

Original Article

Investigation of the relaxant effects of propofol on ovalbumin-induced asthma in guinea pigs

I. Bagcivan*, O. Cevit†, M. K. Yildirim*, S. Gursoy‡, S. Yildirim*, T. Kaya*, C. Mimaroglu‡

*Cumhuriyet University School of Medicine, Departments of Pharmacology; †Pediatry; ‡Anesthesiology, Sivas, Turkey

Summary

Background and objective: Because the incidence of asthma appears to be increasing, the importance of proper perioperative management of individuals with asthma will also continue to increase. Although its mechanism of smooth muscle relaxation is unknown, propofol has been associated with less bronchoconstriction during anaesthetic induction. The aim of this study was to investigate the possible mechanism of these effects and the effects of propofol on the isolated trachea preparations from control and ovalbumin-sensitized guinea pigs. **Methods:** Adult male guinea pigs, weighing 280–330 g, were randomly allocated to two experimental groups, each consisting of 10 animals. Ten guinea pigs were sensitized by intramuscular injections of 0.30 mL of a 5% (w/v) ovalbumin/saline solution into each thigh (0.6 mL total) on days 1 and 4, whereas the remaining 10 served as controls receiving a total of 0.6 mL distilled water on days 1 and 4 as placebo. The isolated trachea preparations were mounted in tissue baths with modified Krebs–Henseleit solution and aerated with 95% oxygen and 5% carbon dioxide. We tested the effects of propofol (10^{-7} – 10^{-3} M) on resting tension and after precontraction with carbachol and histamine on isolated trachea preparations from control and ovalbumin-sensitized guinea pigs. We also tested the effect of propofol on isolated trachea preparations precontracted with carbachol and histamine in the absence and presence of different inhibitors or antagonists. We investigated propofol responses in tracheal smooth muscle precontracted with CaCl_2 . **Results:** Propofol (10^{-7} – 10^{-3} M) produced a concentration-dependent relaxation of isolated tracheal preparations precontracted by carbachol (10^{-6} M) and histamine (10^{-6} M) in both groups. Preincubation with *N*(w)-nitro *L*-arginine methyl ester (3×10^{-5} M), indomethacin (10^{-5} M) or propranolol (10^{-4} M) did not produce a significant alteration on propofol-induced relaxation responses ($P > 0.05$), while preincubation with tetraethylammonium (3×10^{-4} M) significantly decreased the propofol-induced relaxation responses in both groups ($P < 0.05$). Propofol (10^{-7} – 10^{-3} M) induced concentration-dependently relaxations in isolated trachea rings precontracted with CaCl_2 in both the control and ovalbumin-sensitized groups. **Conclusion:** Propofol induced concentration-dependent relaxations in precontracted, isolated trachea smooth muscle of guinea pigs in both the control and ovalbumin-sensitized groups. These relaxations were independent of epithelial function and stimulation of β adrenergic receptors. Opened Ca^{2+} -sensitive K^+ channels and inhibited *L*-type Ca^{2+} channels can contribute to these relaxations.

Keywords: PROPOFOL; TRACHEA; GUINEA PIGS; OVALBUMIN, sensitization.

Introduction

Because the incidence of asthma appears to be increasing [1], the importance of proper perioperative management of individuals with asthma will also continue to increase [2]. The occurrence of significant perioperative respiratory complications such as bronchospasm and pulmonary barotrauma is thought to be increased in persons with asthma, with reported frequencies as high as 30%. These reports suggest that such patients have a significant risk for perioperative respiratory complications [3–5].

The rising prevalence of asthma in childhood means that anaesthetists are encountering children with this disorder scheduled for surgery with increasing frequency [6–8]. The increase in the volume of day case surgery has limited the time available for the assessment of the child's medical condition and possible anaesthetic risk [9]. However, adverse events during anaesthesia of children with asthma are fortunately rare [10].

Although its mechanism of smooth muscle relaxation is unknown, propofol has been associated with less bronchoconstriction during anaesthetic induction [11] and has reversed bronchoconstriction associated with fentanyl [12]. It has also proven useful for decreasing airway resistance in patients with reactive airway disease [13,14].

Allergic asthma is characterized by airway hyperresponsiveness, allergen-specific immunoglobulin E in serum and infiltration of inflammatory cells into the airways [15–17]. Ovalbumin-induced asthma in guinea pigs is widely accepted as an experimental model of bronchial asthma [18]. The aim of this study was to investigate the possible mechanism of these effects and the effects of propofol on isolated trachea preparations from control and ovalbumin sensitized guinea pigs.

