MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 9045-9053
DOI: 10.12659/MSM.910766

Received: 2018.04.23
Accepted: 2018.08.14
Published: 2018.12.13

# Peroxisome Proliferator Activated Receptor gamma (PPARγ) Agonist Rosiglitazone Ameliorate Airway Inflammation by Inhibiting Toll-Like Receptor 2 (TLR2)/Nod-Like Receptor with Pyrin Domain Containing 3 (NLRP3) Inflammatory Corpuscle Activation in Asthmatic Mice

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Source of support:** This work was supported by Key Lab of Geriatric Molecular Medicine of Anhui Province (1206c0805028), Research Project of Anhui Province (No. 10021303028)

**Background:** The purpose of this study was to explore the function and mechanism of peroxisome proliferator activated receptor agonist (PPARγ) in the toll-like receptor 2 (TLR2)/nod-like receptor with pyrin domain containing 3 (NLRP3) inflammatory corpuscle pathway of asthmatic mice.

**Material/Methods:** Eighteen female mice (C57) were randomly divided into 4 groups: the control group, the asthma model group challenged by ovalbumin (OVA), the rosiglitazone group, and the PPARγ agonist rosiglitazone treatment group. The infiltration of peribronchial inflammatory cells as well as the proliferation and mucus secretion of bronchial epithelial goblet cells were observed by hematoxylin and eosin and periodic acid-Schiff staining. Western blots were employed to detect the expression levels of TLR2, PPARγ, nuclear factor-kappa B (NF-kappaB), $NLRP_3$, and ASC [apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]).

**Results:** The number of inflammatory cells and eosinophils, and the levels of OVAs IgE, interleukin-4 (IL-4), and IL-13 were significantly higher in the C57 asthma group compared to the C57 control group and the treatment group ($P<0.05$). The infiltration of peribronchiolar inflammatory cells, wall thickening, goblet cell hyperplasia, and mucus secretion in the treatment group were all significantly decreased compared to those in the asthma group. PPARγ expression in the treatment group was significantly higher compared to the asthma group and the control group ($P<0.05$). The protein expression levels of TLR2, NF-kappaB, $NLRP_3$, and ASC were significantly lower compared to the asthma group but were higher compared to the control group ($P<0.05$).

**Conclusions:** PPARγ rosiglitazone ameliorates airway inflammation by inhibiting NF-kappaB expression in asthmatic mice, and further inhibits the activation of TLR2/$NLRP_3$ inflammatory corpuscles.

**MeSH Keywords:** Airway Management • Asthma • Inflammation

**Full-text PDF:** https://www.medscimonit.com/abstract/index/idArt/910766

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## Background

Bronchial asthma is a chronic allergic airway inflammation mainly dominated by eosinophil infiltration and mast cell reaction [1]. After onset of the disease, a large number of inflammatory cells are activated, and they release large quantities of inflammatory mediators and cytokines [2]. Allergic airway inflammation and increased immunoglobulin IgE in the serum are the characteristic signs of bronchial asthma. The pathogen-associated molecular patterns released by inflammatory cells activate pattern recognition receptors (PRRs) and causes inflammation. In recent years, nod-like receptor with pyrin domain containing 3 (NLRP3) has been recognized as an important inflammatory molecule in the PRR pathways. NLRP3 plays an important role in the human immune response and the development of disease, mainly through the development of a multiprotein inflammasome complex comprised of NLRP3, ASC [apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]), and caspase-1 proteins [3]. After activation, it promotes the shearing and secretion of various inflammatory cytokines, including IL-13, and IL-18 [4,5]. Consequently, NLRP3 plays a key role in the induction and progression of inflammation [6]. Toll-like receptor 2 (TLR2) is a classic pattern recognition receptor. TLR2 activation depends on myeloid differentiation protein 88 (MyD88) binding [7], which activates the downstream nuclear transcription factor NF-kappaB and the signaling molecules such as the mitogen activated protein [8]. This suggests that TLR2 plays an important role in regulating $NLRP_3$ inflammatory inflammasome to induce inflammatory reactions.

Peroxisome proliferator activated receptor (PPARγ) is mainly expressed in adipose tissue and the immune system; it was also initially found to be involved in lipid and glucose metabolism and interacts with the target molecule of insulin enhancers – thiazolidinediones [9,10]. In in-depth studies, PPARγ was found to also be expressed in epithelial cells, macrophages, lymphocytes, and dendritic cells of the airway mucosa. The binding of PPARγ to specific ligands and the subsequent activation regulates the transcription of target genes, inhibits the activation of immune cells and the expression of inflammatory factors, and subsequently reduces the airway inflammation response further [11,12]. However, the mechanism of airway inflammation in asthma is still not clear and the synthesized PPARγ agonist rosiglitazone has become a common topic in recent research. In this study, we constructed a C57 mouse asthma model to observe the protective effect of a PPARγ agonist on asthmatic mice, and preliminarily explore its functional mechanism in airway inflammation.

