

Propofol Attenuates Ovalbumin-Induced Smooth Muscle Contraction of the Sensitized Rat Trachea: Inhibition of Serotonergic and Cholinergic Signaling

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Propofol is considered suitable for induction of anesthesia in patients with bronchial asthma. However, the mechanisms of its action on bronchi are not fully understood. We examined the effects of propofol on ovalbumin (OA)-induced contraction of OA-sensitized rat trachea. Male Wistar rats were sensitized by a single intraperitoneal injection of OA 10 μ g mixed with aluminum hydroxide, 10 mg, as adjuvant. Fourteen days later, the experiment was performed using the tracheal rings. We observed the effects of ketanserin, a 5-HT₂ receptor antagonist, and atropine on OA-induced contraction. Next, the effects of propofol on OA-, serotonin (5-HT)-, acetylcholine-, or electrical field stimulation-induced contractions were observed. OA-induced contraction was 90% attenuated by the combination of ketanserin and atropine. Propofol significantly attenuated OA-induced contraction in a dose-dependent manner. 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 by propofol of OA-induced contraction is inhibition of the actions of 5-HT. Propofol should be a useful anesthetic in patients with immunoglobulin E-related asthma.

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Propofol attenuates tracheal smooth muscle contraction induced by carbachol (1), histamine (2,3), and other mediators (4,5). The mechanisms involved in this effect include a propofol-induced decrease in the release of Ca²⁺ from internal stores and also inhibition of Ca²⁺ influx (1). In addition, propofol attenuates inositol phosphate accumulation (1) and inhibits voltage-dependent Ca²⁺ channels of tracheal smooth muscle cells (6).

Bronchial asthma is a disease characterized by airway inflammation and airway hyper-responsiveness to constrictor agents. Immunoglobulin E (IgE) and mast cells play important roles in allergic inflammation and airway hyper-responsiveness. IgE binds the antigen, and the immune complexes thus formed augment allergic airway response in a high-affinity IgE receptor-dependent manner. IgE activates mast cells to release mediators that induce airway inflammation, acute bronchoconstriction, bronchial mucosa

edema, and mucus secretion. In the ovalbumin (OA)-sensitized asthma model, immunization increases antigen-specific IgE (7,8). After antigen challenge, mast cells release constrictor mediators such as serotonin (5-HT), acetylcholine (ACh) (9), and other mediators (10,11) that cause airway smooth muscle contraction.

Propofol is the drug of choice for induction of anesthesia in asthmatics (12). It was reported that propofol reduced histamine-induced contraction in human isolated airway smooth muscles passively sensitized with asthmatic serum (3). However, other mechanisms involved in smooth muscle of sensitized airway have not been fully understood. We investigated the effects of propofol on OA-induced smooth muscle contraction of OA-sensitized rat trachea.

METHODS

The studies were conducted under the guidelines approved by our Institutional Animal Care Committee. Ninety male Wistar rats weighing 160-180 g were used for the experiments.

The rats were sensitized by a single intraperitoneal injection of OA, 10 μ g, mixed with aluminum hydroxide 10 mg as adjuvant. The nonsensitized group was injected with saline intraperitoneally as controls. Fourteen days later, the experiments of contractile response and electrical field stimulation (EFS) were performed using isolated tracheal rings (Fig. 1).