Methods

Adult male guinea pigs, weighing 280–330 g, were randomly allocated to two experimental groups, each consisting of 10 animals. The animal's weight was recorded. Animals were individually placed in metal cages in a temperature-controlled room ($22 \pm 0.2^\circ\text{C}$) in which a 12–12 h light–dark cycle was maintained. They were provided with food and water *ad libitum*. Guinea pigs in the experimental group were sensitized by intramuscular injections of 0.30 mL of a 5% (w/v) ovalbumin/saline solution into each thigh (0.6 mL total) on days 1 and 4. Guinea pigs in the control group similarly received 0.30 mL of saline solution into each thigh (0.6 mL total) on days 1 and 4. Twenty-five days were then allowed for the development of sensitization. All protocols

described in this study were approved by the local Ethical Committee for animal experimentation of the Cumhuriyet University Medical Faculty.

To test whether treated animals were sensitized to ovalbumin, the back of each guinea pig was shaved. Through a 27-G needle, 0.03 mL of each of the following solutions was injected intradermally: isotonic saline, histamine (30 μg) and ovalbumin (0.5, 1.0 and 5 μg). To quantitatively evaluate the response, two perpendicular diameters of the resulting wheal were measured 60 min after the injection, and the average was then calculated [19].

Guinea pigs were stunned and killed by decapitation. The trachea was removed rapidly and transverse rings (3 mm long) were cut and then mounted in thermostatically controlled (37°C) organ baths. The organ baths contained 10 mL Krebs–Henseleit solution of the following composition (in mmol L^{-1}): NaCl, 120; KCl, 4.6; MgSO_4 , 1.2; NaHCO_3 , 22; NaH_2PO_4 , 1.2; CaCl_2 , 2.5; glucose, 11.5. The pH of the solution was 7.4 and was aerated with 5% CO_2 and 95% O_2 . Isometric tension was continuously measured with a force transducer (Grass FT 03; Quincy, MA, USA). The tissues were stretched initially to a tension of 1 g for 30 s and thereafter maintained for 60 min under a resting tension of 0.5 g, which was found to be optimal for measuring the changes in tension. The preparations were washed with bathing solution every 15 min during the equilibration period.

After the equilibration period, the tissues were contracted with a submaximal concentration of carbachol (10^{-6} M) and histamine (10^{-6} M). These concentrations of carbachol and histamine were determined from preliminary experiments to elicit 70% of its maximum concentration. We tested the effects of propofol (10^{-7} – 10^{-3} M) on resting tension and after precontraction with carbachol and histamine on isolated trachea preparations from control and ovalbumin-sensitized guinea pigs. After the addition of each dose, we waited until a plateau response was obtained before adding the next one. Propofol was added in a cumulative manner to the organ bath. At the end of the experiment, papaverine (10^{-4} M) was added to the organ bath to obtain maximal relaxation and to control the relaxing ability of tracheal preparations. The preparations were then washed three times before inhibitors or antagonists were applied. *N*(w)-nitro-L-arginine methyl ester (L-NAME) ($3 \times 10^{-5}\text{ M}$), a non-specific inhibitor of nitric oxide synthase, indomethacin (10^{-5} M), an inhibitor of cyclo-oxygenase, tetraethylammonium (TEA) ($3 \times 10^{-4}\text{ M}$) and propranolol (10^{-4} M) were added to the tissue bath. Twenty minutes later, the trachea preparations were contracted with carbachol and histamine

separately, and relaxation responses to propofol were obtained. The doses of inhibitors or antagonists were chosen based on previous studies.

Three antagonists were tested in each preparation. The order of addition of drugs was randomized, and there was no observable correlation between the order of the drug addition and the measured response; approximately 30–40 min elapsed between studies. Bathing solution was replaced three times after each study and the tissue was allowed to return to baseline tension. The effects of antagonists or inhibitors on propofol-induced relaxation were evaluated by comparing the response before and after the addition of antagonists or inhibitors in the same preparation.

To determine whether calcium antagonist activity plays a role in the relaxation induced by propofol, rings were placed in a calcium-free solution containing 80 mmol K^+ . Propofol (10^{-7} – 10^{-3} M) was added to the organ bath and 30 min later calcium (2.5 mmol) was added and a contraction was developed. At the end of the experiment, verapamil (10^{-4} M) was added to the organ bath to obtain maximal relaxation.

