CO₂. One of the hooks was anchored, and the other was connected to a strain gauge transducer to measure isometric tension. For protocols using pulmonary venous strips, first and second generation veins were cut into strips (4 × 8 mm). Larger veins were used for the strip studies compared with the ring studies to accommodate the equipment used for fluorescence measurements (described below). After washing of the veins, the strips were mounted between two stainless steel hooks in a temperature-controlled cuvette (volume = 3 ml) that was continuously perfused (12 ml/min) with KRB solution gassed with 95% O₂ and 5% CO₂ (pH 7.4). One hook was anchored, and the other was connected to a strain gauge transducer to measure isometric tension. The resting tension was adjusted to 1.5 g, which was determined in preliminary studies to be optimal for achieving a maximum contractile response to 40 mM KCl. We used a lower concentration of KCl in the strip studies compared with the ring studies, because the higher concentration was associated with a prolonged washout period before tension and [Ca\(^{2+}\)] were returned to baseline values. Fluorescence measurements were performed using a dual-wavelength spectrophotometer (Deltascan RFK6002; Photon Technology International, South Brunswick, NJ) at excitation wavelengths of 340 and 380 nm and an emission wavelength of 510 nm. The 340-to-380 fluorescence ratio was used as an indicator of [Ca\(^{2+}\)].

**Solution and chemicals.** All drugs were of the highest purity commercially available: U46619 (Cayman Chemical, Ann Arbor, MI); levcromakalim (Tocris Cookson, Ellisville, MO); L-NAME, indomethacin, propofol, thio-menthol, nifeledipine, and glybenclamide (Sigma Chemical, St. Louis, MO); and fura-2/AM (Texas Fluorescence Labs, Austin, TX). All concentrations are expressed as the final molar concentration in the study chamber. U46619, propofol, glybenclamide, and fura-2/AM were dissolved in dimethyl sulfoxide and diluted with distilled water. The final concentration of dimethyl sulfoxide in the study chamber was <0.1% (vol/vol). Thio-menthol and indomethacin were dissolved in NaHCO₃ and diluted in distilled water (final study chamber NaHCO₃ concentration, 2 × 10^{-4} M). None of the agents or solutions caused significant shifts in isometric tension or the 340-to-380 ratio at the concentrations used in these studies.

**Data analysis.** All data are expressed as means ± SD. Vasorelaxant responses to levcromakalim are expressed as the percent relaxation of precontraction induced by U46619. The maximal relaxation response (R_{max}) to levcromakalim was measured, with R_{max} = 100% indicat-
ing complete reversal of U46619 precontraction. Statistical analysis was performed using Student’s t-test for paired comparisons or one-way analysis of variance followed by Bonferroni correction. Differences were considered statistically significant at \( P < 0.05 \); \( n \) refers to the number of dogs from which PV rings or strips were studied in each protocol.

RESULTS

Effects of sequential application of U46619. U46619 (10\(^{-8}\) M) was approximately the log EC\(_{75}\) for both endothelium-intact and -denuded rings. Figure 1A illustrates changes in tension in endothelium-intact PV rings in response to U46619. The U46619-induced increase in tension was not sustained, so cumulative concentration-response studies for levomakalim could not be performed. Each ring was precontracted with U46619, and the relaxation response to each concentration of levomakalim was assessed in a sequential fashion. Changes in tension in response to sequential treatment of U46619 were highly reproducible (Fig. 1B).

Effects of endothelial denudation on levomakalim-induced vasorelaxation. As summarized in Fig. 2, levomakalim vasorelaxation in PV was attenuated \( (P < 0.05) \) by removing the endothelium. Levomakalim vasorelaxation was essentially abolished by the K\(_{ATP}\) channel antagonist glybenclamide in both endothelium-intact and -denuded PV (Fig. 3).

Effects of propofol and thiopental on levomakalim vasorelaxation. To achieve the same degree of precontraction observed in control rings, a higher concentration \( (10^{-7} \text{ M}) \) of U46619 was required in rings treated with high-dose anesthetic. As summarized in Figs. 4 and 5, propofol \( (10^{-5}, 3 \times 10^{-5}, \text{ and } 10^{-4} \text{ M}) \) and thiopental \( (10^{-4} \text{ and } 3 \times 10^{-4} \text{ M}) \) attenuated levomakalim relaxation in endothelium-intact PV in a dose-dependent manner. Only higher concentrations of propofol \( (3 \times 10^{-5} \text{ and } 10^{-4} \text{ M}) \) and thiopental \( (3 \times 10^{-4} \text{ M}) \) attenuated levomakalim relaxation in endothelium-denuded PV.

