Animal model of allergy and asthma; protocol for researches

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Abstract

Allergic diseases and asthma are an important problem in health system and effects large amounts of people in the worlds. Exposure to outdoor and indoor allergens promote the sensitization towards these allergens. Th2 cytokines are main stimulators allergic diseases initiation. Allergic diseases similar to other diseases have been studied in animal for understanding of pathophysiology and treatments. Animal models provide a potential approach to investigation of the pathophysiology, mechanism and drugs designing for allergy and asthma. Physicians and veterinarians with collaboration in this field could improve best animal model. In this review, it will be discussed the various models (especially in mouse) and protocols by focusing on the allergic diseases. Animal models in allergy field, are applicable for important goals. Moral discussion in all procedures should be remarkable.

Introduction

1. Introduction

Allergic diseases are a common problem in all countries and effects large amounts of people in the worlds (1). Allergic diseases and asthma affect up to 20% of the Western countries populations (2). Allergic disease are relapsing in nature and allergen exposure is associated with exacerbations frequently. Sensitizations for environmental allergen can be against a variety of agents (1). Development of allergic disease may be influenced by hereditary predisposition and environmental factors. Exposure to allergens (outdoor, indoor), microbial infections, nutrition, occupational environment, airborne pollutants (diesel exhaust particles) may promote the sensitization towards these allergens (2).

In allergic diseases, sensitization and elicitation phase are done. Antigen-presenting cells (such as dendritic cells, macrophages and B cells) take up arrived allergens and transport to the lymph nodes. Allergen-specific T and B lymphocytes are activated and Th2 cytokines stimulate B cells to class switching and IgE production. Produced IgE bound to high-affinity Fcε-receptors on mast cells and also basophils (sensitization phase) (2, 3). After re-enters of the allergen in the body and crosslink the IgE bound to the mast cells, causes immediate degranulation of the cells and release of mediators (such as histamine, serotonin, eicosanoids, cytokines, chemokines and etc.). Inflammatory cells are attracted, cause the acute phase symptoms of allergic diseases (elicitation phase). A late phase reaction occurs 4-6 hours later and are caused by the inflammatory cells accumulation, cytokines and chemokines releasing (2-4).

In the laboratory animals, the first cases of allergic symptoms was reported in the 1950s (5, 6). Allergic diseases have been studied in animal for understand of diseases pathophysiology and design of applicable treatments. In this review, it will be discussed the animal models (especially mouse model) by focusing on the allergic diseases that would be used in experimental study. Mice have some advantage in research using. For example, low cost, easy handling and breeding, easy manipulation with transgenic

technology, available of different strains, genetic details was known, available of reagents, short gestational period, easily sensitized and challenged in allergic modeling and available methods for studying allergic outcomes (7, 8). Animal models in allergy field, are applicable for purposes includes, Human allergy mimicking, policies making, drug development and allergic disease pathophysiology studies and Figure 1 shows details of mentioned purposes. Therefore, this review focus mostly on mouse model.

Reagents

Equipment

Procedure

2. Asthma

Asthma is a chronic inflammatory disease of the respiratory system with breathlessness, airway hyper-responsiveness, recurrent cough and wheezing (1). Airway inflammation of asthmatic patients is dominantly eosinophillic inflammation. Asthmatic patients often have a family history of the allergic disease (9). Asthma is significantly associated with quality of life, anti-asthmatic drugs and Healthcare costs. In 2007 in the USA, for asthma treatment, the annual direct medical expenditure was 37.2 billion dollars [10-12]. Animal models using has largely contributed to the study of asthma, lungs diseases and development of new drugs. Rats, quina pig, pet cats and other animal can be used as model but handling of mice is easy. Mouse model has been used for identification of immunological alterations of inflammatory diseases and asthma (1).

2.1. Acute ovalbumin allergic asthma model

A common protocol of allergic asthma modeling is the ovalbumin (OVA) model in mice (9). Ovalbumin is used for asthma and airway inflammation model induction. For design of model, there are two stages sensitization and challenge. In the sensitization stage, 20 µg of OVA with 50 µl aluminum hydroxide (alum adjvant) are solute in PBS (last volume would be 100 µl) then injected intraperitoneal (IP) on day 0 and 14. In the next stage, the mice are challenged by inhalation (IT) of 1% OVA solution (in PBS) aerosolized by an nebulizer for 30 min per day on days 24, 26, 28 and 30 (Figure 2). It is better that mice with 6-8 weeks old and female would be used (13). If asthma model would be used for treatment protocol, according of the drug characteristics, type of nebulizer (ultrasonic, jet or mesh nebulizer) will be determined. Aluminium salts enhance humoral immune responses (immunoglubolin production via Th2 stimulation) and activate immune cells (9, 13).