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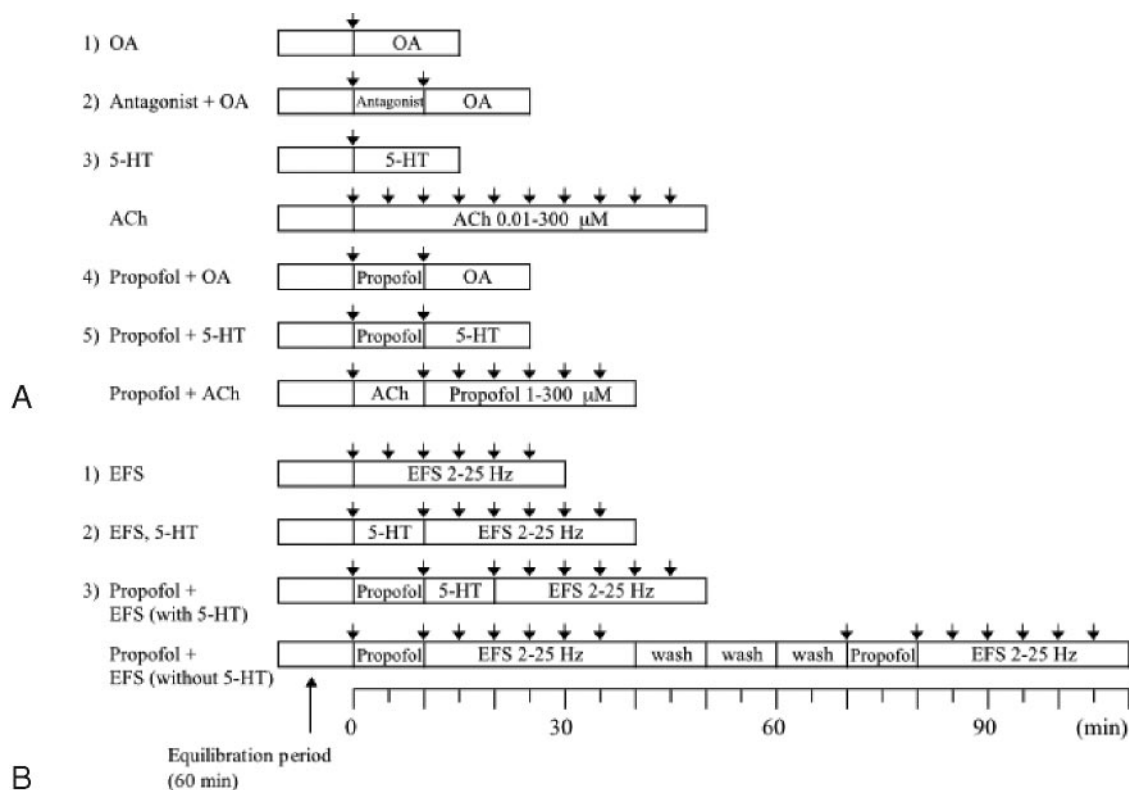


Figure 1. Experimental protocol. OA = ovalbumin; antagonist = ketanserin or atropine or both; 5-HT = serotonin; ACh = acetylcholine; EFS = electrical field stimulation.

The rats were anesthetized with pentobarbital 50 mg/kg intraperitoneally, and the tracheas were rapidly isolated. Nonsensitized and OA-sensitized tracheal rings were used. Each trachea was cut into 3-mm wide segments with a McIlwain tissue cutter (Mickle Laboratory Engineering, Gomshall, UK). Each tracheal ring segment was suspended between 2 stainless steel hooks and placed in a 5-mL water-jacketed organ chamber (Kishimotoika, Kyoto Japan) containing Krebs-Henseleit solution (composition in mM: 118 NaCl, 4.7 KCl, 1.3 CaCl₂, 1.2 KH₂PO₄, 1.2 MgSO₄, 25 NaHCO₃, 11 glucose, 0.05 Na₂-EDTA). The solution was continuously aerated with O₂ 95%/CO₂ 5% at a temperature of 37°C. Isometric tensions were measured using an isometric transducer (Kishimotoika, Kyoto Japan), and the changes in isometric force were recorded using a MacLab system (Milford, MA). The resting tension was adjusted periodically to 0.5 g during the equilibration period. The ring was washed every 15 min for 60 min. We used the distal segments corresponding to the last 3–5 cartilaginous rings closest to the bifurcation of the trachea because OA-induced contraction of distal segments was significantly greater than that of proximal segments (13).

First, the tissues were challenged by addition of OA at a final concentration of 50 µg/mL and the tension was measured. Second, we investigated whether 5-HT and ACh would participate in OA-induced contraction. After a 60-min equilibration period, ketanserin 1 µM, a 5-HT₂ receptor antagonist, or atropine 1 µM, or both was added, and 10 min later, OA at a final