Drugs such as carbachol chloride, histamine, propofol, papaverine hydrochloride, L-NAME, indomethacin, propranolol, TEA and verapamil were obtained from Sigma Chemical Co. (St Louis, MO, USA). All drugs were dissolved in distilled water except for indomethacin, which was dissolved in dimethyl sulfoxide (DMSO) and then diluted with distilled water. All drugs were freshly prepared on the day of the experiment. No effect of DMSO was observed on the isolated trachea preparations.

Data analysis

Carbachol and histamine-induced (10^{-6} M) contractions were considered as reference responses. Relaxation responses were expressed as a percentage of the carbachol and histamine-induced contractions. The effect of cumulative concentrations of propofol on carbachol and histamine-induced contractions in the absence or presence of antagonists or inhibitors was measured and values for $\log_{10}$

EC_{50} (pD_2) and mean maximal inhibition (E_{max}) were compared. Maximal inhibitor effects were calculated for each concentration–response curve. The EC_{50} value represents 50% of the maximal inhibitor effect. EC_{50} values were calculated by linear regression of the probit of response vs. $\log_{10}$ molar concentration for propofol. Experimental values were presented as means $\pm$ SEM and analysed by repeated measures of analysis of variance (ANOVA) with the Newman–Keuls test, and a *t*-test when appropriate. A *P* value of <0.05 was considered significant. All statistical analyses were performed using Statistica for Windows 6.0. (Statsoft Inc., Tulsa, USA).

Results

The results obtained from the skin test (Table 1) showed distinct differences between the sensitized and control groups in their reactions to all three doses of ovalbumin injections, whereas no difference was found in their reactions to histamine injections. Neither group showed any positive skin reaction to saline injection.

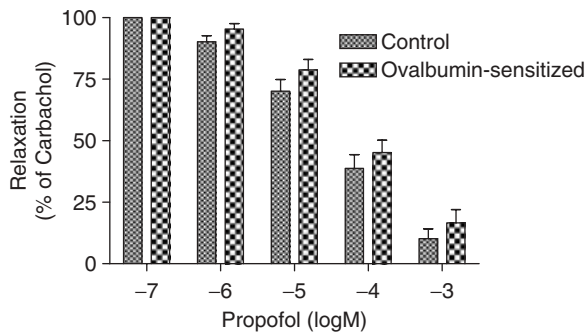
Propofol (10^{-7} – 10^{-3} M) did not produce any effect on basal tension of isolated trachea preparations from control and ovalbumin-sensitized guinea pigs. Propofol (10^{-7} – 10^{-3} M) produced concentration-dependent relaxation on preparations precontracted with carbachol (10^{-6} M) and histamine (10^{-6} M) in both groups (Figs 1 and 2). In preparations from ovalbumin-sensitized guinea pigs, E_{max} and pD_2 values of propofol did not change in comparison to the control group ($P < 0.05$). Propofol induced almost total relaxation in trachea rings precontracted with both carbachol and histamine in both groups (Table 2).

None of the antagonists or inhibitors investigated had a significant influence on basal tone of isolated trachea preparations from control and ovalbumin-sensitized guinea pigs. Preincubation with L-NAME (3×10^{-5} M), indomethacin (10^{-5} M) and propranolol (10^{-4} M) did not produce a significant alteration on propofol-induced relaxation responses, while preincubation with TEA

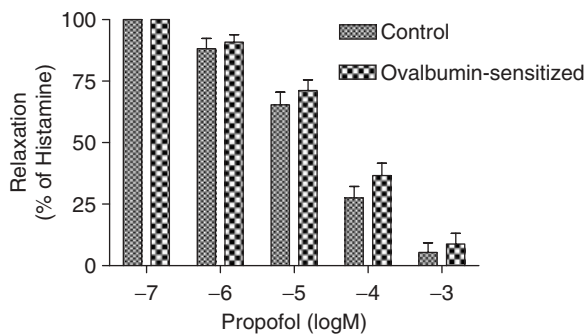
Table 1. Average group responses to skin reaction test with ovalbumin.

Group	Saline	0.5 μ g	1.0 μ g	5.0 μ g	Histamine 30 μ g
Control	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.5 $\pm$ 0.3	8.8 $\pm$ 0.6
Sensitized	0.0 $\pm$ 0.0	7.6 $\pm$ 0.5*	8.7 $\pm$ 0.4*	12.1 $\pm$ 0.5*	11.7 $\pm$ 0.5

Data are presented as means $\pm$ SEM of the average diameter (mm) of the wheals at 60 min after injection. *Significant difference between control and sensitized guinea pigs.