There are some points for OVA method. The route of sensitization in current model is via IP, whereas large amount of asthmatic patient are sensitized via the airway. Ovalbumin is not main allergens and triggers

for Asthma in human. But, with mentioned negative points, for researchers about allergic asthma and inflammatory airways disease, this protocol is the best model (9, 13). BALB/c and A/J strains of the mice are suitable for asthma model. After sensitisation and exposure to allergens, airway inflammation hyperresponsiveness, and asthma developed. The advantages of using such models are high-IgE responder strains and the similarities with humans in the IgE-mediated response mechanisms (14, 15).

2.2. Chronic allergic asthma mouse models

Female BALB/c mice are sensitized with OVA and alum adjuvant IP on days 0, 7, 14 and 21 and then challenged intranasally with OVA on days 27, 29, 31 and then repeated challenging twice a week for 3 months (Figure 3) (8, 16, 17)

2.3. Antigen-independent mouse models

Another mouse models of asthma is produced without sensitization and antigen re-exposure. Cationic proteins (such as chlorine, ozone and poly-l-lysine) are instilled intratracheal. In this model, airway epithelium is damaged by used components. Exposure to cationic proteins results airway neutrophilia and increased collagen deposition which can be lead airway hyperresponsiveness and remodeling (9, 18, 19).

2.4. Aspergillus-induced allergic airways disease model

Aspergillus induced allergy is common from other fungi. Therefore, this part focus in this fungus. Animals are received 10 µg of Aspergillus fumigatus cellular Antigen (Ag) in IFA by IP and subcutaneous (SC) on day 0, then are received 10 µg Ag in PBS on day 14, 21 and 28 intranasally. On day 35, mice are inoculated intratracheal of $5x10^6$ Aspergillus fumigatus conidia. For Ag preparation, Aspergillus fumigatus mycelia are grown on enriched trypticase media, then extracted in 0.01 M ammonium bicarbonate and at least, the extract is dialyzed against distilled water. For Conidia preparation, culturing Aspergillus fumigatus is cultured on Sabouraud's dextrose agar plates at 37°C, after 1-2 week, the plate surface is washed with sterile 0.1% Tween 80 in PBS, filtered and the spores are counted (under a hemacytometer) (Figure 4) (20-24).

2.5. House dust mite allergic asthma model

For production of acute allergic pulmonary inflammation mice models, C57BL/6 male mice are sensitized with Dermatophagoides farinae (house dust mite allergen) plus alum adjuvant IP on day 0 and challenged with house dust mite allergen aerosol on days 14 for 7 consecutive days (8, 25). For production of chronic allergic pulmonary inflammation mice models, Female BALB/c are challenged with house dust mite allergen intranasally 5 days/week for 7 weeks (8, 26)

3. Food Allergy

Food allergy is one of the extremely important problems in people and has increased prevalence in the last decades. Fish, shellfish, peanuts, soybeans, cow's milk, hen's egg and wheat are most commonly food which are cause of food allergy. Anaphylaxis is the most serious reaction of food allergy. Immediate and a delayed hypersensitivity of the immune responses are associated with food allergy (1).

3.1. Animal models

Small animal models (mice, rats, and guinea pigs) and large animal models (dogs, pigs, and sheep) are used to know the immunological mechanisms and develop therapeutic strategies for food allergy (1). For the good sensitization in food allergy, some points should be notable: 1) The allergen concentration (high-doses leads to tolerance; low-dose cannot sufficiently stimulate) 2) The allergen should be taken oral (feeding or gavage) 3) Age of the animal (adult animals are suitable) 4) allergen sources 5) Animal genetic predisposition and 6) The use of adjuvants (27). The rat based food allergy model is routinely used for toxicological studies (1).

3.2. Murine Models of Food Allergy

BALB/c, C57/Bl6, A/J, DBA/2, C3H/HeJ and BDF-1 strains of the mice are suitable model for food allergy study. Anaphylactic antibodies (IgE and IgG1) are strongly produced in the C3H/HeJ and the BALB/c strains (1, 28, 29). The BALB/c mice have been sensitized to food through intraperitoneal administration of food proteins (for example, peanut agglutinin, OVA and bovine serum albumin) (1, 30).

3.3. Cow's Milk Allergy Model

According to study by Li et al, 1999, female 3 week old C3H/HeJ mice are sensitized with cow's milk intragastrically (and cholera toxin; as an adjuvant). Mice receive 1.0 mg/g body weight of cow's milk with 0.3 μg/g cholera toxin (sensitizing doses). Mice are boosted five times at weekly intervals. Then mice after fasting, are challenged with two doses of 30 mg/ml cow's milk intragastrically (given 30 minutes) at six weeks after the initial sensitization dose. At least, cow's milk food allergy (IgE-mediated) are induced (1, 31).

