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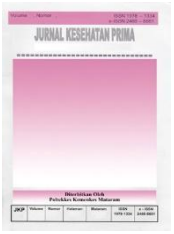

Ovalbumin as an Allergen Inducing Allergic Rhinitis in A Mouse Model: A Preliminary Study

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Abstract
Ovalbumin is the most commonly used allergen in modelling allergic rhinitis in mouse, but there is no standard method for modelling it. The purpose of this study was to demonstrate a method for modeling allergic rhinitis in mouse using ovalbumin allergen that can be used in further researches in allergic rhinitis. This study is an experimental laboratory study with a post-test only control group design. The study used 12 mice (*Mus musculus*) which were grouped into control group and allergic rhinitis group containing 6 mice in a group. The sensitized began with the administration of 50 µg of ovalbumin intraperitoneal as systemic sensitization (day 0, 7, 14) followed by 500 µg of ovalbumin intranasal as local sensitization for 7 consecutive days (day 21-27), while the control was given phosphate buffer saline. Nasal symptoms (sneezing and nasal rubbing), serum OVA-specific immunoglobulin E (IgE) levels, and eosinophil counts in the nasal mucosa were assessed. A T-test was used to examine the differences between groups. The AR group exhibited markedly elevated nasal symptoms, serum OVA-specific IgE levels, and eosinophil counts in comparison to the control group ($p < 0.05$). The method above can be considered to apply in a model of allergic rhinitis in mouse.

Keywords: Allergic rhinitis; Ovalbumin; Ovalbumin-specific Ig E, Allergen

INTRODUCTION

Allergic rhinitis (AR) is one of the most common diseases found worldwide. Allergic rhinitis was previously considered trivial because of its non-life-threatening symptoms, but it is now increasingly recognized that this disease has a major impact on quality of life, emotional stability, sleep disturbances, daily activities, and productivity (Blaiss et al., 2018). Several studies have shown that the increasing prevalence of AR is not only occurring in developed countries, but also in developing countries, especially in urban areas where the prevalence was previously low (Brożek et al., 2017).

Allergic rhinitis is defined as a group of symptoms in the nose (sneezing, itchy, runny, and stuffy nose) caused by inflammation mediated by immunoglobulin E (IgE) due to exposure to allergens (Blaiss et al., 2018; Brożek et al., 2017). Allergens are harmless foreign molecules that can cause abnormalities in immunological responses and allergic reactions. Allergens come from various sources, such as plants, animals and fungi. Allergic rhinitis is an inflammatory disease that begins with a sensitization phase and followed by an allergic reaction. The sensitization phase begins with exposure of the nasal mucosa to certain allergens such as house dust mites, pollen, and/or animal dander (Bjermer et al., 2019).

Research on allergic diseases including allergic rhinitis is often observed using experimental animals. This experimental animal model can be applied for various purposes such as: policy making, drug development and pathophysiology studies. Mice and rats are the most commonly used animals in AR research. Allergic symptoms such as sneezing or nose rubbing are easily observed in mice, while rats are a better choice for assessing nasal obstruction. In other words, if observation for active symptoms such as sneezing and nose rubbing are considered important, mice are excellent candidates (Ko et al., 2015).The use of mice as experimental animals has several advantages such as: low cost, easy handling and breeding, easy manipulation, available in various strains, known genetic details, reagents available, short gestation period, easy to sensitize and expose in allergy modeling and can observe the symptoms of allergies (Masoume et al., 2019).

Ovalbumin (OVA) is the most commonly used allergen for animal studies in the literature. Ovalbumin is the main protein found in egg white. Besides OVA, pollen, mold or house dust mites can be alternative choices to increase allergen sensitivity (Lee et al., 2020; Zhu et al., 2023). After selecting the appropriate allergen, the most important step in modeling is how to exposed it into the mouse to sensitize and induce AR symptoms. Two main steps that have been widely accepted and used are: systemic sensitization and local challenge. Systemic sensitization is usually done by intraperitoneal (IP) or subcutaneous (SC) injection of allergens to generate an IgE-mediated systemic immune response. Once an IgE-mediated systemic response is established, continued exposure of the same allergen to the nasal mucosa can lead to the development of a Th2-dominated local atopic reaction, resulting in nasal symptoms. This step is defined as local challenge, which is mediated mainly by the homing effect. For models of respiratory allergies such as AR or asthma, intranasal (IN) administration of allergens through the nostrils is the most common method for local challenge in animal studies (Ko et al., 2015).