concentration of 50 µg/mL was added and the tension was measured. The values for tension were expressed as the changes from baseline tension. Because contraction induced by OA of the tracheal smooth muscle occurs by the release of 5-HT, ACh (9), and other mediators (10,11), we used different rats in each experiment. Third, we examined whether airway hyper-responsiveness to 5-HT or ACh was seen in this sensitized model. Contractions were induced by 5-HT 0.01–100 µM or ACh, 0.01–300 µM, in the nonsensitized and the sensitized tracheas. Because 5-HT acts the cholinergic nerve to release ACh (14,15), the concentration-response curve of 5-HT was obtained by using different rats for each concentration. After a 60-min equilibration period, each concentration of 5-HT was added, and tension was measured in the nonsensitized and the sensitized tracheas. After a 60-min equilibration period, ACh was added stepwise-cumulatively, and tension was measured in the nonsensitized and the sensitized tracheas. Fourth, the effects of propofol on OA-induced contraction of the tracheal rings were observed. After a 60-min equilibration period, propofol 3–300 µM was added, and 10 min later, OA at a final concentration of 50 µg/mL was added and the tension was measured. The values for tension which were the changes from baseline tension were expressed as a percentage of the response induced by OA 50 µg/mL without propofol. Fifth, the effects of propofol on 5-HT or ACh-induced contractions of the nonsensitized and the sensitized tracheas were observed. Because contraction induced

Table 1. The Values of Tension on OA 50 $\mu\text{g/mL}$ -Induced Contraction of the Nonsensitized and OA-Sensitized Trachea and the Effects of Ketanserin or Atropine

Group	Antagonist	Tension (g)
Nonsensitized	None	-0.008 ± 0.003
OA-sensitized	None	$1.120 \pm 0.410^*$
	Ketanserin (1 μM)	$0.285 \pm 0.117^\ddagger$
	Atropine (1 μM)	$0.582 \pm 0.136^\ddagger$
	Ketanserin + Atropine	$0.088 \pm 0.039^\ddagger$

Data are mean $\pm$ sd. $n = 6$. OA = ovalbumin. The values for tension were expressed as the changes from baseline tension. * $P < 0.01$ versus the non-sensitized trachea; $^\ddagger P < 0.05$; $^\ddagger P < 0.01$ versus OA alone. Ten rats were used.

by 5-HT spontaneously decreases to the baseline within 30 min, the concentration-response curve of propofol on contraction induced by 5-HT was obtained by addition of 5-HT 3 μM in the presence of propofol 3–300 μM using different rats for each concentration of propofol. After the contraction induced by ACh 10 μM , propofol 3–300 μM was added stepwise-cumulatively. The values for tension that were the changes from baseline tension were expressed as a percentage of the response induced by 5-HT or ACh without propofol.

Rectangular pulses (pulse duration 0.5 ms, 50 V) of 2- to 25-Hz frequencies were delivered for 10 s every 5 min to the fields from an electrical stimulator (SEN-7203; Nihon Koden, Tokyo, Japan) (Fig. 1). First, we examined whether airway hyper-responsiveness to EFS was seen in this sensitized model. Contractions were induced by EFS in the nonsensitized and the sensitized trachea. The values for tension were expressed as the changes from the tension just before each EFS was performed. Second, we examined whether 5-HT would enhance EFS-induced contraction. Contractions were induced by EFS after the maximal contraction was induced by 5-HT 3 μM in the nonsensitized and the sensitized trachea. Third, the effects of propofol on EFS-induced contraction were observed. Contractions were induced by EFS in the presence of propofol 10–300 μM with and without 5-HT 3 μM . In the group without 5-HT, EFS responses at 2–25 Hz were obtained, the tracheal ring was washed 3 times, and then EFS responses at 2–25 Hz were obtained in the presence of different concentrations of propofol. The experiments were performed only twice for each tracheal ring. In the group with 5-HT, contractions were induced by 5-HT 3 μM in the presence of propofol 10–300 μM , and then the experiment of EFS was performed.