Effects of cyclooxygenase inhibition or nitric oxide synthase inhibition on propofol- and thiopental-induced changes in levomakalim vasorelaxation. We tested the hypothesis that propofol and thiopental attenuated levomakalim relaxation by inhibiting vasodilator metabolites of the cyclooxygenase pathway or the nitric oxide synthase pathway. Indomethacin \( (10^{-5} \text{ M}) \) had no effect on levomakalim relaxation compared with the no-drug condition (Fig. 6A). Moreover, propofol \( (3 \times 10^{-5} \text{ M}) \)- or thiopental \( (10^{-4} \text{ M}) \)-induced attenuation of levomakalim pulmonary relaxation was still observed after indomethacin pretreatment. In contrast, 1-NAME \( (10^{-4} \text{ M}) \) attenuated levomakalim relaxation (Fig. 6B). Moreover, the anesthesia-induced attenuation of levomakalim relaxation was either reduced (propofol) or abolished (thiopental) after 1-NAME pretreatment (Fig. 7). These results indicate that propofol and thiopental attenuated the endothelium-dependent component of K\(_{ATP}\) channel-mediated pulmonary venous relaxation via an inhibitory effect on the nitric oxide synthase pathway but not the cyclooxygenase pathway.
Effects of propofol and thiopental on levcromakalim-induced changes in tension and $[\text{Ca}^{2+}]_i$. As summarized in Fig. 8, levcromakalim decreased tension and $[\text{Ca}^{2+}]_i$ in U46619-precontracted strips. Propofol ($10^{-4}$M) and thiopental ($3 \times 10^{-4}$M) attenuated these levcromakalim-induced decreases in tension and $[\text{Ca}^{2+}]_i$ (Fig. 8). Lower concentrations of propofol ($10^{-5}$M), but not thiopental ($3 \times 10^{-5}$M), also attenuated the levcromakalim-induced decreases in tension and $[\text{Ca}^{2+}]_i$.

**DISCUSSION**

This is the first study to assess the effects of propofol and thiopental on $K_{\text{ATP}}$ channel-induced relaxation in PV. Our results demonstrate that levcromakalim causes endothelium-dependent, glybenclamide-sensitive, and L-type VGCC-dependent PV vasorelaxation. Propofol and thiopental attenuate the endothelium-dependent component of $K_{\text{ATP}}$ channel-induced relaxation via an inhibitory effect on the nitric oxide pathway. Moreover, both anesthetics attenuate the PV vascular smooth muscle component of $K_{\text{ATP}}$ channel-induced relaxation by reducing the decrease in $[\text{Ca}^{2+}]_i$ via an inhibitory effect on L-type VGCCs.

As in previous in vivo (8, 22, 29) and in vitro studies (28, 34), we used levcromakalim to activate $K_{\text{ATP}}$ channels. In the current study, levcromakalim-induced relaxation was inhibited by glybenclamide, a highly selective $K_{\text{ATP}}$ channel inhibitor, which indicates that levcromakalim causes $K_{\text{ATP}}$ channel-dependent vasorelaxation in PV. Moreover, this relaxation by levcromakalim was attenuated by endothelial denudation, suggesting that $K_{\text{ATP}}$ channel-induced relaxation involves both endothelial and smooth muscle components.

**Fig. 4.** Propofol attenuated ($P < 0.05$) levcromakalim relaxation in a dose-dependent fashion in endothelium-intact (A) and endothelium-denuded (B) pulmonary venous rings.

**Fig. 3.** The adenosine triphosphate-sensitive potassium ($K_{\text{ATP}}$) channel antagonist glybenclamide essentially abolished ($P < 0.05$) levcromakalim relaxation in endothelium-intact (A) and endothelium-denuded (B) pulmonary venous rings. Glybenclamide was dissolved in dimethylsulfoxide (DMSO).
endothelium-dependent and vascular smooth muscle components.

Recent reports indicate that $K_{\text{ATP}}$ channel agonists such as levocromakalim and pinacidil relax vascular smooth muscle by opening $K_{\text{ATP}}$ channels on endothelial cells (13, 14), suggesting that $K_{\text{ATP}}$ channel agonists could modulate the release of endothelium-derived relaxing factors (17–20) such as nitric oxide or prostacyclin. We previously demonstrated in canine pulmonary artery that the endothelium-dependent component of levocromakalim-induced vasorelaxation requires the activity of the cyclooxygenase pathway but is independent of nitric oxide synthase activity (28, 34). In contrast to pulmonary arteries, cyclooxygenase inhibition had no effect on levocromakalim-induced relaxation in PV, whereas nitric oxide synthase inhibition attenuated levocromakalim-induced relaxation.

Although the cellular mechanism responsible for these differences has not been identified, nitric oxide has been reported to play a larger role in PV relaxation compared with pulmonary artery (9).