Many studies using OVA as allergen-induced AR in mice have been done with variation on dose of OVA and on the time and duration performing IP or IN. Choi et al create AR mice by performed sensitization by an IP injection of 50 μg OVA with 2 mg aluminum hydroxide in a total volume of 200 μL on days 0, 7, and 14. The mice were challenged by an IN instillation of OVA (400 μg) on days 21, 23, 25, and 27 (Choi et al., 2021). Liu et al made AR mice by sensitized via IP injection of 0.2 mL suspension of 0.5 mg/mL OVA and 20 mg/mL aluminum hydroxide on days 0, 7, and 14. Then, the mice were administered IN with 100 μg of OVA daily from days 21–28 (Liu et al., 2021). Mice were sensitized on each alternative day starting from day 1 to 13 using OVA (50 mg triturated in aluminum hydroxide (1000 mg, in saline (500 ml). The mice were challenged with OVA intranasally on day 21. On day 24, mice were challenged with histamine dihydrochloride (Yang et al., 2022). All the researches above showed in AR group had significantly higher incidence of nasal symptoms (sneezing and rubbing the nose), level of ova-specific IgE, and others allergic markers.

There is no standard method that can be followed universally. For example, the time and duration for performing IP or IN vary from one another, not to mention the dose of allergen used. Because of different methods are produced by different researchers, it is difficult to compare the efficiency and therapeutic effects of these methods. Thus, a standard and widely accepted animal model for AR is needed (Ko et al., 2015).

In this study, we used OVA as an allergen intraperitoneally for systemic sensitization and intranasally for local challenge with modified doses

and duration. The purpose of this study to demonstrate a method for modelling allergic rhinitis in a mouse using ovalbumin as an allergen.

METHOD

This study is an experimental laboratory study with a post-test only control group design to see the difference responses after treatment between control group and AR group. This study is a preliminary study to create mice model of allergic rhinitis that will be used for further research. The study received ethical clearance from the ethics committee of the Faculty of Medicine, Universitas Andalas (certificate no. 438/UN.16.2/KEP-FK/2024). The study was conducted at the experimental animal house of the Faculty of Pharmacy, Universitas Andalas and the ELISA examination was carried out at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas. The study was conducted in January 2025.

Animals

The study used male white mice (*Mus musculus*) *Deutschland Denken Yoken* (DDY) strain, aged 6-8 weeks obtained from the animal house of the Faculty of Pharmacy, Universitas Andalas. The sample size was counted using resource equation method which is E = N-k. We used E=10, k=2, so we got 12 as total number of samples. The mice were randomly divided into 2 groups, each group consist of 6 mice. Group 1 as a control, and group 2 as AR group. The mice were placed in a special cage, where 1 cage contained 2 mice. Food and water were provided ad libitum.

Establishment of Allergic Rhinitis

Before starting the treatment, the mice were adapted for 7 days and given standard feed. Treatment began with the administration of 50 µg OVA (chicken egg albumin grade V, Sigma-Aldrich) + 1mg Aluminum Hydroxide (AL(OH)3) dissolved in 200 µl PBS given intraperitoneally as systemic sensitization. Injections were given on days 0, 7, 14 sequentially. On day 21 began nasal challenged, mice are sensitized intranasally with 500 µg OVA dissolved in 30 µl PBS for 7 consecutive days until day 27.

Nasal Symptoms

After the last allergen exposure in day 27, the signs and symptoms of allergic rhinitis (sneezing and rubbing the nose) were observed and counted for 15 minutes by observers who blind for the mice group.

Blood samples

Blood samples were obtained intracardial by syringe injection under anaesthesia. Mice were anaesthetized using intraperitoneal 0.03 ml ketamine (120 mg/kg) and 0.01 ml xylazine (5 mg/kg).

Measurement of OVA-specific IgE Levels

The blood samples were centrifuged at 3000 rpm for 10 minutes. The serum obtained was used to measure OVA-specific IgE levels using an enzyme-linked immunosorbent assay (ELISA) kit (Mybiosource).