Data are expressed as mean $\pm$ sd. Concentration-effect curves were fitted by nonlinear regression (GraphPad Prism; GraphPad, San Diego, CA). The results of repeated measures and groups were analyzed by two-way analysis of variance. Comparisons between groups were assessed by Student's *t*-test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The sensitized but not the nonsensitized trachea was significantly contracted by OA (Table 1). Both

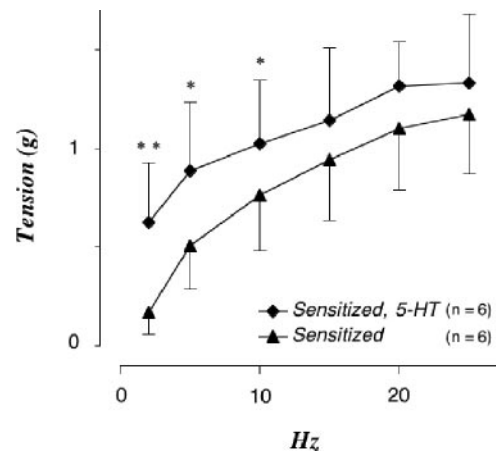


Figure 2. Effects of serotonin (5-HT) 3 μM on electrical field stimulation-induced contraction of the sensitized trachea. The values for tension were expressed as the changes from the tension just before each stimulation was performed. Data are mean $\pm$ sd * $P < 0.05$, ** $P < 0.01$ versus the sensitized trachea without 5-HT. Four rats were used.

ketanserin and atropine significantly attenuated OA-induced contraction, and the combination of these attenuated OA-induced contraction by nearly 90% (Table 1). EFS-induced contraction was abolished by atropine 1 μM (data not shown). 5-HT significantly enhanced EFS-induced contraction at 2–10 Hz of the sensitized trachea (Fig. 2, Table 3), and atropine 1 μM significantly attenuated 5-HT 3 μM -induced contraction of the sensitized trachea (Table 2). There were no significant differences in 5-HT-, ACh-, and EFS-induced contractions between the nonsensitized and the sensitized tracheas (Fig. 3). Propofol had no effect on the basal tone but significantly attenuated OA-induced contraction in a dose-dependent manner (Fig. 4). Propofol almost abolished 5-HT-induced contraction (Fig. 5) and significantly attenuated ACh-induced contraction, and there were no significant differences in the effects of propofol between the nonsensitized and the sensitized trachea (Fig. 5). Propofol significantly attenuated EFS-induced contraction in a dose-dependent manner both with and without 5-HT (Table 3). The extent of attenuation by propofol 300 μM of EFS-induced contraction was similar in the sensitized trachea with and without 5-HT (Table 3).

DISCUSSION

In the present study, OA induced smooth muscle contraction in OA-sensitized trachea, but not in the nonsensitized trachea. During OA-sensitization, antigen-specific IgE is produced, and IgE activates mast cells at

Table 2. Effects of Atropine on 5-HT 3 μM -Induced Contraction of Ovalbumin-Sensitized Trachea

Antagonist	Tension (g)
None	1.55 ± 0.28
Atropine (1 μM)	$0.76 \pm 0.15^*$

Data are mean $\pm$ sd. $n = 6$. 5-HT = serotonin. The values for tension were expressed as the changes from baseline tension. * $P < 0.05$ versus 5-HT without atropine. Four rats were used.