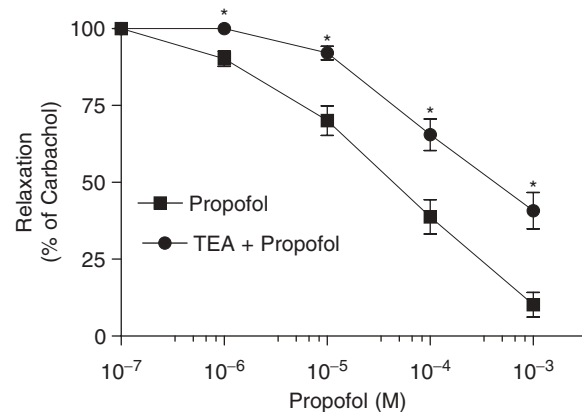
**Figure 1.**

The effect of propofol (10^{-7} – 10^{-3} M) in isolated tracheal preparations precontracted with carbachol (10^{-6} M) from control and ovalbumin-sensitized guinea pigs. Relaxation responses are expressed as a percentage of carbachol-induced contraction and shown as mean $\pm$ SEM ($n = 10$).

**Figure 2.**

The effect of propofol (10^{-7} – 10^{-3} M) in isolated tracheal preparations precontracted with histamine (10^{-6} M) from control and ovalbumin-sensitized guinea pigs. Relaxation responses are expressed as a percentage of histamine-induced contraction and shown as mean $\pm$ SEM ($n = 10$).

(3×10^{-4} M) significantly decreased the propofol-induced relaxation responses in both groups (Table 2, Figs 3–6). There was no significant difference between propofol-induced $E_{\max}$ and pD_2 values in the presence of antagonists or inhibitors ($P > 0.05$), except for TEA in both groups ($P < 0.05$) (Table 2). Propofol (10^{-7} – 10^{-3} M) induced concentration-dependent relaxations in trachea rings precontracted by $CaCl_2$ in both groups, $50.2\% \pm 6.2$ and $57.8\% \pm 5.7$, respectively (Fig. 7). Verapamil (10^{-4} M) induced almost 100% relaxation in tissues precontracted by $CaCl_2$.

**Figure 3.**

The effect of propofol (10^{-7} – 10^{-3} M) in the absence or presence of TEA (3×10^{-4} M) in isolated tracheal preparations precontracted with carbachol (10^{-6} M) from control guinea pigs. Relaxation responses are expressed as a percentage of carbachol-induced contraction and shown as mean $\pm$ SEM ($n = 10$).

* $P < 0.05$, from propofol alone.

Table 2. $E_{\max}$ (percentage of 10^{-6} M carbachol and 10^{-6} M histamine) and pD_2 values ($-\log EC_{50}$) for propofol in the absence or presence of antagonists or inhibitors in tracheal preparations from control and ovalbumin-sensitized guinea pigs.

Drug	Control group		Ovalbumin-sensitized group	
	Carbachol-induced	Histamine-induced	Carbachol-induced	Histamine-induced
Propofol (alone)				
$E_{\max}$ (%)	89.8 $\pm$ 4.0	94.6 $\pm$ 3.9	83.4 $\pm$ 5.4	91.2 $\pm$ 4.3
pD_2	4.46 $\pm$ 0.10	4.60 $\pm$ 0.08	4.38 $\pm$ 0.11	4.54 $\pm$ 0.10
L-NAME + propofol				
$E_{\max}$ (%)	84.9 $\pm$ 5.8	89.6 $\pm$ 4.2	79.8 $\pm$ 4.9	85.8 $\pm$ 4.4
pD_2	4.38 $\pm$ 0.08	4.56 $\pm$ 0.10	4.42 $\pm$ 0.11	4.47 $\pm$ 0.07
Indomethacin + propofol				
$E_{\max}$ (%)	85.6 $\pm$ 4.6	92.2 $\pm$ 4.7	82.6 $\pm$ 5.0	86.3 $\pm$ 4.9
pD_2	4.50 $\pm$ 0.09	4.55 $\pm$ 0.10	4.43 $\pm$ 0.08	4.51 $\pm$ 0.11
Propranolol + propofol				
$E_{\max}$ (%)	87.4 $\pm$ 4.9	91.2 $\pm$ 3.6	85.6 $\pm$ 4.3	89.4 $\pm$ 5.3
pD_2	4.48 $\pm$ 0.12	4.50 $\pm$ 0.09	4.54 $\pm$ 0.09	4.46 $\pm$ 0.10
TEA + propofol				
$E_{\max}$ (%)	59.2 $\pm$ 5.9 ^a	63.6 $\pm$ 4.0 ^a	62.6 $\pm$ 5.2 ^a	65.6 $\pm$ 4.9 ^a
pD_2	4.42 $\pm$ 0.12	4.50 $\pm$ 0.10	4.40 $\pm$ 0.10	4.48 $\pm$ 0.12

