Propofol Attenuates Acetylcholine-induced Pulmonary Vasorelaxation

Role of Nitric Oxide and Endothelium-derived Hyperpolarizing Factors

Mayumi Horibe, M.D.,* Koji Ogawa, M.D.,* Ju-Tae Sohn, M.D.,* Paul A. Murray, Ph.D.†

**Background:** The mechanism by which propofol selectively attenuates the pulmonary vasodilator response to acetylcholine is unknown. The goals of this study were to identify the contributions of endogenous endothelial mediators (nitric oxide [NO], prostacyclin, and endothelium-derived hyperpolarizing factors [EDHFs]) to acetylcholine-induced pulmonary vasorelaxation, and to delineate the extent to which propofol attenuates responses to these endothelium-derived relaxing factors.

**Methods:** Canine pulmonary arterial rings were suspended for isometric tension recording. The effects of propofol on the vasorelaxation responses to acetylcholine, bradykinin, and the guanylyl cyclase activator, SIN-1, were assessed in phenylephrine-precontracted rings. The contributions of NO, prostacyclin, and EDHFs to acetylcholine-induced vasorelaxation were assessed in control and propofol-treated rings by pretreating the rings with a NO synthase inhibitor (L-NAME), a cyclooxygenase inhibitor (indomethacin), and a cytochrome P450 inhibitor (clotrimazol or SKF 525A) alone and in combination.

**Results:** Propofol caused a dose-dependent rightward shift in the acetylcholine dose–response relation, whereas it had no effect on the pulmonary vasorelaxant responses to bradykinin or SIN-1. Cyclooxygenase inhibition only attenuated acetylcholine-induced relaxation at high concentrations of the agonist. NO synthase inhibition and cytochrome P450 inhibition each attenuated the response to acetylcholine, and combined inhibition abolished the response. Propofol further attenuated acetylcholine-induced relaxation after NO synthase inhibition and after cytochrome P450 inhibition.

**Conclusion:** These results suggest that acetylcholine-induced pulmonary vasorelaxation is mediated by two components: NO and a cytochrome P450 metabolite likely to be an EDHF. Propofol selectively attenuates acetylcholine-induced relaxation by inhibiting both of these endothelium-derived mediators. (Key words: Endothelium-derived relaxing factors; lung; pulmonary circulation; vasomotor tone.)

NITRIC oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factors (EDHFs) are the three primary mediators of endothelium-dependent vasodilation.1,2 NO is produced by the L-arginine–NO synthase pathway, and prostacyclin is produced by the arachidonic acid–cyclooxygenase pathway. The chemical nature of the EDHFs has not been fully characterized, but increasing evidence suggests that one form of EDHF is a cytochrome P450-derived metabolite of arachidonic acid.3–6 The pattern of endothelial dilator mediators depends on the nature of the endothelial stimulus.7 Several different endothelium-derived mediators, acting alone or in synergy with other mediators, can be the target for inhibitory effects of anesthetic agents on endothelium-dependent vasodilation.8,9

We have observed in chronically instrumented dogs that the pulmonary vascular response to the endothelium-dependent vasodilator, acetylcholine, was attenuated during propofol anesthesia compared with the conscious state, whereas the response to another endothelium-dependent vasodilator (bradykinin), as well as the response to an endothelium-independent NO donor (proline/NO) was not altered during propofol anesthesia. The goal of the present study was to investigate the mechanism responsible for this selective effect of propofol on acetylcholine-induced pulmonary vasodilation. Specifically, we tested the hypothesis that propofol exerts its effect by...
inhibiting one or more of the endothelium-derived relaxing factors that mediate acetylcholine-induced pulmonary vasodilation.

**Materials and Methods**

All surgical procedures and experimental protocols were approved by the Institutional Animal Care and Use Committee.