3.4. Peanut Allergy Model

To mimic the clinical and immunological characteristics of the Peanut Allergy model, C3H/HeJ mice (similar to cow's milk allergy) are sensitized orally with peanut and cholera toxin (as adjuvant). For this model, 5 week old female mice are sensitized with 5 mg/ml of ground whole peanut equivalent to 1 mg of peanut protein with 10 μg cholera toxin on day 0 and 25 mg equivalent to 5 mg of peanut protein with 10 μg cholera toxin on day 7 by intragastric gavage. Sensitized mice (3-5 weeks after initial sensitization) are fasted overnight and challenged with crude peanut extract (10 mg, divided into two doses at 30-40-minute intervals) intragastrically. Symptoms may be followed secondary challenges two weeks later (1, 32).

4. Eczema and Atopic Dermatitis

Eczema (in medicine) or atopic dermatitis (veterinary medicine) is recurrent chronic pruritic dermatitis and is associated with allergen specific IgE (1). Erythematous and pruritic Lesions are seen in eczema. Basophils and mast cells are dominant cells in pathophysiology of eczema and atopic dermatitis (31, 32).

4.1. Mouse Models of Atopic Dermatitis

SKH-1 hairless mice and null mutation in the filaggrin gene mice are easily sensitized cutaneous with allergens. For adaptation, mice are kept at standard condition. After adaptation period, atopic dermatitis are induced in mice by Chloro-2,4-dinitrobenzene (DNCB). The hair of the dorsal skin region are shaved carefully. In order to the induction of atopic dermatitis, 100 µL of 1% DNCB solution is topically applied to the each mouse skin for two days once daily (for 2%: 100 mg DNCB powder is dissolved in 20 mL of acetone/olive oil solution and half dilution makes the solution 1%). In the 3th day, 120 µL of 2% DNCB is applied. After the visual confirmation of skin sensitization parameters mice will be ready (33, 34).

5. Anaphylaxy

Anaphylactic responses to agents are dominant problem in allergic reactions (35). In the allergic and anaphylactic reactions, IgE is produced against allergen (via Th2-B cell pathway) and bound to FceRI on the mast cells that leads to mast cells sensitization. After the secondary exposure of antigen, antigen induces cross-linking of IgE (that is bound to FceRI of mast cell) which leads rapidly to mast cell degranulation and mediator releasing (35-38). Main responsible of the shock development are histamine and PAF (platelet-activating factor) (35, 39, 40). Treatment and prophylaxis with allergen avoidance and desensitization, Immunotherapy, and medications using (antihistamines and epinephrine) have important limitations (35).

5.1. Mouse models of anaphylaxis

Sometimes oral allergens can induce the shock and anaphylaxis but commonly induces food allergy (35, 41, 42). There are 3 mouse models of intestinal anaphylaxis: 1) mice are sensitized by allergen orally (for example peanut extract-cholera toxin); 2) mice are sensitized by OVA intraperitoneal injection with aluminum hydroxide (alum) as adjuvant; 3) mice are sensitized by hazelnut extract via transdermal immunization. According to recent studies, peanut extract is the best allergen for production mouse models of anaphylaxis (35, 43-45).

There is one type of anaphylaxis that called penicillin-induced anaphylaxis. For this model study, mice are sensitized with a conjugation of penicillin and OVA plus adjuvant and then challenged with conjugation of penicillin with different protein (35). Because anaphylaxis model designing is easy, it can be used as penicillin-induced anaphylaxis.

Anaphylaxis prophylaxis and important treatments were achieved by animal model studies and now, people have effective treatments or would receive in future. For example; anti-IgE monoclonal antibody, PAF antagonists, IL-4 receptor antagonists, IL-12, IL-10, Agents that activate tyrosine phosphatases, IgE

Fc–IgG Fc fusion protein, antigen-specific desensitization, bifunctional antibody that cross-links the ITIM-containing molecule CD300a with IgE and oral immunotherapy (35, 46-50).

6. Allergic conjunctivitis

Allergic conjunctivitis is type 1 hypersensitivity reaction and archstrated by Th2 cytokines (51, 52). It has 25% prevalence in the North American population (53). Animal models of allergic conjunctivitis are developed to study of pathophysiology and therapeutic Interventions of disease (54).

