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Propofol inhibits T-helper cell type-2 differentiation by inducing apoptosis via activating gamma-aminobutyric acid receptor

Jingxia Meng, MD,[a] Xin Xin, MD,[a] Zhen Liu, MD,[a] Hao Li, MD,[b] Bo Huang, PhD,[c] Yuguang Huang, MD,[a] and Jing Zhao, MD[a,]*

[a] *Department of Anesthesiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[b] *Department of Anesthesiology, Beijing Aerospace General Hospital, Beijing, China*
[c] *Department of Immunology, Institute of Basic Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

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ABSTRACT

Background: Propofol has been shown to attenuate airway hyperresponsiveness in asthma patients. Our previous study showed that it may alleviate lung inflammation in a mouse model of asthma. Given the critical role of T-helper cell type-2 (Th2) differentiation in asthma pathology and the immunomodulatory role of the gamma-aminobutyric acid type A ($GABA_A$) receptor, we hypothesized that propofol could alleviate asthma inflammation by inhibiting Th2 cell differentiation via the GABA receptor.
Methods: For *in vivo* testing, chicken ovalbumin-sensitized and challenged asthmatic mice were used to determine the effect of propofol on Th2-type asthma inflammation. For *in vitro* testing, Th2-type cytokines as well as the cell proliferation and apoptosis were measured to assess the effects of propofol on Th2 cell differentiation and determine the underlying mechanisms.
Results: We found that propofol significantly decreased inflammatory cell counts and interleukin-4 and inflammation score *in vivo*. Propofol, but not intralipid, significantly reduced the Th2-type cytokine interleukin-5 secretion and caused Th2 cell apoptosis without obvious inhibition of proliferation *in vitro*. A GABA receptor agonist simulated the effect of propofol, whereas pretreatment with an antagonist reversed this effect.
Conclusions: This study demonstrates that the antiinflammatory effects of propofol on Th2-type asthma inflammation in mice are mediated by inducing apoptosis without compromising proliferation during Th2 cell differentiation via activation of the GABA receptor.
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Introduction

Asthma is generally characterized by airway inflammation, wall remodeling, and hyperreactivity of the bronchial tree, which results in inappropriate, variable, inducible and reversible bronchoconstriction with excessive and abnormally viscous mucus secretion.[1] The incidence of acute perioperative bronchospasm in asthmatic patients undergoing

* *Corresponding author*. Department of Anesthesiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.1 Shuaifuyuan, Dongcheng District, Beijing, China. Tel.: +86 010 69155583; fax: +86 010 69155593.
E-mail address: zhaojing1009@aliyun.com (J. Zhao).
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general anesthesia is approximately 10.2%.[2] Severe asthma attacks may be induced by tracheal intubation, surgical manipulation, and some drugs, causing hypoxia or even death.[3] Anesthetic agents that will not irritate the airway or even possess airway protective properties will be preferable for asthmatic patients.

Propofol is one of the most commonly used intravenous anesthetics. Several studies have shown that propofol is preferable for sedation and anesthesia in severe asthmatic patients because of its bronchodilatory effects and low incidence of inducing bronchospasm.[4,5] Furthermore, propofol has also been shown to have antiinflammatory effects in many cell and animal models.[6-9] Our previous work also demonstrated that propofol may alleviate lung inflammation in asthmatic mice. However, it remains unclear how propofol mitigates asthmatic airway inflammation.

T-helper cell type-2 (Th2)-type asthma inflammation is characterized by increased infiltration of inflammatory cells into the lungs along with prominent Th2 cell differentiation. The Th2 cell differentiation process begins with the activation of T cells by interleukin (IL)-4 cytokine signaling, followed by continuous cell proliferation and apoptosis, and ultimately results in secretion of downstream cytokines. Typical Th2-type cytokines, such as IL-4, IL-5, and IL-13, play critical roles in asthma pathogenesis. The two opposing cellular processes, proliferation and apoptosis, regulate the balance between cell death and survival,[10] thus influencing the cytokine production, which indicates the level of differentiation.