**Organ Chamber Experiments**

Healthy male mongrel dogs weighing 25–30 kg were anesthetized with pentobarbital sodium (30 mg/kg intravenously) and fentanyl citrate (15 µg/kg intravenously) and placed on positive-pressure ventilation. The blood volume was removed by controlled hemorrhage via a femoral artery catheter, a left lateral thoracotomy was performed, and the dogs were euthanized with electrically induced ventricular fibrillation. The heart and lungs were removed en bloc. Using aseptic technique, the right and left lower intralobar pulmonary arteries (2–4-mm ID) were dissected free and immersed in cold modified Krebs-Ringer bicarbonate solution of the following composition: 118.3 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO₄, 1.2 mM KH₂PO₄, 2.5 mM CaCl₂, 25.0 mM NaHCO₃, 0.016 mM CaEDTA, and 11.1 mM glucose. The arteries were cut into 0.5-cm-wide rings with care taken not to damage the endothelium. In some rings, the endothelium was intentionally removed by inserting forcep tips into the vessel lumen and rolling the rings over damp filter paper. Endothelial denudation was later confirmed by the absence of relaxation to acetylcholine (10⁻⁶ M). The rings were suspended horizontally between two stainless steel stirrups in organ chambers filled with 25 ml modified Krebs-Ringer bicarbonate solution (37°C) gassed with 95% O₂–5% CO₂. One of the stirrups was anchored, and the other was connected to a strain gauge (Grass Model FT03, Quincy, MA) for measurement of isometric tension. The rings from the same relative anatomic locations in the right and left lungs were used as paired rings.

**Experimental Protocols**

Pulmonary arterial rings were stretched at 10-min intervals in increments of 0.5 g to reach optimal resting tone. Optimal resting tone is defined as the minimum level of stretch required to achieve the largest contractile response to KCl (40 mM) and was determined to be 5 g for these studies. After the rings had been stretched to their optimal resting tone, the contractile response to 60 mM KCl was measured. After washout of KCl from the organ chambers and the return of isometric tension to prestimulation values, a concentration–effect curve for the sympathetic α-adrenoreceptor agonist, phenylephrine, was performed in each ring. This was achieved by increasing the concentration of phenylephrine in half-log increments (10⁻⁸ to 3 × 10⁻⁵ M) after the response to each preceding concentration had reached a steady state. All rings were pretreated with the β-adrenoreceptor antagonist, propranolol (5 × 10⁻⁶ M; incubated for 30 min) to inhibit the β-agonist effects of phenylephrine. After washout of phenylephrine from the organ chamber and return to baseline tension, the rings were again pretreated with propranolol and contracted to 50% of their maximal response to phenylephrine (ED₅₀ level of tension). When the contractile response was stabilized, concentration–response curves to the endothelial cell activators, acetylcholine, and bradykinin were generated. The rings were exposed to only one endothelial cell activator. Responses to SIN-1 (activates vascular smooth muscle guanylyl cyclase) and papaverine (non-specific vasorelaxant) were measured in rings denuded of endothelium.

To identify the specific endothelium-derived mediators involved in the relaxation responses to acetylcholine, endothelium-intact rings were incubated with one or more of the following pharmacologic inhibitors: Nω-nitro-arginine methyl ester (L-NAME: 3 × 10⁻⁵ M), an inhibitor of NO synthase; indomethacin (3 × 10⁻⁵ M), an inhibitor of cyclooxygenase; and either clotrimazole (3 × 10⁻⁵ M) or SKF 525A (3 × 10⁻⁵ M), inhibitors of cytochrome P450. Rings were pretreated with these inhibitors, alone or in combination, for 30 min before contraction to the ED₅₀ level of tension with phenylephrine. The inhibitors remained in the bath solution for the duration of the experiment. Vasorelaxant responses to acetylcholine in inhibitor-treated rings were compared with responses in untreated rings that were size- and position-matched (right vs. left lung lobe). None of the inhibitors had an effect on baseline tension.

The effects of propofol (10⁻⁶ M to 10⁻⁴ M) on the acetylcholine concentration–effect curve were assessed by comparing vasorelaxant responses to acetylcholine in rings with and without propofol pretreatment. Propofol was added to the organ bath 30 min before phenylephrine precontraction. The intralipid vehicle for propofol had no effect on acetylcholine-induced vasorelaxation. The effects of propofol (10⁻⁴ M) on the bradykinin and SIN-1 concentration–effect curves were assessed in a similar manner. The effect of propofol (10⁻⁴ M) on the
NO-mediated component of acetylcholine-induced vasorelaxation was assessed in rings pretreated with the combined inhibitors of cyclooxygenase and cytochrome P450. The effect of propofol (10^{-6} M) on the EDHF-mediated component of acetylcholine-induced vasorelaxation was assessed in rings pretreated with the combined inhibitors of cyclooxygenase and NO synthase.