Data are expressed as mean $\pm$ SEM ($n = 10$ in each group); ^a $P < 0.05$, statistically different from $E_{\max}$ values of all groups.

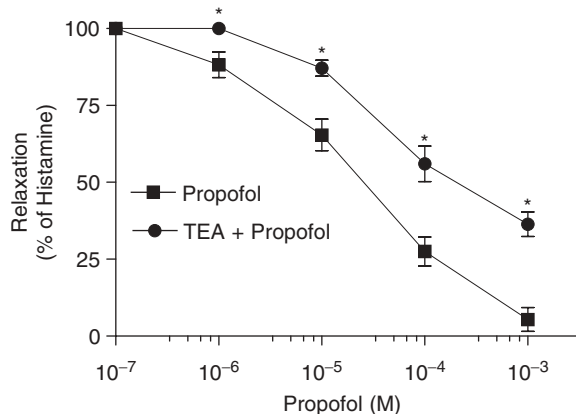


Figure 4. The effect of propofol (10^{-7} – 10^{-3} M) in the absence or presence of TEA (3×10^{-4} M) in isolated tracheal preparations precontracted with histamine (10^{-6} M) from control guinea pigs. Relaxation responses are expressed as a percentage of histamine-induced contraction and shown as mean $\pm$ SEM ($n = 10$). * $P < 0.05$, from propofol alone. (TEA: tetraethylammonium).

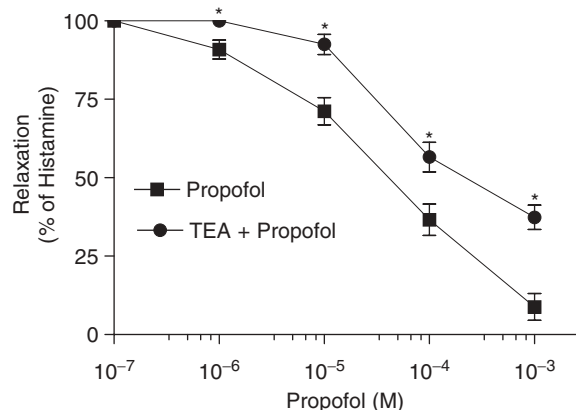


Figure 6. The effect of propofol (10^{-7} – 10^{-3} M) in the absence or presence of TEA (3×10^{-4} M) in isolated tracheal preparations precontracted with histamine (10^{-6} M) in ovalbumin-sensitized guinea pigs. Relaxation responses are expressed as a percentage of histamine-induced contraction and shown as mean $\pm$ SEM ($n = 10$). * $P < 0.05$, from propofol alone. (TEA: tetraethylammonium).

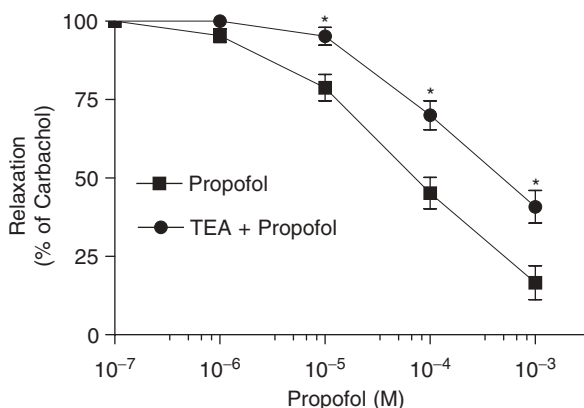


Figure 5. The effect of propofol (10^{-7} – 10^{-3} M) in the absence or presence of TEA (3×10^{-4} M) in isolated tracheal preparations precontracted with carbachol (10^{-6} M) in ovalbumin-sensitized guinea pigs. Relaxation responses are expressed as a percentage of carbachol-induced contraction and shown as means $\pm$ SEM ($n = 10$). * $P < 0.05$ from propofol alone. (TEA: tetraethylammonium).