6.1. Dermatophagoides pteronyssinus allergic conjunctivitis model

C57Bl/6 or BALB/c mice (with 4-8 weeks old) are used for this model. There are two stages (immunization/sensitization and challenging) for production of allergic conjunctivitis mice model. 500 µg of Dermatophagoides pteronyssinus extract as allergen are mixed with 100 µl alum adjuvant which are used for mice immunization. Lyophilized Dermatophagoides pteronyssinus extract was diluted in phosphate-buffered saline with pH 7.2 (4.18 µg/µl concentration) which is used for the ocular challenge (54, 55).

On day 1, immunization solutions are injected subcutaneously. Half of the dose is injected at the base of both hind legs and the remaining half of the dose is injected into the lower abdomen. After 10 days, ocular challenge is done in mice with two drops of challenging solution in each eye. After twenty minutes, clinical signs will be appeared (conjunctival hyperemia and edema, palpebral edema and lacrimation) (54, 55).

6.2. Ovalbumin allergic conjunctivitis model

C57Bl/6 or BALB/c mice are sensitized IP on day 0 with mixture of 100 µg OVA, 1 mg alum and 300 µl pertussis toxin. Immunization is boosted subcutaneously (SC) on day 4 with 50 µg OVA. Then 1.5 mg ragweed in 10 µl PBS is used topical administration to the conjunctivae. After 17 days, challenging will be continued with 750 µg ragweed in 5µl PBS topical administration to the conjunctivae (56-58).

7. Allergic Rhinitis Model

There are some differences allergic rhinitis animal model according to allergen and adjuvant. In mice model, antigens administration via intranasal, intratracheal or aerosolized are performed (59, 60).

7.1. Staphylococcal enterotoxin B allergic rhinitis model

Guinea pigs (male 8 week old, 250-300 g) are sensitized with 1 µg Staphylococcal enterotoxin B intranasally that is dissolved in 40 µl saline every day for 2 weeks. To stop quickly elimination of Staphylococcal enterotoxin B by mucuciliary system, before each sensitization, lidocaine hydrochloride solution (4%) is used intranasal instillation for anesthetization of upper airway mucosal surface. 7 days

after the last sensitization, the same method should be applied once every 4 days for 30 times intranasally (Figure 5) (61).

7.2. Ovalbumin-Induced allergic rhinitis model

For allergic rhinitis induction, 0.3 mg ovalbumin and 30 mg aluminum hydroxide powder are suspended in 1 mL of normal saline (0.9%) and injected IP every day for 7 times under anesthesia (2% isoflurane in O2). In the next stage, 2 mg ovalbumin in 20 µL normal saline is intranasally instilled daily for 7 times under anesthesia (Figure 6). Every day intranasal administration of ovalbumin is necessary to maintain allergic signs. Sneezing, nasal itching (nasal rubbing), rhinorrhea and congestion are useful signs to indications of allergic rhinitis (62, 63).

7.3. Pollen Allergic Rhinitis model

For pollen induced allergic rhinitis, 6 week old female BALB/c mouse is better and if there is special pollen in suggestion, the extract of purposed pollen may be used. In modeling, 10 µl of 3 mg/ml pollen extract in PBS is intranasally administered on days 0 and this is repeated on day 7, 14, 21, 22, 23, 24, 27, 28, 29, and 30 (Figure 7). Pollen extract Administration should be done without anesthesia to stop pollen extract reaching to the lower airways (64-67). Administration methods are shown in Figure 8.

Troubleshooting

Time Taken

Anticipated Results

8. Conclusion

Animal models provide a potential approach to investigation of the pathophysiology, mechanism and drugs designing for allergy and asthma. Working with model can provide useful information about allergic diseases. With benefit model, inflammatory process, pathology of allergy and asthma, structural and physiological mechanisms of atopic diseases can be developed and identical. Access to suitable model not only give benefit approach to understand disease but also the development of novel treatments and upgrade of current therapies. Physicians and veterinarians with collaboration in this field could improve best animal model and develop new, benefit and species therapies. In future studies in the animal models, some applicable goals can be reached. Identification of the mast cell receptor antagonists, identification of pathways anaphylaxis checkpoints, determination of the allergens nature in different diseases and determination of the TH2 responses mechanisms in allergic diseases. With

development of suit and applicable animal models, safer, better, effective and long term activation methods and drugs would be produced that can be treat target organs. At least, all animals should be housed in standard and allergen-pathogen free conditions according to the laboratory animal's guidelines. Ethics Committee approval should be taken for all procedures on animals.