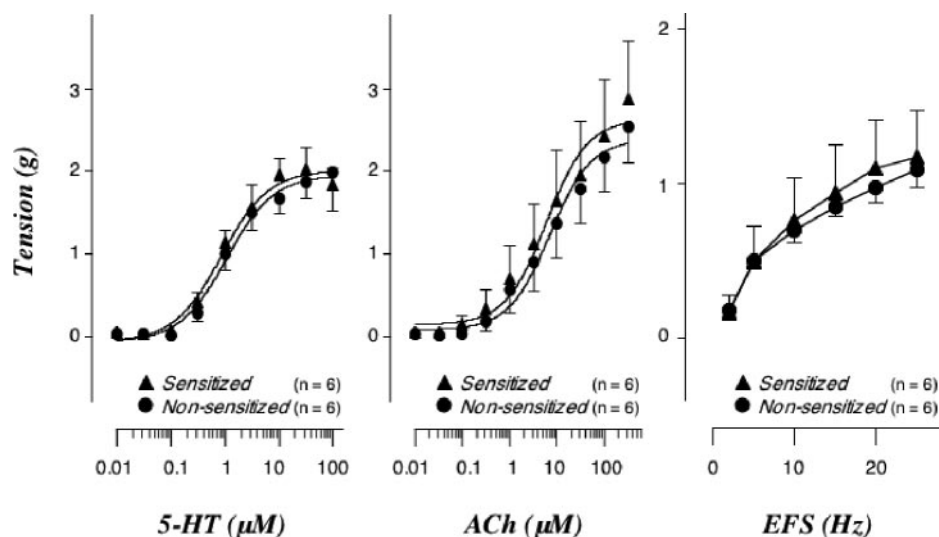


Figure 3. Effects of serotonin (5-HT), acetylcholine (ACh), and electrical field stimulation (EFS) on tension of the nonsensitized and ovalbumin-sensitized trachea. The values for tension were expressed as the changes from baseline tension in a 5-HT and ACh concentration-response curve. The values for tension were expressed as the changes from the tension just before each stimulation was performed in EFS frequency-response curve. Data are mean $\pm$ SD. Thirty-six rats were used.

OA challenge to release bronchoconstrictor mediators that are important for bronchial asthma (7). It was reported that after immunization of Wistar rats with OA, OA-specific IgE was produced (8), and administration of OA to OA-sensitized Wistar rats produced a rapid protein exudation, which was associated with marked mast cell degranulation determined by histological examination (16). We considered that the OA-sensitized model used in the present study was a reasonable model for human IgE-related asthma.

OA-induced contraction was significantly attenuated by both ketanserin and atropine and almost completely attenuated by the combination of these, suggesting that 5-HT and ACh play major roles in tracheal smooth muscle contraction induced by OA through 5-HT₂ and muscarinic M₃ receptors. Eum et al. (9) observed that immunized mice developed an acute bronchoconstriction *in vivo* and airway smooth muscle contraction *in vitro* in response to OA and found that methysergide, a 5-HT receptor antagonist, or atropine inhibited OA-induced bronchoconstriction *in vivo* and airway smooth muscle contraction *in vitro*,

and when the two antagonists were administered together, the response was completely inhibited. The present results are consistent with those of Eum et al. (9).

EFS-induced contraction was abolished by atropine in the present study (data not shown), suggesting that EFS-induced contraction was mediated by ACh from the cholinergic nerve. In the present experiments with 5-HT, EFS-induced contraction was elicited after the contraction was induced by 5-HT. Because values for tension were the changes from the tension just before each EFS was performed, 5-HT would potentiate EFS-induced contraction at 2–10 Hz rather than have a simple additive effect. Atropine significantly attenuated but did not completely abolish 5-HT-induced contraction in the present study. These results indicate that 5-HT released by OA-challenge causes contraction through two mechanisms (Fig. 6). One is mediated by a direct action of this agonist to the 5-HT receptors of tracheal smooth muscle cell membrane, and the other is by activation of 5-HT receptors on parasympathetic nerve endings. Dupont et al. (14) reported that 5-HT facilitated EFS-induced contraction in human airways, and tropisetron, a 5-HT₃ and 5-HT₄ antagonist, blocked the facilitatory effects of 5-HT. Szarek et al. (15) also reported that alkylation of muscarinic receptors with propylbenzylcholine mustard decreased maximal responses elicited by 5-HT. Our results are consistent with those of Dupont et al. (14) and Szarek et al. (15).

It was reported that administration of propofol produced an important bronchodilation in a patient mechanically ventilated for status asthmatics (17). In isolated human bronchi sensitized with asthmatic serum, propofol reduced histamine reactivity to a greater degree than in nonsensitized tissues (3). In the present study, IgE-related OA-induced tracheal smooth muscle contraction was significantly attenuated by propofol. Klockgether-Radke et al. (18) reported that propofol attenuates 5-HT-induced contraction of isolated coronary segments of human and porcine coronary