## Material and Methods

### Experimental animals

SPF grade C57 (C57BL/6) female mice (6–8 weeks of age) (Shanghai SLAC Laboratory Animal Co., Ltd., Shanghai, China) were used. These animals were maintained in the SPF animal laboratory center of the School of Life Sciences, University of Science and Technology of China.

### Reagents and instruments

ELISA kit (Wuhan Huamei Bio-engineering Co., Ltd.); rosiglitazone (purchased from GlaxoSmithKline); aluminum potassium sulfate (purchased from Shanghai SANGON Biological Engineering Technology Service Co., Ltd); ovalbumin (OVA, Sigma); glycogen stain (PAS) kit (purchased from Fuzhou Maixin Biotechnology Development Co., Ltd.); ELISA kit (OVAs IgE, IL-4, and IL-13) were purchased from Wuhan Huamei Bio-engineering Co., Ltd.); 402AI type ultrasonic atomizer (purchased from Jiangsu Yuyue Medical Equipment & Supply Co., Ltd.); Microplate reader (purchased from USA BioTek Company); inverted microscope (purchased from Olympus company in Japan).

### Experimental animal groupings and model establishment

Eighteen SPF-grade C57 female mice were randomly divided into 4 groups of 6 mice each: the control (vehicle group), the asthma group (OVA group), the rosiglitazone group (ROS group), and the treatment group (PPARγ agonist rosiglitazone treatment OVA + ROS group). An OVA suspension (10 μg OVA, 1 mg/L aluminum potassium sulfate and 0.5 mL of normal saline) was given to the mice in the asthma group on days 0 and 7 by intraperitoneal injection for sensitization. On day 14, a 7-day treatment began where 1% OVA saline was given for 30 min/day for atomization excitation. The mice in the treatment group were given 50 μM rosiglitazone by pulverization inhalation for 30 min before the 1% OVA (rosiglitazone tablets dissolved in saline) treatment [13]. In the control group, OVA treatments were replaced with an equal volume of saline and all other procedures were performed in the same manner as the asthma group.

### Sample collection

Each mouse was sacrificed 24 hours after the last excitation. Blood was drawn from the retro-orbital vein, and the serum was isolated through low-speed centrifugation (4°C, 700 g, 5 min). The chest and primary bronchi were exposed, the right main bronchus was ligated, and 0.3 mL of phosphate buffer saline (PBS) was applied to lavage the left lung at a pump back the rate greater than 80%. The operation was conducted 5 times, the bronchoalveolar lavage fluid (BALF) was collected





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for centrifugation (4°C, 700 g, 5 min), and the BALF was reserved for the detection of various inflammatory factors. The serum and BALF supernatants were stored at –80°C. The middle lobe of the right lung was fixed in 4% polyformaldehyde for hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS) staining. The remaining lung tissues were preserved at -80°C for the detection of the expression levels of related proteins.

### White blood cell and eosinophil counts in alveolar lavage fluid

Aliquots of the lavage cell suspensions were adjusted to $1.25\times10^6$ cells per mL. A sediment in alveolar lavage fluid, after centrifugation, was placed on a cell counting plate and all cells, except epithelial cells and erythrocytes, were counted under a microscope. Cells were classified, prepared in a smear, stained with Wright-Giemsa stain, and the eosinophils were counted with a low-magnification microscope. Smears were used only if the number of cells was greater than 200.

### ELISA

ELISA was performed to detect IgE (OVAs IgE) in mouse serum and the expression levels of IL-4 and IL-13 in the BALF supernatant. The procedure was performed according to the manufacturer's instructions. After the reaction was stopped, OD values at a wavelength of 450 nm were measured and IgE concentrations were calculated using the Curve Expert software (OVAs IgE expression levels are reflected by the OD values).

### H&E and PAS staining of lung tissue

H&E staining was used to observe the infiltration of inflammatory cells around the lung tissue and the bronchial wall and the thickening of the wall. PAS staining was adopted to observe the proliferation of goblet cells and mucus secretion in the bronchial epithelium of mice. The lung tissue and the bronchial wall and the thickening of the wall were fixed by 95% alcohol for 10 min, prior to being washed, dried, stained by 1% periodic acid for 20 min and washed and dried once more. Then stained by a Schiff reagent for 60 min, washed and dried, and subsequently stained by hematoxylin for 5 min, washed and dried. The lung tissue and the bronchial wall and the thickening of the wall were observed using light microscopy. Wright-Giemsa staining was also performed, following standard protocols [14].

### Extraction of whole proteins from lung tissues

Lung tissue (50 mg) was collected from each mouse, placed in a Petri dish, cut into small pieces, divested of connective and adipose tissues, added to 500 µL of 4°C protein lysate buffer (20 µL protease inhibitor, 50 µL phosphatase inhibitors, and 430 µL RIPA lysate mixture), and homogenized for 10 min with a glass homogenizer in an ice bath. The homogenate was transferred to a pre-cooled EP tube and centrifuged at 4°C. The supernatant collected after centrifugation was placed in a pre-cooled EP tube and contained whole protein extract from the lung tissue. Protein extract (100 µL) was mixed with an equal volume of 2× loading buffer and boiled for 10 min. After cooling, the resulting solution was stored at –80°C for use in subsequent protein assays.