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Acknowledgements

Figures

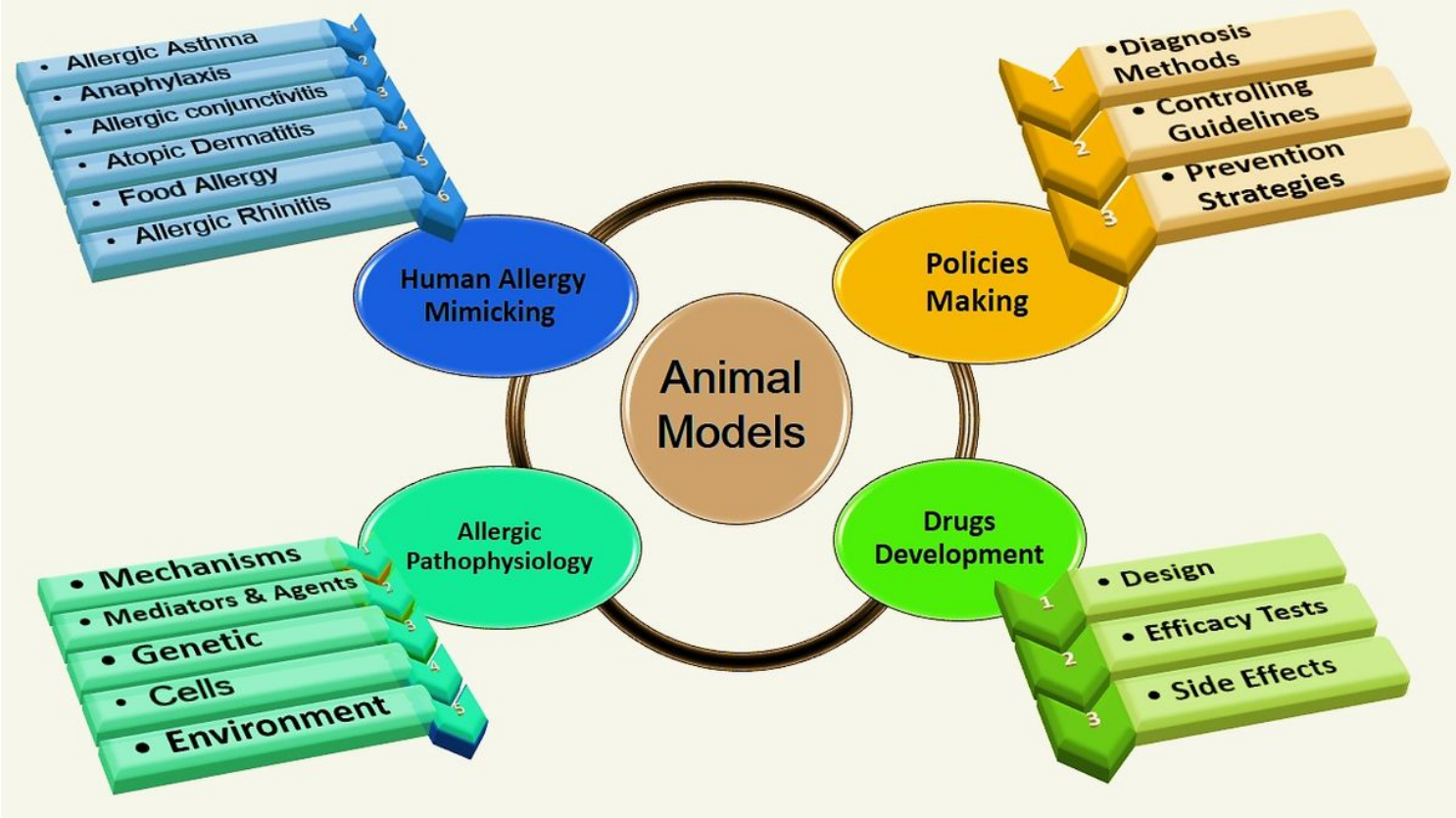

Figure 1

Purposes of the animal models using. Human allergy mimicking (allergic conjunctivitis, anaphylaxis, allergic asthma, atopic dermatitis, food allergy and allergic rhinitis), policies making (diagnosis methods, controlling guidelines and prevention strategies), drug development (design, efficacy tests and side effects) and allergic disease pathophysiology study (mechanisms, mediators & agents, genetic, cells and environment).