Both propofol and thiopental attenuated the PV vasorelaxant response to levocromakalim. At lower concentrations, propofol ($10^{-5}$ M) and thiopental ($10^{-4}$ M) only inhibited the vasorelaxation response to levocromakalim in endothelium-intact rings, whereas higher concentrations of propofol ($3 \times 10^{-5}$ and $10^{-4}$ M) and thiopental ($3 \times 10^{-4}$ M) inhibited relaxation in both endothelium-intact and -denuded rings. Moreover, the endothelium-dependent inhibitory effects of lower concentrations of propofol and thiopental were abolished by L-NAME. It would appear that low concentrations of propofol and thiopental selectively inhibit levocromakalim-induced vasorelaxation mediated by nitric oxide. We recently reported that etomidate and ketamine attenuated vasorelaxant responses to acetylcholine and bradykinin by inhibiting both nitric oxide- and endothelium-derived hyperpolarizing factor-mediated components of the response (25). In the same study (25), these anesthetics attenuated increases in endothelial $Ca^{2+}$ concentration in response to bradykinin. It is possible that propofol and thiopental inhibited a levocromakalim-induced increase in endothelial $Ca^{2+}$ concentration, which in turn would decrease the production of nitric oxide and the endothelium-dependent component of the response.

A previous study in endothelium-denuded rat aorta (16) and the results of the current study indicate that propofol and thiopental attenuated levocromakalim-induced vasorelaxation.
thiopental also attenuated the smooth muscle component of $K_{ATP}$ channel-induced relaxation. However, the underlying mechanism for this effect has not been previously investigated. Because propofol and thiopental have been shown to inhibit L-type VGCCs in vascular smooth muscle (12, 37), tracheal smooth muscle cells (38), and myocardial cells (3), we hypothesized that propofol and thiopental could attenuate levcromakalim-induced PV relaxation via an inhibitory effect on L-type VGCCs. To test this hypothesis, we assessed the effects of the anesthetics on changes in $[Ca^{2+}]_{i}$ induced by levcromakalim. The maintenance of vasomotor tone depends on steady-state $Ca^{2+}$ entry through L-type VGCCs. Membrane hyperpolarization by levcromakalim results in the closing of L-type VGCC and causes decreases in $[Ca^{2+}]_{i}$ and tension (24). Propofol ($10^{-4}$ M) and thiopental ($3 \times 10^{-4}$ M) reduced the levcromakalim-induced decreases in PV $[Ca^{2+}]_{i}$ and tension. Moreover, anesthetic-pretreated rings or strips required higher concentrations of U46619 to achieve similar precontraction values compared with no anesthetic. Taken together, these findings suggest that propofol and thiopental may have inhibitory effects on L-type VGCCs in PV. To confirm this possibility, we assessed the effects of the L-type VGCC blocker

Fig. 7. Attenuated relaxation response to levcromakalim induced by propofol (A) and thiopental (B) was not observed in endothelium-intact pulmonary venous rings pretreated with L-NAME.

Fig. 8. In the absence of anesthetic, levcromakalim ($10^{-5}$ M) decreased tension and intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_{i}$) in endothelium-denuded U46619-precontracted pulmonary venous strips. Propofol and thiopental attenuated ($P < 0.05$) the levcromakalim-induced decreases in tension and $[Ca^{2+}]_{i}$.

Fig. 9. The L-type voltage-gated calcium channel blocker nifedipine attenuated ($*P < 0.05$) levcromakalim relaxation in endothelium-denuded pulmonary venous rings. Attenuated relaxation response to levcromakalim induced by propofol (A) and thiopental (B) was not observed in endothelium-denuded pulmonary venous rings pretreated with nifedipine.
of thiopental immediately after induction reach 4.5
results demonstrate that experimental findings of vascular reg-

The plasma concentration of propofol in patients during
maintenance of general anesthesia has been reported to be in
the range of 10−5 to 10−4 M (33). Peak serum concentrations
of thiopental immediately after induction reach 4.5×10−4 M
(4). Because 97–98% propofol (30) and 75% thiopental (10)
are bound to plasma proteins, the free concentrations of prop-
ofol and thiopental are estimated to be 10−6–10−5 and 5 ×
10−6–5 × 10−5 M, respectively. However, it was recently
reported that 28% propofol is taken up by the lung during a
single passage through the lung and released back into the
circulation by back diffusion (11). This results in a higher
concentration of propofol in the pulmonary circulation than in
the systemic circulation (7). In this study, propofol (10−5 M)
and thiopental (10−4 M) significantly attenuated levcro-
malakalim-induced relaxation, indicating that propofol can at-
tenuate KATP channel-mediated relaxation at a clinically re-
clevant concentration, whereas thiopental only attenuates KATP
channel-mediated relaxation at a supraclinical concentration.

In summary, propofol and thiopental attenuated KATP
channel-induced PV vasorelaxation. At lower concentrations,
propofol and thiopental attenuated the endothelium-dependent
component of vasorelaxation in response to KATP channel
activation, and this effect was dependent on the nitric oxide
pathway. On the other hand, both anesthetics attenuated the
smooth muscle component of KATP channel-induced relaxation
via reducing the KATP channel-mediated decrease in PV
[Ca2+]i by an inhibitory effect on L-type VGCCs. These results
demonstrate that experimental findings of vascular reg-
ulation in pulmonary artery cannot necessarily be extrapolated
to PV.

GRANTS

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