**Drugs and Solutions**

All drugs were of the highest purity commercially available. The following drugs were obtained from Sigma Chemical (St. Louis, MO): acetylcholine chloride, bradykinin, clotrimazole, indomethacin, L-NAME, papaverine, phenylephrine, propranolol, SKF 525A (proadifen), and SIN-1 (3-morpholinosydnonimine). Propofol and the intralipid vehicle were obtained from the Cleveland Clinic Pharmacy (Cleveland, OH). All drug concentrations are expressed as the final molar concentration in the organ chamber. Stock solutions were prepared on the day of the experiment. Unless stated otherwise, drugs were dissolved in distilled H_2O. Indomethacin was dissolved in a NaHCO_3 solution (final bath concentration of NaHCO_3: 0.2 mM). Clotrimazole was dissolved in dimethyl sulfoxide followed by dilution in distilled H_2O (final bath concentration of dimethyl sulfoxide: 0.00004% to 0.013% vol/vol). At these concentrations, the vehicles have no effect on isometric tension.7

**Table 1. Effect of Propofol on Acetylcholine-induced Relaxation**

<table>
<thead>
<tr>
<th></th>
<th>Log IC_{50}</th>
<th>Rmax (%)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>-7.30 ± 0.04</td>
<td>99.3 ± 0.7</td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-6} M</td>
<td>-7.28 ± 0.09</td>
<td>97.6 ± 0.7</td>
</tr>
<tr>
<td>10^{-5} M</td>
<td>-7.13 ± 0.10*</td>
<td>96.9 ± 2.5</td>
</tr>
<tr>
<td>10^{-4} M</td>
<td>-6.97 ± 0.14*</td>
<td>96.3 ± 1.7</td>
</tr>
<tr>
<td>10^{-4} M</td>
<td>-6.81 ± 0.07*</td>
<td>90.4 ± 2.6*</td>
</tr>
</tbody>
</table>

* Significantly different from control (P < 0.05).
Data Analysis

Values are expressed as mean ± SEM, and n equals the number of dogs from which pulmonary arterial rings were isolated. Vasorelaxant responses of the agonists are expressed as a percentage of phenylephrine precontraction. The effects of the antagonists on the agonist concentration–effect curves were evaluated by comparing the concentration of agonist causing 50% relaxation of the contraction to phenylephrine (inhibitory concentration: IC₅₀). This value was interpolated from the linear portion of the agonist concentration–effect curve by regression analysis and is presented as log IC₅₀.

The effects of propofol (10⁻⁶ to 10⁻⁴ M) on the acetylcholine concentration–effect curve are summarized in figure 1. The IC₅₀ and Rmax values are summarized in table 1. Low-dose propofol (10⁻⁶ M) had no effect on acetylcholine-induced relaxation (fig. 1A), whereas 10⁻⁵.₅ M and higher doses caused dose-dependent rightward shifts in the acetylcholine concentration–effect curves (figs. 1B–1D). In contrast, propofol (10⁻⁴ M) had no effect on endothelium-dependent relaxation induced by bradykinin (fig. 2A; IC₅₀: control = -7.90 ± 0.06, 10⁻⁴ M).

Results

Effect of Propofol on Pulmonary Vasorelaxation

The effects of propofol (10⁻⁶ to 10⁻⁴ M) on the acetylcholine concentration–effect curve are summarized in figure 1. The IC₅₀ and Rmax values are summarized in table 1. Low-dose propofol (10⁻⁶ M) had no effect on acetylcholine-induced relaxation (fig. 1A), whereas 10⁻⁵.₅ M and higher doses caused dose-dependent rightward shifts in the acetylcholine concentration–effect curves (figs. 1B–1D). In contrast, propofol (10⁻⁴ M) had no effect on endothelium-dependent relaxation induced by bradykinin (fig. 2A; IC₅₀: control = -7.90 ± 0.06, 10⁻⁴ M).

Fig. 2. Effect of propofol on the relaxation induced by bradykinin (A) and SIN-1 (B). Arterial rings were precontracted to the ED₅₀ level of tension with phenylephrine. Relaxations are expressed as percentages of phenylephrine contraction and are presented as mean ± SEM. Propofol (10⁻⁴ M) had no effect on bradykinin- or SIN-1-induced vasorelaxation (n = 5).
Table 2. Effects of Individual Inhibitors on Acetylcholine-induced Relaxation

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Log IC_{50}</th>
<th>Rmax (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-7.30 ± 0.04</td>
<td>99.3 ± 0.7</td>
</tr>
<tr>
<td>L-NAME</td>
<td>NC</td>
<td>46.0 ± 2.5*</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>-7.29 ± 0.01</td>
<td>80.0 ± 2.0*</td>
</tr>
<tr>
<td>SKF 525A</td>
<td>-6.13 ± 0.05*</td>
<td>95.7 ± 2.5*</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>-6.38 ± 0.10*</td>
<td>77.7 ± 2.7*</td>
</tr>
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</table>

NC = Not calculated because Rmax < 50%.
* Significantly different from control (P < 0.05).

propofol = -7.84 ± 0.06) or on endothelium-independent relaxation induced by SIN-1 (fig. 2B; IC_{50} = -6.93 ± 0.04, propofol = -6.99 ± 0.13).