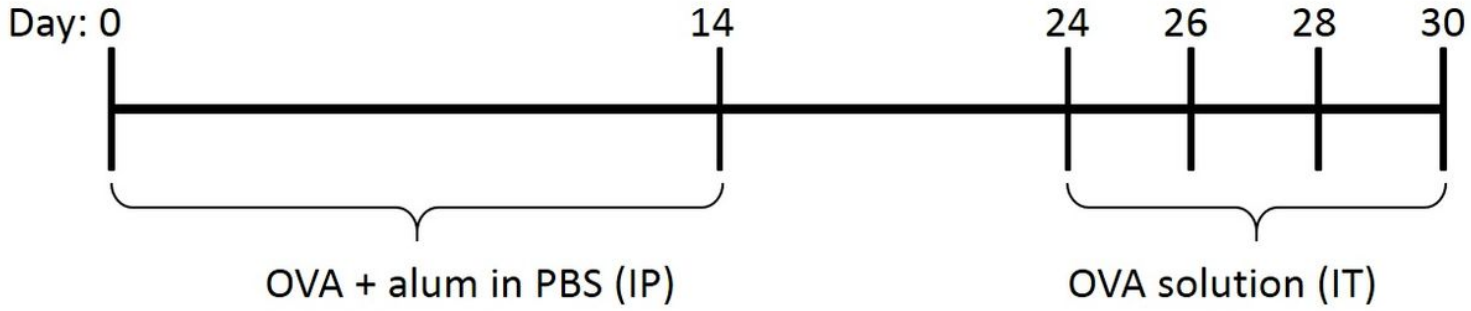

Figure 2

Acute ovalbumin model. There are two stages sensitization and challenge for design of this model. In the sensitization stage, OVA with alum are saluted in PBS then injected IP. In the challenge stage, the mice are received OVA solution aerosolized by IT. OVA: Ovalbumin, alum: aluminum hydroxide adjuvant, IP: Intraperitoneal, IT: Inhalation Intratrachea.

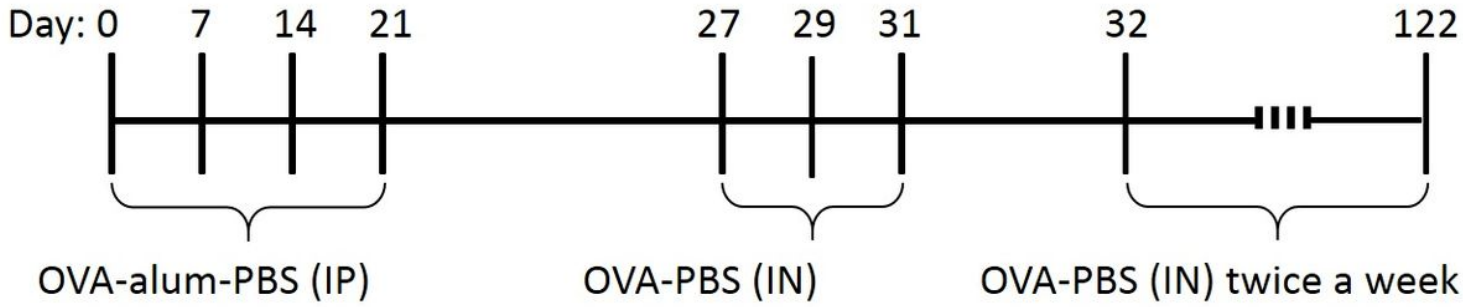

Figure 3

Chronic allergic asthma models. Mice are sensitized with OVA and alum IP and then challenged IN with OVA. IN: Intranasal

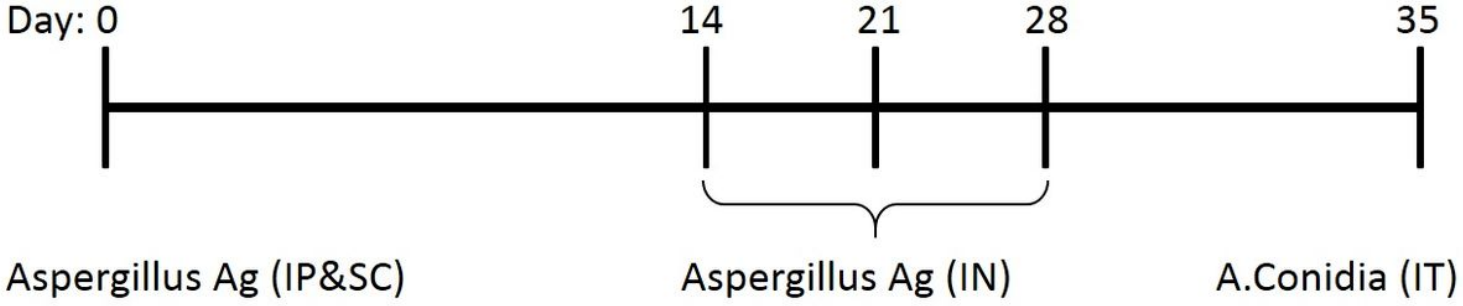

Figure 4

Aspergillus-induced allergic airways disease. Aspergillus Ag is injected IP and SC then is administrated IN. after this period, mice are inoculated IT conidia. Aspergillus Ag: Aspergillus fumigatus cellular Antigen, SC: Subcutaneous