It has been shown that propofol exerts the hypnotic and anesthetic effect by acting on the gamma-aminobutyric acid type A ($GABA_A$) receptor in the central nervous system. In addition to the central nervous system, the GABA receptor also exists on the peripheral immune cells and is involved in immune suppression.[11]

Given the critical role of Th2 cell differentiation in asthma pathogenesis and the immunoinhibitory role of the GABA receptor in the peripheral immune system, especially on T cells, the present study aimed to determine the effect and mechanism of propofol on Th2 cell–mediated asthmatic inflammation, as well as the role of the GABA receptor. We hypothesized that propofol alleviates asthmatic inflammation via the GABA receptor by inhibiting Th2 cell differentiation through inducing Th2 cell apoptosis and/or inhibiting proliferation.

Materials and methods

Animals

A total of 100 female BALB/c mice (6-8 wk old) were purchased from the animal experimental center of Peking Union Medical College and Chinese Academy of Medical Sciences. Female mice were used because they display more severe Th2-type cytokine infiltration compared with male mice.[12] They were maintained in a specific pathogen-free room at temperatures between 22°C-24°C and humidity between 50%-70%. The mice were provided with sterilized tap water and standard rodent chow. Before the study, the mice were acclimatized in this environment for 1 wk. This experiment was approved by the Chinese Institute of Animal Care and Use Committee.

Ovalbumin sensitization and challenge

Ovalbumin sensitization and challenge is a classic method for establishing an asthma mouse model. Except for the control group, mice were sensitized on days 0, 7, and 14, with intraperitoneal injections of 50-μg grade V chicken ovalbumin (OVA; Sigma–Aldrich, St. Louis, MO) emulsified in 2-mg Inject Alum (Pierce, Rockford, IL) in a total volume of 200 μL.[13] Mice in the control group received normal saline only. Subsequently, OVA-sensitized mice were intranasally challenged with 100-μg OVA (100 μg dissolved in 40 μL normal saline) on days 21, 22, and 23,[14] whereas mice from the control group received normal saline alone under light isoflurane anesthesia (1.5%-2% inhalation). Five groups of mice were studied: (1) the normal saline-treated control group (control, $n = 20$); (2) the OVA-sensitized and OVA-challenged asthma group (asthma, $n = 20$); (3) the OVA-sensitized, OVA-challenged, and propofol-treated group (PPF, $n = 20$) (Diprivan, 100 mg/kg administration 8 min before challenge[15,16]); (4) the OVA-sensitized, challenged, and $GABA_A$ receptor agonist-treated group (MUS, $n = 20$; muscimol, 1 mg/kg, 30 min before OVA challenge)[15]; and (5) the OVA-sensitized, challenged and propofol-treated group with $GABA_A$ receptor antagonist pretreatment (PIC + PPF, $n = 20$; picrotoxin, 10 mg/kg, 9 min before the administration of propofol 100 mg/kg injection).[17] The concentration of propofol *in vivo* was determined based on our pilot study, which indicated that dosages greater than 100 mg/kg would cause high mouse mortality.

Bronchoalveolar lavage

All mice were deeply anesthetized by intraperitoneal injection of pentobarbital (50 mg/kg, Merck, Germany) 24 h after the last challenge. Bronchoalveolar lavage was performed with injection of 0.5-mL ice-cold normal saline into the trachea through a cannula. Then, the lungs were rinsed and gently massaged for approximately 1 min before the liquid was suctioned. After three repetitions, 1.2-1.3 mL of bronchoalveolar fluid (BALF) was harvested from each animal. The BALF supernatants were stored at −80°C until cytokine measurement. The sediment was used for total and differential cell counting with an automated analyzer.

Histological assessment

For evaluation of peribronchial and perivascular inflammatory changes, lung tissues were harvested, fixed in 10% formalin overnight and embedded in paraffin. Five micrometer sections were affixed to slides and stained with hematoxylin-eosin (H&E). Images of H&E-stained slides were obtained on a Leica DM3000 microscope using a × 20 objective. The images were blindly scored by an experienced pathologist, and the scores were recorded by another independent observer. The scoring is based on a subjective scale of 0-5 points according to the method reported in a previous study.[18] Briefly, inflammatory changes were graded using a semiquantitative scale of 0-5 for perivascular eosinophilia, bronchiolar eosinophilia, epithelial damage, and edema. The scoring is as follows: 0, normal; 1, low grade; 2, low to

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