### Western blotting

Protein concentrations were determined with the BCA Protein Quantitation Kit. Proteins were separated using 10% SDS-PAGE and blotted electrophoretically onto polyvinylidene difluoride membranes. Membranes were blocked, followed by incubation with primary antibodies NLRP3, ASC, P65 (Abcam, MA, USA) and TLR2, PP65, PPARγ (Cell Signaling Technology, MA, USA) overnight at 4°C. Horseradish peroxidase-linked secondary antibodies (Cell Signaling Technology, MA, USA) were incubated with the membranes for 1 h at 25°C, followed by chemiluminescent detection. Densitometry of the western blot protein bands was analyzed using ImageJ software.

### Statistical analysis

SPSS17.0 software was employed for data analysis, and all data were represented by the mean ± standard deviation ($\bar{\chi}\pm s$). Single factor analysis of variance using the LSD method was employed in the case of normal distribution and equal variance, and the rank sum test was used when the variances were not equal. $P<0.05$ was considered statistically significant.

## Results

### Behavioral changes of mice

Symptoms including shortness of breath, dysphoria, restlessness, blue lips, hair loss and reduced luster, nose scratching with forelimbs, increased defecation and urination, and abdominal spasms to varying degrees were observed in mice in the asthma group after atomization inhalation of OVA. These symptoms decreased in the treatment group, and did not occur in mice from the control group (Table 1).

### Pathological effect of rosiglitazone on lung tissue, inflammatory cells, and eosinophil count in asthmatic mice

H&E staining observed under a low-power optical microscope displayed increased peribronchial inflammatory cell infiltration, wall thickening, stenosis, structural collapse of pulmonary alveolitis, and falling and necrotic bronchial mucosa epithelial





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**Table 1.** Behavioral changes of mice.

| Groups | Shortness of breath (%) | Dysphoria (%) | Restlessness (%) | Blue lips (%) | Hair loss (%) | Reduced luster (%) | Nose scratching with forelimbs (%) | Defecation (%) | Urination (%) | Abdominal spasms (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Vehicle | 1% | 0 | 0 | 0 | 0 | 0 | 0 | 1% | 1% | 0 |
| ROS | 1% | 0 | 0 | 2% | 0 | 0 | 0.5% | 2% | 1% | 0 |
| OVA | 100% | 83.3 | 93% | 94% | 89% | 92% | 91% | 89% | 85% | 95% |
| ROS + OVA | 16.7% | 4% | 5% | 11% | 12% | 13% | 11% | 12% | 8% | 6% |