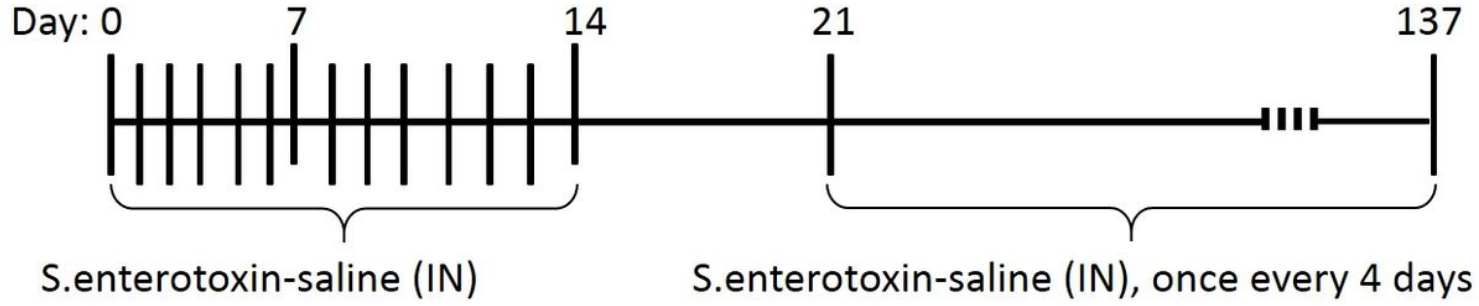

Figure 5

Staphylococcal enterotoxin B Allergic Rhinitis model. S. enterotoxin is administrated IN for modeling. S. enterotoxin: Staphylococcal enterotoxin B

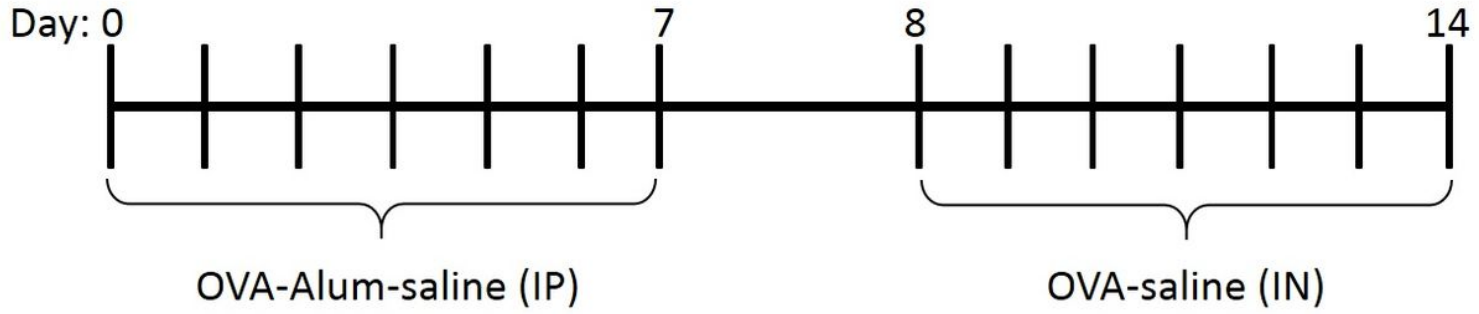

Figure 6

Ovalbumin-Induced Allergic Rhinitis Model. OVA and alum are suspended in saline and injected IP. In the next stage, OVA is solved in saline and instilled IN.

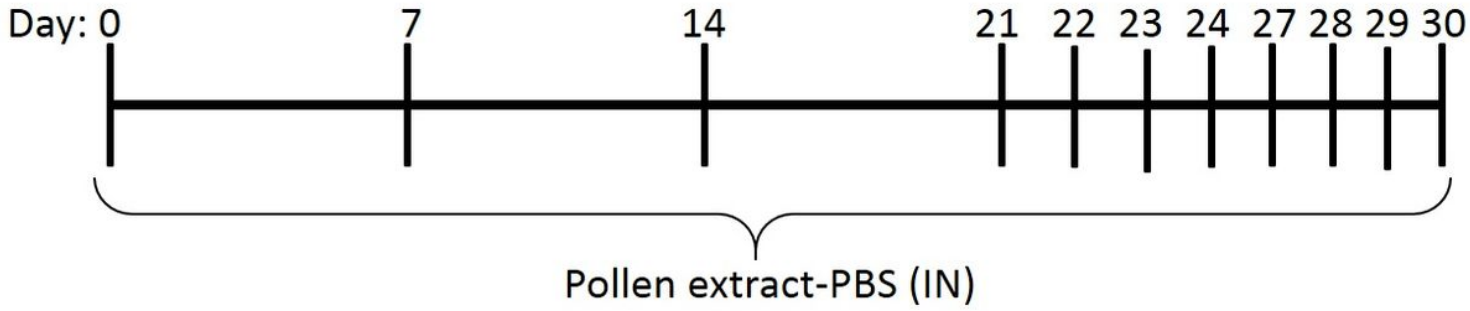

Figure 7

Pollen -Induced Allergic Rhinitis. Pollen extract in PBS is administered IN.