Eosinophils count in nasal mucosal tissues

Each mouse's head was severed and stored for 24 hours in 10% paraformaldehyde. After that, nasal mucosal tissues were gathered and embedded in blocks of paraffin. Tissue sections that were 5 µm thick were stained with haematoxylin and eosin. A Leica optical microscope was used to examine the slides at 400× magnification in 10 different fields to count the eosinophils. Due to their unique morphology, eusinophils were identified as a bilobed nucleus and eosinophilic granules in the cytoplasm (Kim et al., 2017)

Statistical Analysis

Univariate analysis was used to determine each group's characteristics, and the mean value ± standard

deviation was used to express each parameter. If the data is normally distributed, a t-test was used to examine group differences. If the p value < 0.05, the results are regarded significant.

RESULT AND DISCUSSION

Nasal Symptoms

Observation of symptoms that appeared after the last exposure to ovalbumin allergen for 15 minutes showed that the average sneezing symptom in the control group was 0.33 ± 0.52 times, while in the AR group was 5.67 ± 1.75 times. There was a significant difference in the incidence of sneezing between the control and AR groups ($p<0.05$). The average symptom of rubbing the nose in the control group was 2.83 ± 2.86, while in the AR group was 8.00 ± 4.00 times. There was a significant difference in the incidence of rubbing the nose between the control and AR groups ($p<0.05$) (Figure 1).

We found the significance difference of sneezing and rubbing the nose between control and AR group. The methods and time intervals used in calculating the number of rubbing the nose and sneezing vary among researchers, but the results are almost the same (Ryu et al., 2020). Kim et al found that the number of rubbing the nose was 5.11 ± 3.62 times in the control group, and 25.78 ± 15.66 times in the AR group, while the number of sneezing was 1.44 ± 1.51 in the control group and 21.33 ± 7.48 in the AR group observed for 10 minutes after the last intranasal sensitization with OVA (Kim et al., 2017). Shi et al also evaluated nasal symptoms within 10 min after OVA challenge and found the incidences of nasal rubbing and sneezing increased in the AR mice when compared to normal mice (Shi et al., 2023).

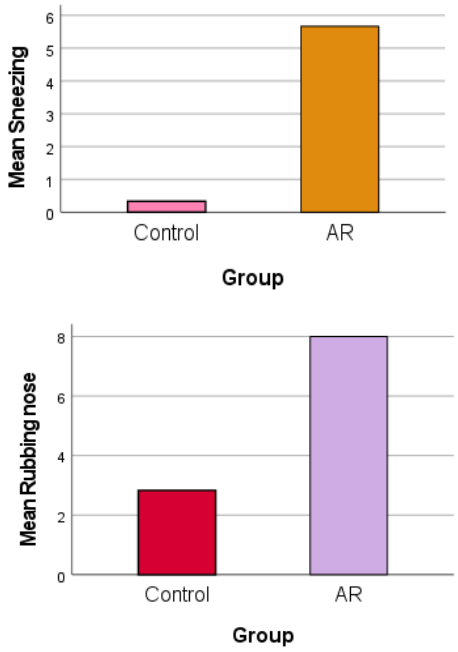

Figure 1. Symptom of sneezing and rubbing the nose in the control and AR group

Almost the same thing was obtained by Nguyen et al, Kang et al, Piao et al and Liu et al who found that the frequency of nasal rubbing and sneezing on the last day after intranasal sensitization calculated for 15 minutes in the ovalbumin-induced AR groups were significantly higher than in the control group (Kang et al., 2023; Liu et al., 2021; Piao et al., 2020; Van Nguyen et al., 2020).

Wang et al found that the number of nose rubbing or sneezing was significantly higher in the AR group than in the control group calculated for 20 minutes after last intranasal OVA sensitization (Wang et al., 2022). Aswar et al found sneezing 15.83±1.86 and nose rubbing 19.33±1.44 in the control group and 79.17±3.17 and 71.67±3.29 in the AR group which were calculated continuously for 40 minutes after intranasal sensitization (Aswar et al., 2015). Choi et al recorded the number of nasal rubbing and sneezing only for five minutes and found that nasal rubbing and sneezing behavior had significantly increased in OVA-induced AR mice compared to the control group (Choi et al., 2021).