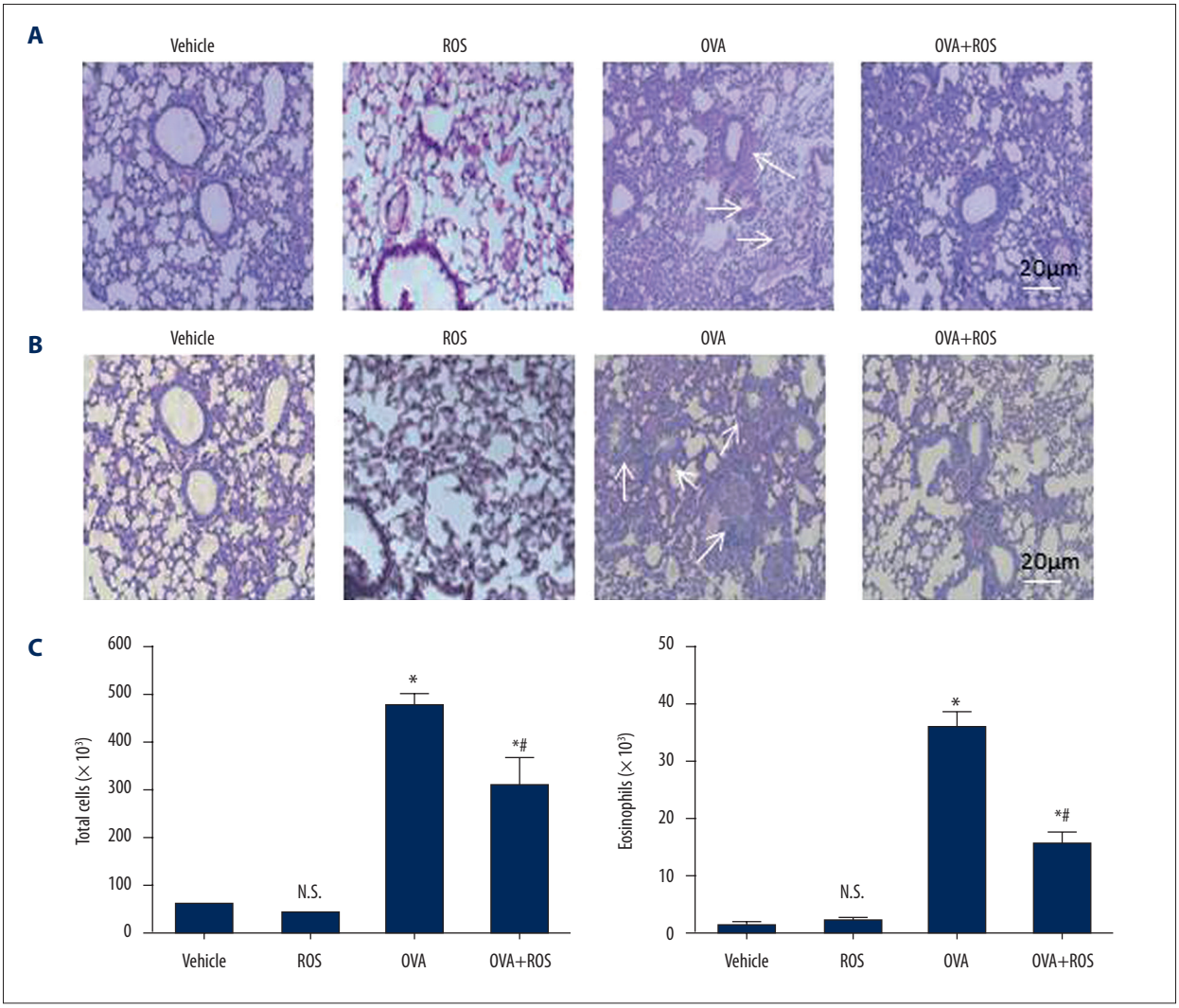


**Figure 1.** Airway inflammation after rosiglitazone treatment was diminished in asthmatic mice. (**A**) Airway inflammation as shown by hematoxylin and eosin staining. (**B**) Goblet cell and mucus secretion as shown by periodic acid-Schiff staining. (**C**) The total number of inflammatory cells and eosinophils in the alveolar lavage fluid. Data were collected from 6 mice per group and are represented as the mean ±SD. * $P<0.05$ compared with the control group. # $P<0.05$ compared with the asthma group.





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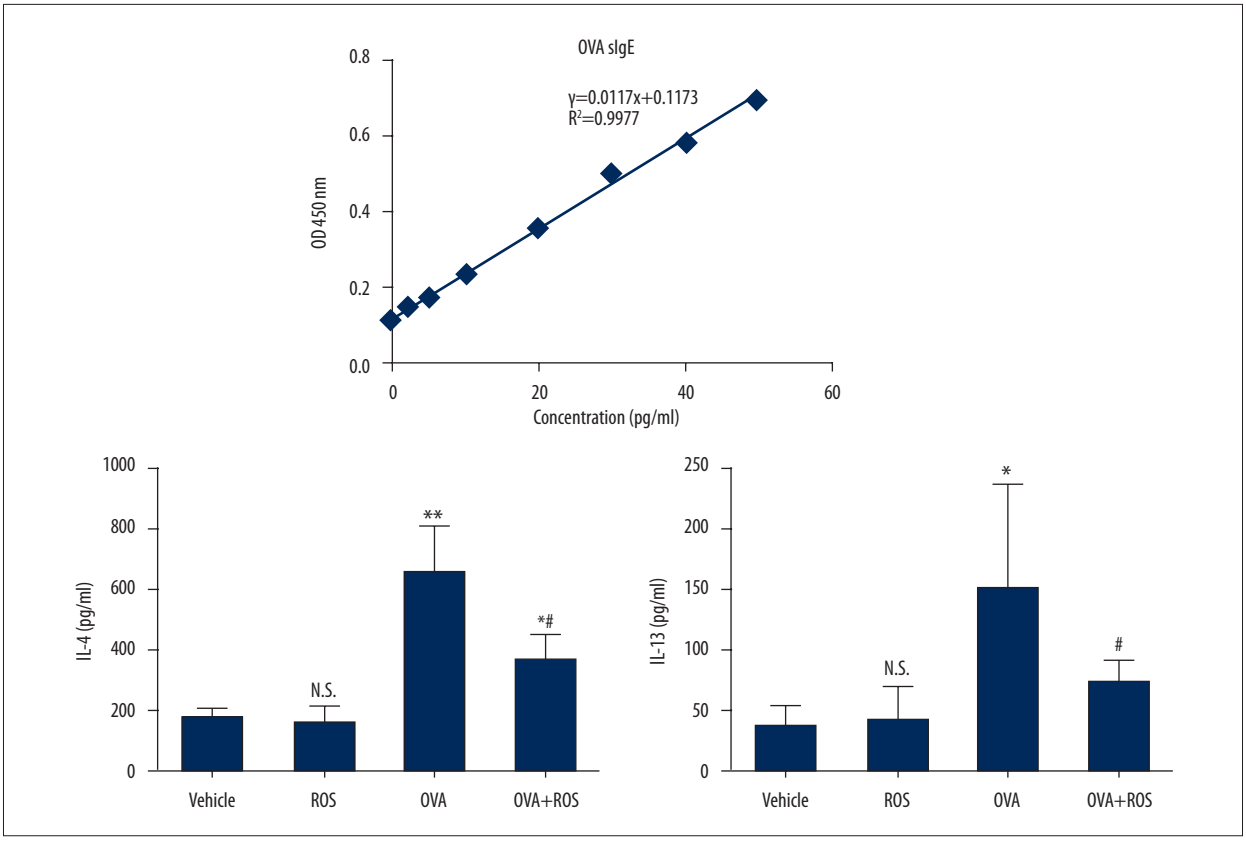