Fig. 4. Effect of inhibition of cytochrome P450 monoxygenase (SKF 525A, 3 \times 10^{-5} M, A; and clotrimazole, 3 \times 10^{-5} M, B) on vasorelaxation induced by acetylcholine (n = 5).

Fig. 5. Effect of inhibition of cytochrome P450 monoxygenase (clotrimazole) on L-NAME–indomethacin-resistant component of relaxation induced by acetylcholine (n = 5). Pretreatment with clotrimazole totally abolished acetylcholine-induced relaxation. L = L-NAME pretreated; I = indomethacin pretreated; CLT = clotrimazole pretreated.

Effects of Nitric Oxide Synthase, Cyclooxygenase, and Cytochrome P450 Inhibition on Acetylcholine-induced Pulmonary Vasorelaxation

The effects of the individual inhibitors on the acetylcholine concentration–effect curves are summarized in figures 3 and 4. The IC_{50} and Rmax values are summarized in table 2. NO synthase inhibition with L-NAME caused a marked attenuation in the relaxation response to acetylcholine. The acetylcholine concentration–effect curve was rightward shifted (fig. 3A), and the Rmax value was decreased (table 2). Cyclooxygenase inhibition with indomethacin only attenuated the relaxant response to acetylcholine at high concentrations of the agonist (fig. 3B), with no effect on the IC_{50} value and a decrease in Rmax (table 2). The cytochrome P450 inhibitors, SKF 525A and clotrimazole, each attenuated acetylcholine-induced relaxation. Both inhibitors caused rightward shifts in the acetylcholine concentration–effect curves (fig. 4), increased the IC_{50} values, and decreased the Rmax values (table 2). Combined treatment with L-NAME, indomethacin, and clotrimazole abolished acetylcholine-induced relaxation (fig. 5).

Effect of Propofol on Nitric Oxide-mediated and Endothelium-derived Hyperpolarizing Factor-mediated Acetylcholine-induced Vasorelaxation

The results summarized in figs. 3–5 indicate that acetylcholine-induced relaxation is primarily mediated by NO and a P450 metabolite likely to be an EDHF, with only a small contribution from prostacyclin at high
concentrations of acetylcholine. To examine the effects of propofol on the NO-mediated component of acetylcholine-induced relaxation, we performed acetylcholine concentration–effect studies after combined cytochrome P450 inhibition and cyclooxygenase inhibition. During these conditions, acetylcholine-induced relaxation is mediated by NO. As summarized in figure 6, combined inhibition attenuated the relaxation response to acetylcholine. Propofol further reduced this NO-mediated component of acetylcholine-induced relaxation (fig. 7 and table 3).

Effects of Cytochrome P450 Inhibition on Pulmonary Vasorelaxation Induced by Bradykinin, SIN-1, and Papaverine

The effects of the cytochrome P450 inhibitors, SKF525A and clotrimazole, on the concentration–effect curves for bradykinin, SIN-1, and papaverine are summarized in figure 8 and table 4. In endothelium-intact rings, both cytochrome P450 inhibitors attenuated the pulmonary vascular relaxant response to bradykinin, increasing the IC50 value and decreasing Rmax. In endothelium-denuded rings, the EDHF inhibitors had no effect on the pulmonary vasorelaxant responses to SIN-1 (guanylyl cyclase activator) or papaverine (nonspecific vasorelaxant).

Discussion

We observed that propofol selectively attenuates the pulmonary vascular response to the endothelium-dependent vasodilator, acetylcholine, in chronically instrumented dogs. The goal of the present in vitro study was to investigate the mechanism(s) responsible for this endothelial defect. Our results indicate that acetylcholine-induced relaxation in isolated canine pulmonary arterial rings is mediated primarily by NO and a metabolite of the cytochrome P450 pathway likely to be an EDHF. Propofol attenuates acetylcholine-induced pulmonary vasorelaxation by inhibiting both the NO- and EDHF-mediated components of the response.