Ovalbumin is one of the first proteins isolated in pure form and is known as a phosphorylated globular protein belonging to the serpin superfamily. Ovalbumin has 386 amino acids, half of which are considered hydrophobic. Ovalbumin has a size of 45 kDa and a diameter of 5.5 nm. Ovalbumin is the main protein found in egg white. The percentage of ovalbumin in egg white varies from species to species with the highest percentage found in chickens (54%). This protein is considered as food allergen (Maggonage et al., 2024). Ovalbumin is the most commonly used allergen in various allergy research literature using experimental animals (Ko et al., 2015).

The allergen will be processed and presented by Antigen Presenting Cells (APC) to Major Histocompatibility Complex (MHC) class II molecules. Furthermore, in AR, there is a strong response from Th2 cells. These Th2 cells produce various cytokines such as IL-4, IL-5 and IL-13, which stimulate B cells to produce IgE. This Ig E spreads freely in the circulation and some bind to its receptors on the surface of basophils and mast cells. This condition is called the sensitization phase. If there is re-exposure to the same allergen, this allergen can bind between two adjacent IgE molecules on the surface of mast cells or basophils. In the rapid phase of allergic reaction, which lasts less than 1 hour, mast cell degranulation occurs, causing the release of histamine shortly after exposure to the allergen, followed by the release of other inflammatory mediators such as leukotrienes and prostaglandins. This phase is responsible for the onset of acute symptoms such as sneezing, itchy nose, runny nose, and ocular symptoms such as itchy, red, and watery eyes (Bjermer et al., 2019). Type 2 inflammatory markers show a positive correlation with the number of sneezes and nose rubbing (Ryu et al., 2020).

Serum OVA-specific IgE Levels

Serum OVA-specific IgE levels were higher in the AR group compared to the control group. In the AR group, the average OVA-specific IgE level was 137.99 ± 5.13 ng/ml, while in the control group was 4.82 ± 4.01 ng/ml. There was a significant difference in OVA-specific IgE levels between the control and AR groups ($p < 0.05$) (Figure 2).

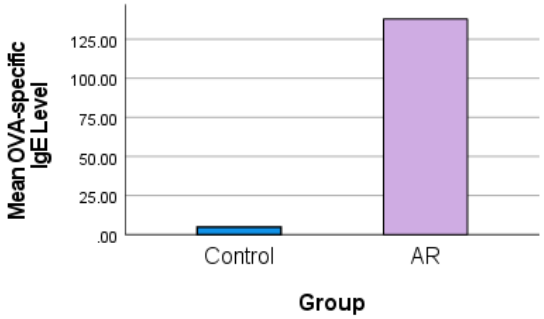

Figure 2. OVA-specific IgE levels in the control and AR group

We found that serum OVA-specific IgE level in the AR group was higher than in the control group. This indicates that ovalbumin successfully functions as an allergen that triggers the formation of specific IgE that plays a role in the emergence of allergic rhinitis symptoms. Several studies using ovalbumin with varying doses as allergens for sensitization also showed the same results. In this study, the ovalbumin dose we used was 50 µl with 1 mg of alum (AL(OH)3) on days 0, 7 and 14 for systemic sensitization and 500 µl for seven consecutive days from days 21 - 27 for local sensitization showed a fairly good effect on the emergence of allergic rhinitis.

Piao et al used intraperitoneal injection of 50 µg OVA with 1 mg alum on days 0, 7 and 14 for systemic sensitization and from days 21 - 27 these mice were sensitized with OVA (10 mg/mL, 20 µL/nostril) intranasally, obtaining significantly higher OVA-specific IgE levels in the OVA group (Piao et al., 2020). Kang et al used intraperitoneal injection of 250 µg

OVA in 200 µL PBS containing 10 mg aluminum hydroxide on days 0, 7 and 14. One week later the mice were sensitized intranasally for 10 days (from days 21 - 30) with 50 µg OVA in 20 µL PBS into the bilateral nasal cavity. Serum total IgE and OVA-specific IgE levels were significantly increased in the AR group compared with the control group (Kang et al., 2023). Kim et al used 100 µg ovalbumin and 2,000 µg aluminum hydroxide intraperitoneally on days 0, 7, and 14. One week after intraperitoneal sensitization, all mice were exposed intranasally to 500 µg OVA for 7 consecutive days (days 21–27). Serum OVA-specific IgE levels were significantly higher in the AR group (7,965.19±5,285.72 ng/mL) than in the control group (77.57±69.50 ng/mL) (Kim et al., 2017).