**Figure 2.** Airway inflammation in asthmatic mice after rosiglitazone treatment was significantly ameliorated. The data of interleukin-4 (IL-4) and IL-13 were collected from 6 mice per group and are represented as the mean ±SD. * $P<0.05$ compared with the control group. # $P<0.05$ compared with the asthma group.

cells in mice from the asthma group. Inflammatory manifestations in the treatment group were reduced when compared to those in the asthma group. In the control group, the structures of bronchi and alveoli were complete, and no obvious infiltration of inflammatory cells was found. PAS staining showed that the goblet cells in the bronchial epithelium of the asthmatic mice proliferated markedly and the mucus secretion increased. The above symptoms were diminished to a certain extent in mice from the treatment group. The total number of inflammatory cells and eosinophils increased in the asthmatic group, which were abrogated after rosiglitazone treatment but still higher than that in the control group (Figure 1A–1C).

### Effects of rosiglitazone on IL-4 and IL-13 expression levels in alveolar lavage fluid and OVA sIgE in the serum of OVA and OVA/ROS group mice

The levels of IL-4 in BALF, and OVA sIgE in the serum of the asthmatic and rosiglitazone treatment groups were all higher than those in the control group ($P<0.05$). The OVA sIgE in the serum and IL-4 in BALF were both significantly lower in the rosiglitazone treatment group than that in the asthma group ($P<0.05$). The IL-13 in BALF from the treatment group was slightly higher than that in the control group, but this difference was not statistically significant. The IL-13 in the BALF from the rosiglitazone treatment group was significantly lower than that in the asthma group (Figure 2).

### Effect of rosiglitazone on TLR2 and PPARγ protein expression in asthmatic mice

Western blot was used to detect TLR2 and PPARγ protein expression in the lung tissue of asthma mice. The expression of TLR2 protein in asthmatic mice increased significantly, and was significantly inhibited in mice pre-treated with rosiglitazone, but was still higher than that of the control group. The expression of PPARγ protein was increased in asthmatic mice and was further increased in the rosiglitazone treatment group (Figure 3).

### Effect of rosiglitazone on NF-kappaB signaling pathway in asthmatic mice

As detected by western blotting, the expression of NF-kappaB p65 protein phosphorylation in the asthma group





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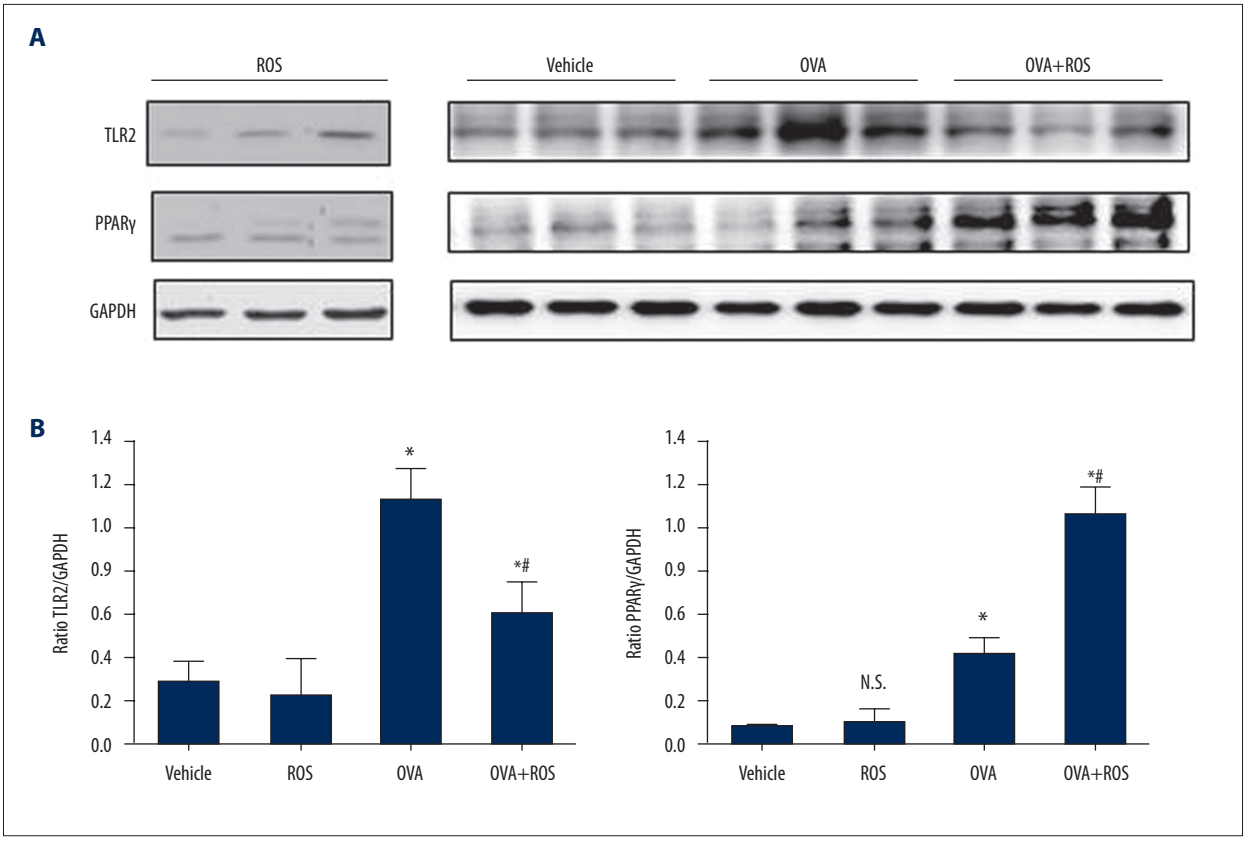