Endothelium-dependent relaxation results from the re-

Table 3. Effects of Combined Inhibition on Acetylcholine-induced Relaxation

<table>
<thead>
<tr>
<th>Inhibitor Combination</th>
<th>Control</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>L-NAME + Indomethacin</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Log IC50 (Rmax (%))</td>
<td>29.8 ± 1.6</td>
<td>22.5 ± 2.1*</td>
</tr>
<tr>
<td>SKF 525A + Indomethacin</td>
<td>-6.40 ± 0.05</td>
<td>-5.89 ± 0.04*</td>
</tr>
<tr>
<td>Log IC50 (Rmax (%))</td>
<td>93.2 ± 2.0</td>
<td>84.0 ± 2.5*</td>
</tr>
<tr>
<td>Clotrimazole + Indomethacin</td>
<td>-5.99 ± 0.13</td>
<td>-5.60 ± 0.05*</td>
</tr>
<tr>
<td>Log IC50 (Rmax (%))</td>
<td>63.0 ± 2.8</td>
<td>52.4 ± 2.7*</td>
</tr>
</tbody>
</table>

NC = Not calculated because Rmax < 50%
* Significantly different from control (P < 0.05).
lease of multiple substances from the endothelium that decrease vascular smooth muscle tone. Three primary endothelium-derived relaxing factors have been identified: NO, prostacyclin, and EDHFs. To evaluate the role of each mediator in acetylcholine-induced pulmonary vasorelaxation, we inhibited the production of each of these endothelium-derived relaxing factors. Cyclooxygenase inhibition with indomethacin only attenuated acetylcholine-induced relaxation at high concentrations of the agonist; therefore, prostacyclin does not appear to play a primary role in the response. In contrast, NO synthase inhibition with l-NAME inhibited acetylcholine-induced vasorelaxation after inhibitions of nitric oxide–mediated component. L = l-NAME pretreated; I = indomethacin pretreated.

Propofol inhibited acetylcholine-induced relaxation in a dose-dependent fashion. In contrast, propofol had no effect on the pulmonary vasorelaxant response to the guanylyl cyclase activator, SIN-1. These results clearly demonstrate that the inhibitory effect of propofol on acetylcholine-induced vasorelaxation is not the result of a defect in pulmonary vascular smooth muscle cyclic guanosine monophosphate production.

To determine whether propofol exerted its inhibitory effect on the NO-mediated component of acetylcholine-induced relaxation, we assessed the effects of propofol on the acetylcholine concentration–effect curve after combined inhibition of the cyclooxygenase and cytochrome P450 pathways. During these conditions, the vasorelaxant response to acetylcholine is mediated by NO and is abolished by NO synthase inhibition. Propofol attenuated, but did not abolish, the NO-mediated component.
component of acetylcholine-induced relaxation, which indicates that propofol exerts a portion of its inhibitory effect on the endothelial signaling pathway for NO production.

To determine whether propofol exerted a generalized inhibitory effect on endothelium-dependent vasodilation, we assessed the effects of propofol on bradykinin-induced vasorelaxation. In canine pulmonary arterial rings, bradykinin-induced vasorelaxation is mediated by a synergistic interaction between NO and prostacyclin. Propofol had no effect on the pulmonary vasorelaxant response to bradykinin. These results suggest that propofol exerts its effect by selectively inhibiting the signaling pathway for acetylcholine-induced NO production, rather than causing a generalized decrease in NO synthesis. The locus of dysfunction would appear to be upstream from NO synthase activity, perhaps involving an effect of propofol on the endothelial muscarinic receptor or the receptor–G-protein interaction. Propofol has been reported to inhibit the rat M1 muscarinic acetylcholine receptor and/or receptor–G-protein interaction in *Xenopus* oocytes, although there is a conflicting report. Propofol has also been reported to inhibit neuronal nicotinic acetylcholine receptor-mediated signaling in *Xenopus* oocytes and in a rat pheochromocytoma cell line. The extent to which propofol alters muscarinic receptor function in endothelial cells has not been investigated.

To determine whether propofol exerted its inhibitory effect on the EDHF-mediated component of acetylcholine-induced relaxation, we assessed the effects of propofol on the acetylcholine concentration–effect curve after combined inhibition of the cyclooxygenase and NO synthase pathways. During these conditions, the vasorelaxant response to acetylcholine is mediated by EDHF and is abolished by cytochrome P450 inhibition. The chemical nature of EDHF has not been fully elucidated, and it is likely that there is more than one form of EDHF. Recent evidence suggests that an EDHF may be a cytochrome P450 metabolite of arachidonic acid, presumably an epoxyeicosatrienoic acid. We used both SKF525A and clotrimazole as EDHF inhibitors. SKF525A is an intermediate metabolite of cytochrome P450, whereas clotrimazole directly binds to the cytochrome P450 monoxygenase to specifically inhibit the enzyme. Both of these cytochrome P450 inhibitors attenuated acetylcholine-induced relaxation by 30–40%, which led us to conclude that EDHFs mediate a component of the response. Propofol inhibited this EDHF-mediated component of acetylcholine-induced relaxation. Whether this inhibitory effect is the result of a decrease in the synthesis or activity of EDHFs remains to be elucidated.