Eosinophil infiltration in nasal mucosa tissues

Eosinophil counts in the nasal mucosa of AR group were significantly higher compared to control group ($p < 0.05$). In the AR group, the average number of eosinophils in the nasal mucosa was 2.67 ± 1.86, while in the control group, 0.67 ± 0.82 (figure 3). Kim et al also observed that eosinophil infiltration was significantly higher in the AR group in comparison with the control ($P<0.001$) (Kim et al., 2017).

The characteristic pattern of allergic inflammatory cell infiltration, is reflected in the rise in eosinophils. This finding is closely linked to the clinical symptoms, like sneezing and rubbing the nose, observed in this study. Eosinophils are known to cause clinical manifestations of AR including tissue damage (Kang et al., 2023).

Within hours of initial exposure, the late phase of allergic reactions begins. This phase is characterized by the involvement of basophils, neutrophils, T lymphocytes, monocytes, and eosinophils, as well as the release of various mediators such as cytokines, prostaglandins, and leukotrienes (Bjermer et al., 2019).

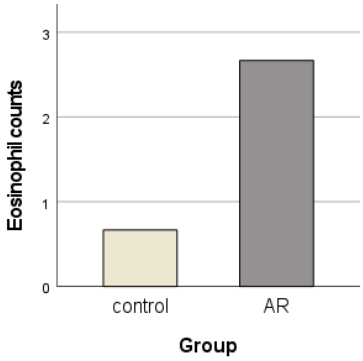

Figure 3. Eosinophil counts in the nasal mucosa of the control and AR group

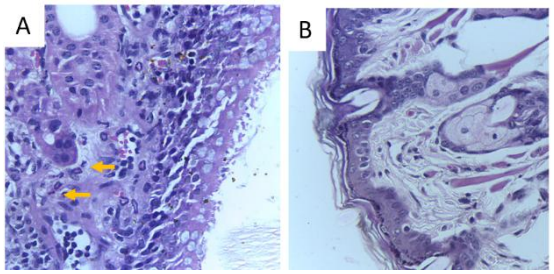

Figure 4. Histopathology of nasal mucosa (Eosinophil infiltration (arrow); A. AR group, B. control group; H&E staining, 400x)

Allergic rhinitis makes alterations in histopathology of nasal mucosa, include pronounced submucosal oedema, injury to the nasal mucosal epithelium, depletion of ciliated cells, thickening of the olfactory groove, and elevated number of mast cells, eosinophils, and goblet cells within nasal mucosal tissues (Kang et al., 2023). The histopathological results showed that eosinophils cell infiltration was higher in the AR group compared to the control group (figure 4).

We used OVA added with alum or Aluminum Hydroxide (AL(OH)3) intraperitoneally for systemic sensitization in this AR model. The function of alum is as an adjuvant. Another material that is often used as an adjuvant is Freund's adjuvant. The aim of adjuvant is to improve the performance of ovalbumin (Mo, 2015). Intraperitoneal administration alone is superior than

combination of subcutaneous and intraperitoneal administration for systemic sensitization (Catur Iswanti et al., 2018).

For local sensitization, OVA is administered intranasally. Intranasal allergen administration is the most common method used for local provocation or sensitization. This method is simple without requiring special instruments. This method can be performed with or without anesthesia. Although simple, precise and careful manipulation is essential to avoid the mouse struggling, fluid being aspirated or lost from the nostrils (Ko et al., 2015).

Although the outcomes of this study are encouraging, there are still several limitations to validate AR models. Future studies should delve further into the molecular pathways, particularly the functions of pro-inflammatory cytokines and other markers of inflammation in nasal tissue.

CONCLUSION

The mouse model of allergic rhinitis can be established using ovalbumin as an allergen for systemic sensitization intraperitoneally and local sensitization intranasally. Research on allergic rhinitis using mice models may consider the approach we presented. A consensus is needed to determine the standard dose and duration required to create an allergic rhinitis in a mouse model.

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