**Figure 3.** Expression of toll-like receptor 2 (TLR2) and peroxisome proliferator activated receptor agonist (PPARγ) proteins were significantly decreased after rosiglitazone treatment. (**A**) Expression of TLR2 and PPARγ proteins by western blot analysis. (**B**) Quantitative analysis of protein test strips. Data are represented as the mean ±SD. * $P<0.05$ compared with the control group. # $P<0.05$ compared with the asthma group.

was significantly increased, and the activation of p65 was inhibited by rosiglitazone treatment (Figure 4).

### Effect of rosiglitazone on NLRP$_3$ inflammatory corpuscle activity in asthmatic mice

Western blot was used to detect NLRP$_3$ and ASC protein expression in lung tissues from asthma mice. The expression of NLRP$_3$ and ASC proteins was significantly increased in the mice with asthma, and inhibited by rosiglitazone treatment (Figure 5).

## Discussion

Bronchial asthma is a chronic allergic inflammatory disease associated with many factors including the immune system, environment, and polygenic inheritance [15]. Asthma is characterized as the activation of mast cells, eosinophils, T lymphocytes, and various other cells as well as the release of multiple inflammatory mediators. Asthma causes repeated injury and chronic airway inflammation, which results in airway remodeling [16]. Innate immunity, as the first defense system to protect the body, plays an important role in eliminating exogenous harmful substances and pathogens as well as guiding the body to generate an effective adaptive immune response [17,18]. Innate immunity identifies a pathogen's conserved structure, namely the molecular mode of the pathogen, through PRRs and induces the expression of downstream inflammatory genes [19]. These inflammatory genes activate the downstream signaling pathways and induce an inflammatory response PRRs are currently classified into 4 categories. The first category is of the TLRs, which identify ligand molecules in the extracellular region, transfer the appropriate signals into the intracellular region, thus leading to the activation of downstream NF-kappaB signaling pathways. The second category is of the NOD-like receptor, which is an intracellular sensing molecule that forms protein complexes such as the inflammatory corpuscle. Approximately 4 categories of inflammatory corpuscles are currently known, of which the NLRP$_3$ inflammatory corpuscle is best researched. NLRP$_3$ recruits and activates the pro-inflammatory protease caspase-1, and activated caspase-1 cleaves the precursors of IL-4 and IL-13 to produce the corresponding mature cytokines. Mature cytokines are then released outside the cell to further inflammation [20]. The third