The EDHF-mediated vasorelaxant response to acetylcholine has been reported to be attenuated by volatile anesthetics in rabbit carotid artery and by etomidate and thiopental in human renal artery. The importance of EDHFs as modulators of vasomotor tone increases as vessel size decreases. Iranami et al. postulated that the inhibitory effect of halothane on acetylcholine-induced relaxation was related to an effect on NO in rat aorta, whereas it was caused by effects on NO and EDHFs in rat mesenteric artery. Akata et al. suggested that the relative importance of NO and EDHFs in acetylcholine-induced relaxation was dependent on the concentration of the agonist, with EDHFs playing a more prominent role at higher concentrations of acetylcholine. Loeb et al. reported that isoflurane altered the balance between NO and EDHFs in the rat cremaster muscle microcirculation, decreasing the role of EDHFs but increasing the contribution of NO. Thus, the mechanism for anesthesia-induced inhibition of acetylcholine-induced relaxation may depend on vessel type and size.

Additional control experiments were performed to assess the specificity of the cytochrome P450 inhibitors. As previously noted, bradykinin-induced pulmonary vasorelaxation is mediated by a synergistic interaction between NO and prostacyclin that is adenosine triphosphate-sensitive potassium channel dependent (presumably involving an EDHF). As expected, both SKF525A and clotrimazole attenuated the pulmonary vasorelaxant response to bradykinin in endothelium intact rings. In contrast, neither inhibitor had a significant effect on the vasorelaxation responses to SIN-1 or papaverine in endothelium-denuded

### Table 4. Effect of Cytochrome P450 Inhibition on Relaxation Induced by Bradykinin, SIN-1, and Papaverine

<table>
<thead>
<tr>
<th>Bradykinin</th>
<th>Control</th>
<th>SKF 525A</th>
<th>Clotrimazole</th>
</tr>
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<tbody>
<tr>
<td>Log IC₅₀</td>
<td>-8.44 ± 0.15</td>
<td>-8.20 ± 0.14*</td>
<td>-8.17 ± 0.10*</td>
</tr>
<tr>
<td>Rmax (%)</td>
<td>12.9 ± 2.0</td>
<td>31.1 ± 3.6*</td>
<td>31.5 ± 5.0*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIN-1</th>
<th>Log IC₅₀</th>
<th>-6.88 ± 0.15</th>
<th>-6.80 ± 0.11</th>
<th>-6.79 ± 0.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rmax (%)</td>
<td>-1.0 ± 5.0</td>
<td>0.0 ± 6.3</td>
<td>3.5 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Papaverine</th>
<th>Log IC₅₀</th>
<th>-5.21 ± 0.04</th>
<th>-5.16 ± 0.06</th>
<th>-5.04 ± 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rmax (%)</td>
<td>-4.9 ± 2.3</td>
<td>-0.3 ± 4.0</td>
<td>14.7 ± 12.9</td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different from control (P < 0.05).
rings. Thus, the inhibitory effects of SKF525A and clotrimazole on bradykinin (and acetylcholine) relaxation are not caused by a nonspecific effect on pulmonary vascular smooth muscle vasorelaxant activity. The fact that the cytochrome P450 inhibitors attenuated the relaxant responses to acetylcholine and bradykinin, whereas propofol only attenuated the response to acetylcholine, may suggest that these agonists stimulate different forms of EDHF.

The plasma concentration of propofol required to prevent the response to a surgical stimulus is approximately 34 μM in humans and dogs. Because more than 90% of propofol is bound to plasma proteins, the free concentration of propofol is estimated to be 3–10 μM. In our study we observed that 3–10 μM concentrations of propofol attenuated the vasorelaxant response to acetylcholine, although it is acknowledged that higher concentrations (100 μM) were used in some protocols.

In summary, our results indicate that propofol selectively inhibits both the NO- and EDHF-mediated components of acetylcholine-induced relaxation in canine pulmonary arterial rings. These effects are apparent over the full concentration range of acetylcholine.

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