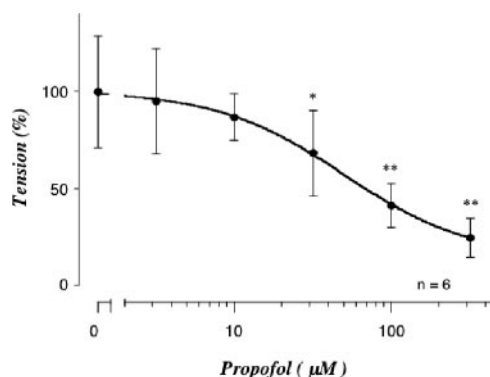
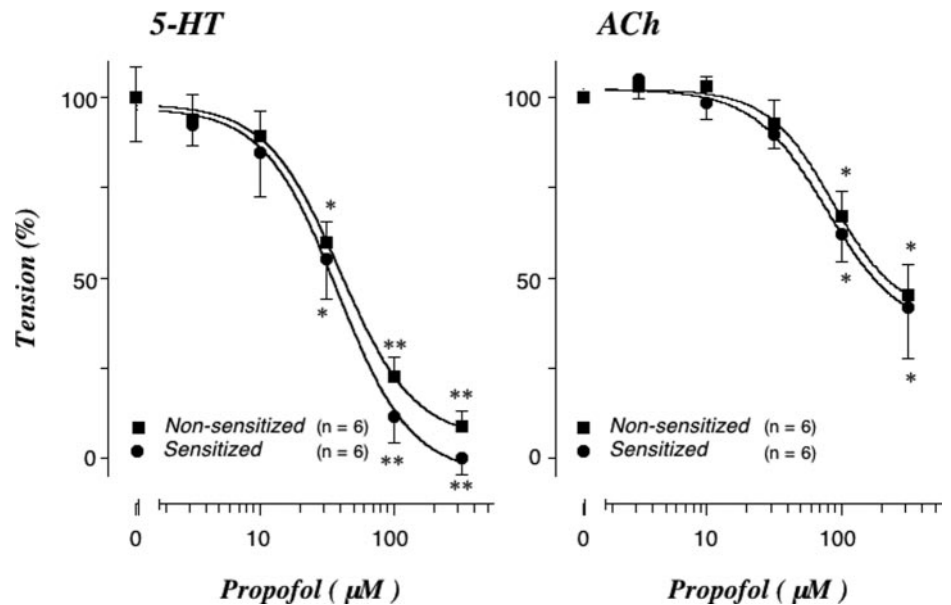


Figure 4. Effects of propofol on ovalbumin (OA)-induced contraction of OA-sensitized trachea. The values for tension that were the changes from baseline tension were expressed as a percentage of the response induced by OA, 50 μ g/mL, without propofol. Data are mean $\pm$ SD. * P < 0.05, ** P < 0.01 versus propofol, 0 μ M. Ten rats were used.

Figure 5. Effects of propofol on serotonin (5-HT)- and acetylcholine (ACh)-induced contractions of the sensitized and the nonsensitized trachea. The values for tension that were the changes from baseline tension were expressed as a percentage of the response induced by 5-HT, 3 μ M, or ACh, 10 μ M, without propofol. Data are mean $\pm$ SD. * P < 0.05, ** P < 0.01 versus propofol, 0 μ M. Twenty rats were used.



artery. Yamanoue et al. (19) reported that propofol attenuated 5-HT-induced contraction of the porcine coronary artery. However, there was no report about the effects of propofol on 5-HT-induced tracheal smooth muscle contraction. In the present study, propofol did not alter basal tone in the tracheal rings, but it attenuated 5-HT-induced tracheal smooth muscle contraction in a dose-dependent manner and at 300 μ M almost completely attenuated the effects of 5-HT. Propofol 300 μ M exerted similar attenuation on the EFS-induced contraction with and without 5HT. The results suggest that propofol at a higher concentration would abolish both kinds of action of 5-HT, i.e., the direct action on the tracheal smooth muscle cell

membrane and the indirect action on the parasympathetic nerve endings (Fig. 6). Propofol is also suggested to block the release of ACh induced indirectly by 5-HT or through some other undisclosed interaction of 5-HT at parasympathetic nerve endings. However, because propofol 300 μ M attenuated both exogenously applied ACh- and EFS-induced contractions to a similar extent, i.e., approximately 50%, propofol would not block the release of ACh but attenuate muscarinic effects of ACh at the muscarinic M_3 receptor.