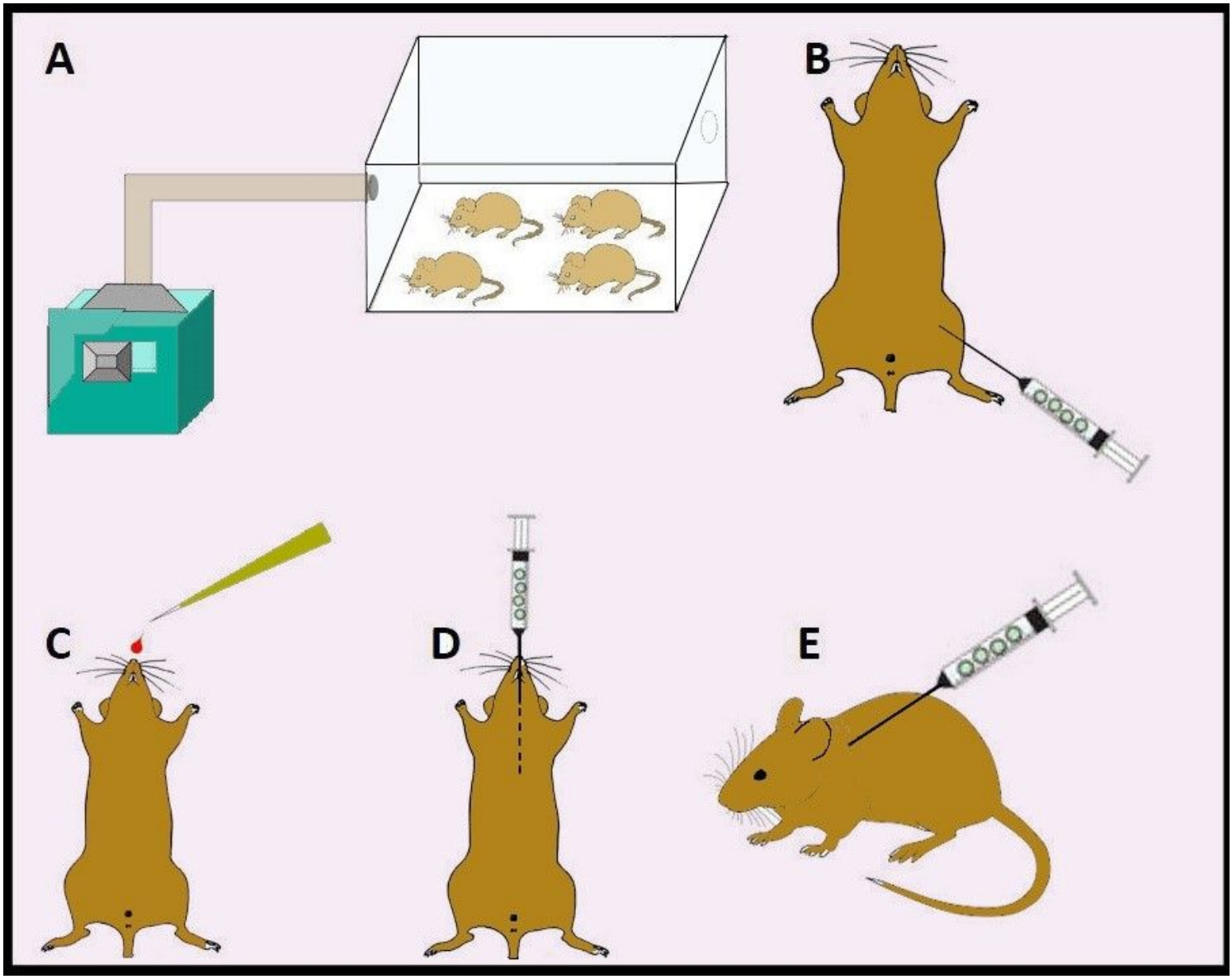

Figure 8

Main administration methods in allergic animal modeling. A: inhalation (IT) aerosols by nebulizer. Mice are kept in chamber and nebulizer set is connected to the chamber. Aerosolized OVA solution is flowed to inhalation air for mice, B: intraperitoneal (IP) injection, C: intranasal (IN) administration, D: intragastric gavage, E: subcutaneously (SC) injection.

Supplementary Files

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