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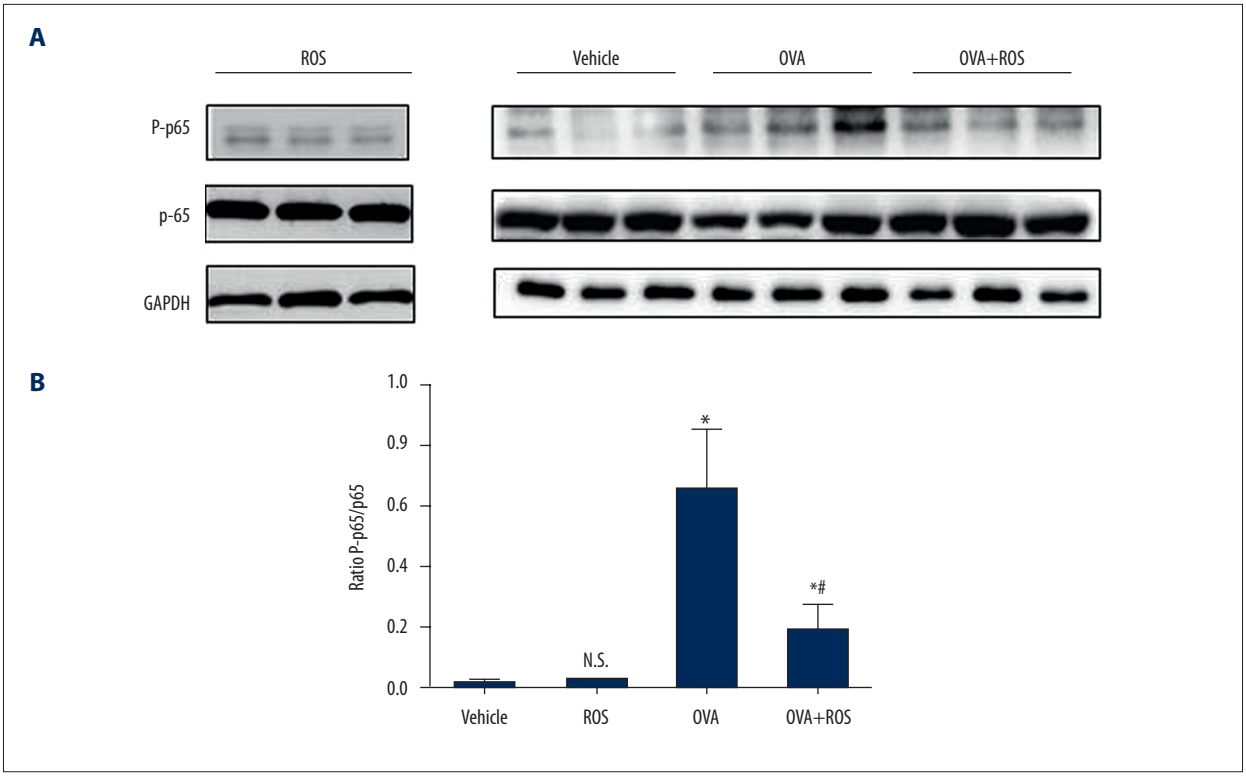


**Figure 4.** Rosiglitazone significantly inhibited the phosphorylation of the nuclear factor-kappa B (NF-kappaB) p65 protein. (**A**) Analysis of NF-kappaB p65 phosphorylation in the asthma and treatment groups by western blot. (**B**) Quantitative analysis with the protein test strip. Data are presented as the mean ±SD. * $P<0.05$ compared with the control group. # $P<0.05$ compared with the asthma group.

category is of the RIG-I like receptor, an intracellular helicase mainly involved in virus recognition and activation of type I interferon for resistance to viral infection. The fourth is the C type lectin receptor, which, in the presence of $Ca^{2+}$, enables the identification of carbohydrates on the surface of pathogenic microorganisms and cause a series of immune responses to resist the invasion of pathogenic microorganisms. Thus far, we have primarily studied more TLRs and NOD-like receptors. Some studies have illustrated that the activation of the $NLRP_3$ inflammatory corpuscle is closely related to the pathogenesis of bronchial asthma.

PPARγ receptors are important nuclear transcription factors, which are expressed in a variety of cells and tissues as well as in organs [20,21], have extensive biological effects, are the key factors for transcription of various signaling pathways, and regulate signaling pathways of other transcription factors such as NF-kappaB [22]. PPARγ receptors also play an important role in the regulation of inflammation [23]. Previous studies have found a significant increase in PPARγ protein expression in the lung tissue of asthmatic mice, which is consistent with our current results.

In the present study, we explored the mechanism of the PPARγ receptor agonist rosiglitazone in an asthmatic mouse model. Eosinophils in BALF increased significantly in the asthmatic mice model sensitized and challenged by OVA, and then significantly reduced after the treatment of rosiglitazone. These data suggest that rosiglitazone may have a protective effect on asthmatic mice, which is consistent with the research result of Smith et al. [24].

Recent studies have discovered that PPARγ ameliorates the inflammatory response by inhibiting NF-kappaB activation [25]. In order to explore the molecular mechanism of PPARγ in airway inflammation, we hypothesized that PPARγ negatively regulates the TLR2 receptor pathway in airway inflammation. We established an asthmatic mouse model sensitized and challenged by OVA and detected the expression of TLR2 protein and the downstream signal protein NF-kappaB in the lung tissue from asthmatic mice. We also assessed the release of the inflammatory factors IL-4 and IL-13 in BALF from the lung tissue of asthmatic mice. Experimental results showed that the expression of TLR2 and NF-kappa B proteins, and the expression of the downstream inflammatory factors IL-4 and IL-13, increased significantly in the asthmatic group. The expressions of TLR2, NF-kappaB, IL-4, and IL-13 were dramatically decreased