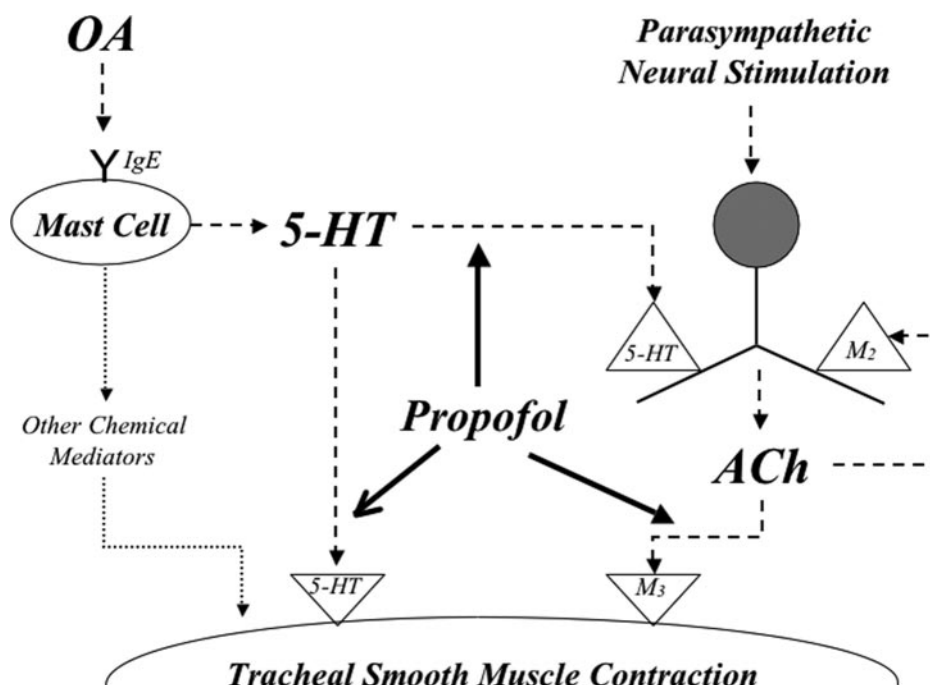
Airway hyper-responsiveness is the important factor for asthma. Hyper-responsiveness to ACh is considered to occur through several mechanisms, i.e., enhanced vagal reflex, loss of muscarinic M_2 receptor

Table 3. The Values of Tension on EFS-Induced Contraction Under Propofol With or Without 5-HT 3 μ M

	Tension (g)					
	2 Hz	5 Hz	10 Hz	15 Hz	20 Hz	25 Hz
OA-sensitized, without 5-HT						
Propofol 0 μ M	0.140 $\pm$ 0.087	0.468 $\pm$ 0.202	0.736 $\pm$ 0.274	0.924 $\pm$ 0.306	1.088 $\pm$ 0.311	1.158 $\pm$ 0.300
Propofol 10 μ M	0.177 $\pm$ 0.083	0.515 $\pm$ 0.169	0.760 $\pm$ 0.191	0.933 $\pm$ 0.252	1.083 $\pm$ 0.274	1.137 $\pm$ 0.308
Propofol 30 μ M	0.107 $\pm$ 0.055	0.403 $\pm$ 0.118	0.625 $\pm$ 0.156	0.792 $\pm$ 0.164	0.980 $\pm$ 0.187	1.042 $\pm$ 0.209
Propofol 100 μ M	0.065 $\pm$ 0.043	0.328 $\pm$ 0.147	0.555 $\pm$ 0.155	0.670 $\pm$ 0.150	0.743 $\pm$ 0.161*	0.812 $\pm$ 0.161*
Propofol 300 μ M	0.037 $\pm$ 0.028*	0.240 $\pm$ 0.140*	0.418 $\pm$ 0.237*	0.535 $\pm$ 0.302*	0.672 $\pm$ 0.327*	0.725 $\pm$ 0.319*
OA-sensitized, 5-HT						
Propofol 0 μ M	0.622 $\pm$ 0.304§	0.887 $\pm$ 0.346‡	1.022 $\pm$ 0.325†	1.143 $\pm$ 0.366	1.202 $\pm$ 0.349	1.333 $\pm$ 0.348
Propofol 10 μ M	0.536 $\pm$ 0.138§	0.813 $\pm$ 0.228‡	1.013 $\pm$ 0.250	1.063 $\pm$ 0.175	1.168 $\pm$ 0.197	1.260 $\pm$ 0.255
Propofol 30 μ M	0.363 $\pm$ 0.180§	0.681 $\pm$ 0.232‡	0.823 $\pm$ 0.341	0.906 $\pm$ 0.358	0.987 $\pm$ 0.358	1.100 $\pm$ 0.282
Propofol 100 μ M	0.140 $\pm$ 0.070*‡	0.408 $\pm$ 0.118†	0.618 $\pm$ 0.118*	0.728 $\pm$ 0.163*	0.752 $\pm$ 0.270*	0.902 $\pm$ 0.238*
Propofol 300 μ M	0.064 $\pm$ 0.044†	0.280 $\pm$ 0.277†	0.529 $\pm$ 0.261*	0.620 $\pm$ 0.287*	0.720 $\pm$ 0.366*	0.818 $\pm$ 0.192*
Non-sensitized, 5-HT						
Propofol 0 μ M	0.605 $\pm$ 0.273§	0.805 $\pm$ 0.306‡	0.933 $\pm$ 0.223‡	1.108 $\pm$ 0.395	1.243 $\pm$ 0.368	1.293 $\pm$ 0.314
Propofol 10 μ M	0.503 $\pm$ 0.273§	0.658 $\pm$ 0.197	0.822 $\pm$ 0.251	0.987 $\pm$ 0.269	1.138 $\pm$ 0.265	1.295 $\pm$ 0.273
Propofol 30 μ M	0.337 $\pm$ 0.103§	0.592 $\pm$ 0.147‡	0.732 $\pm$ 0.157	0.917 $\pm$ 0.178	1.013 $\pm$ 0.169	1.120 $\pm$ 0.188
Propofol 100 μ M	0.107 $\pm$ 0.063*	0.350 $\pm$ 0.151†	0.572 $\pm$ 0.189*	0.693 $\pm$ 0.321	0.803 $\pm$ 0.352	0.935 $\pm$ 0.296
Propofol 300 μ M	0.080 $\pm$ 0.048†	0.292 $\pm$ 0.121†	0.535 $\pm$ 0.118†	0.625 $\pm$ 0.154*	0.758 $\pm$ 0.079*	0.793 $\pm$ 0.168†