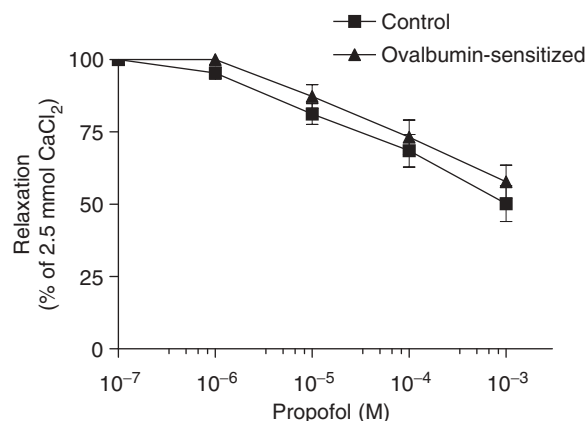


Figure 7. The effect of propofol (10^{-7} – 10^{-3} M) in isolated tracheal preparations precontracted with CaCl_2 (2.5 mmol) from control and ovalbumin-sensitized guinea pigs. Relaxation responses are expressed as a percentage of 2.5 CaCl_2 -induced contraction and shown as mean $\pm$ SEM ($n = 10$). (TEA: tetraethylammonium).

Discussion

As asthma is characterized by increased airway reactivity to different stimuli, the choice of anaesthetic technique must consider the increased risk of bronchospasm. Anaesthesia may induce changes in airway resistance, alter ventilation distribution, produce atelectasis and reduce lung volume [20], any of which may result in hypoxaemia.

Propofol has been shown to reduce the incidence of airway obstruction at induction [21], shorten recovery time and allow earlier discharge for out-

patients [22,23] and reduce postoperative emesis [24,25]. Propofol has been reported to be safe in asthmatic patients [12,26,27].

Whether the relaxant effect of propofol is dependent on endothelial cells in vascular smooth muscle is, however, controversial. Park and colleagues [28] reported that propofol stimulates the release of vasodilating cyclo-oxygenase metabolites from rat vascular rings with intact endothelium. Gagar and colleagues [29] suggested that the relaxing property of propofol on bovine coronary artery rings, at least in part, depends on endothelium-derived relaxing factor which might be nitric oxide. However, Chang

and Davis [30] showed that propofol produces concentration-dependent relaxation that is independent of endothelium function in a rat aortic ring preparation. The epithelium-independent relaxant property of propofol is advantageous for patients with airway hyperreactivity. Because there is significant damage to epithelial cells in airway disease, the epithelial damage may be related to bronchial hyperresponsiveness [31,32]. Yamaguchi and colleagues [33] reported that propofol abolished 5-HT-induced contraction, attenuated acetylcholine-induced contraction, and also almost completely attenuated the enhancement by 5-HT of electrical field stimulation-induced contraction. These results suggest that the mechanism involved in the attenuation of ovalbumin-induced contraction by propofol is inhibition of the action of 5-HT.

We found that the relaxant effect of propofol on guinea pig tracheal smooth muscle is independent of the function of airway epithelium and stimulation of β adrenergic receptors. In addition, propofol possesses tracheal relaxant effect in ovalbumin-sensitized guinea pigs. Both L-NAME and indomethacin did not change relaxation by propofol. This suggests that relaxation by propofol is independent of nitric oxide and cyclo-oxygenase products released from airway epithelium. Relaxation by propofol is not related to stimulation of β adrenergic receptors because they were not changed by propranolol.

In previous studies, it was suggested that dilatation of various smooth muscles is mediated by the activation of different types of potassium channels [34]. In our study, propofol-induced relaxations were decreased by TEA, a Ca^{2+} -sensitive K^+ channel blocker, in precontracted tracheal smooth muscle by both histamine and carbachol. This reduction did not reveal any differences in both groups. It is possible that Ca^{2+} -sensitive K^+ channels have a role in propofol-induced relaxant effects.

In conclusion, propofol induced concentration-dependent relaxations in precontracted isolated tracheal smooth muscle of guinea pigs in both control and ovalbumin-sensitized groups. These relaxations were independent of nitric oxide and cyclo-oxygenase products released from airway epithelium and stimulation of β adrenergic receptors. Opened Ca^{2+} -sensitive K^+ channels and inhibited L-type Ca^{2+} channels can contribute to these relaxations.

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