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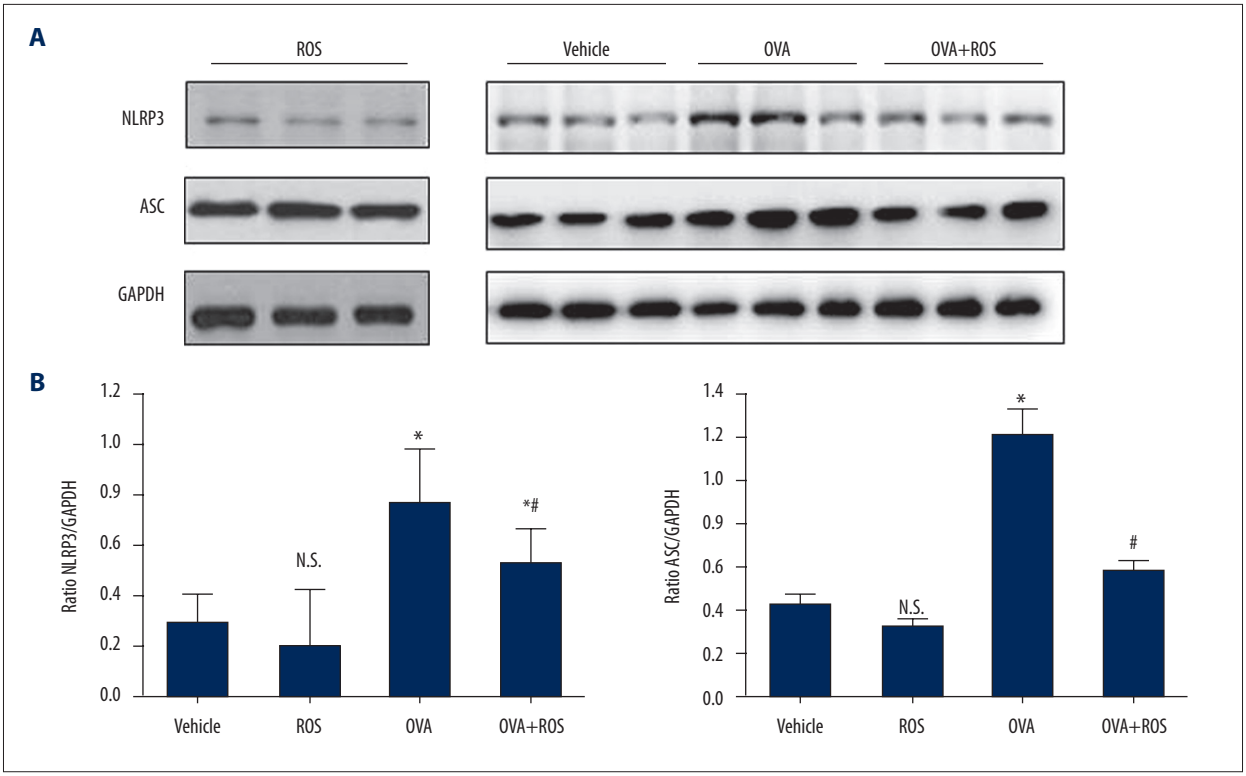


**Figure 5.** Rosiglitazone significantly inhibited the activity of nod-like receptor with pyrin domain containing 3 ($NLRP_3$) inflammatory corpuscles. (**A**) Analysis of the expression of inflammatory corpuscle proteins in the asthma and treatment groups by western blot. (**B**) Quantitative analysis with the protein test strip. Data are represented as the mean ±SD. * $P<0.05$ compared with the control group. # $P<0.05$ compared with the asthma group.

after rosiglitazone treatment, which implied that PPARγ may negatively regulate the TLR2 receptor pathway.

TLRs and NLRs are 2 classic pattern recognition receptors [17]. Recent studies have found that asthma induces the activation of TLR2 and $NLRP_3$ inflammatory corpuscles, and that the inhibition of TLR2 blocks NLRP3 inflammatory corpuscle activation and the release of downstream inflammatory factors IL-4 and IL-13. These data reveal that TLR2 and NLRP3 are closely related to the occurrence and development of asthma [26]. Our study proves that asthma induces the activation of TLR2 and the NLRP3 inflammatory corpuscle. Additionally, rosiglitazone treatment inhibits NLRP3 inflammatory corpuscle activation; therefore, rosiglitazone may play a protective role for asthmatic mice through inhibition of NLRP3 inflammatory corpuscle activation.

## Conclusions

Our research revealed that rosiglitazone has a protective effect on asthmatic mice, and that the mechanism of this protection reduces airway inflammation by inhibiting the expression of NF-kappaB in asthmatic mice and further inhibiting activation of the TLR2/$NLRP_3$ inflammatory corpuscle. Therefore, this study suggests the PPARγ agonist rosiglitazone as a potential treatment option for asthma, and provides the theoretical basis needed for its future application in the clinical treatment of asthma.

### Conflict of interests

None.

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