Data are mean $\pm$ SD. n = 6–7. EFS = electrical field stimulation; 5-HT = serotonin, OA = ovalbumin. The values for tension were expressed as the changes from the tension just before each stimulation was performed. * P < 0.05, † P < 0.01 versus propofol; 0 μ M. ‡ P < 0.05; § P < 0.01 versus the group without 5-HT in same concentration of propofol. Six rats were used.

Figure 6. Serotonin (5-HT) and acetylcholine (ACh) play major roles in the smooth muscle contraction induced by ovalbumin (OA) of the sensitized rat trachea through 5-HT₂ and muscarinic M₃ receptors. Propofol at a higher concentration abolished both kinds of action of 5-HT, i.e., the direct action on the tracheal smooth muscle cell membrane and the indirect action on the parasympathetic nerve endings.



function, and reduced activity of acetylcholinesterase. It was reported that a significant increase in EFS response was associated with increased release of ACh and with loss of function of muscarinic M₂ receptor in IgE-immune allergen-exposed BALB/c mice (20). Brown-Norway rats that were challenged by OA after sensitization had significantly increased responsiveness to inhaled ACh compared with the nonsensitized rats *in vivo*, but there were no significant differences in exogenously applied ACh- or EFS-induced tracheal response between the OA-challenged and the nonsensitized rats *in vitro* (21). In Elwood et al.'s study (21), bilateral cervical vagotomy failed to reduce the increase in airway responsiveness. The authors argued the possibility that ganglionic transmission might be increased after allergen challenge, which caused the release of stimulatory mediators from mast cells. Our sensitized model did not cause hyper-responsiveness to ACh or EFS. We considered that our sensitization procedures or the species of rat might not cause loss of muscarinic M₂ receptor function and reduction of acetylcholinesterase activity.

In the present study, the effective concentration of propofol for inhibiting OA-induced contraction of rat tracheal rings was 30 μ M ($P < 0.05$). In the clinical setting, the plasma concentration of propofol immediately after 2 mg/kg infusion at a constant rate of 250 μ g/kg/min is 1.6–6.6 μ g/mL (22), which corresponds to 8.5–36.5 μ M. Our results suggest a benefit of this drug when used to treat patients with IgE-related asthma.

In conclusion, propofol attenuates OA-induced smooth muscle contraction of OA-sensitized rat trachea mainly by inhibiting the actions of 5-HT.

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