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Observation on the Therapeutic Effect and Mechanism of Activated Polyethylene Glycol on Allergic Rhinitis Animal Models

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ABSTRACT

Allergic rhinitis (AR), as a chronic disease, seriously affects the quality of life of patients while concurrently exerting a significant economic and healthcare burden on the medical system. However, the existing treatment methods have certain limitations, and more effective treatment strategies are needed. To this end, we proposed an ovalbumin-induced guinea pig model of AR to investigate the potential impact of activated polyethylene glycol (PEG) with varying molecular weights and concentrations in local nasal treatment.

The therapeutic effect was evaluated by behavioral score, serological detection, and histopathological observation.

The behavioral assessment demonstrated significant alleviation of sneezing frequency, nasal pruritus, and clear nasal discharge in the activated PEG-600 treatment groups relative to the sham group. However, statistical analysis revealed no appreciable intergroup differences between the activated PEG-3400 treatment groups and the sham group. Histopathological evaluation disclosed a marked reduction in eosinophilic infiltration in the activated PEG-600 group, accompanied by preservation of nasal mucosal structural integrity and notable attenuation of inflammatory infiltration. In contrast, the activated PEG-3400 group exhibited comparatively limited therapeutic efficacy, demonstrating only a subtle reduction in inflammatory cell counts and more pronounced disorganization of mucosal epithelial architecture compared to the PEG-600-treated group. Serum immunological profiling indicated that while local inflammatory markers showed evidence of mitigation, systemic immune parameters remained unaffected by either activated PEG formulation.

These findings underscore the differential efficacy profile between PEG-600 and PEG-3400 derivatives in ameliorating AR symptoms, among which PEG-600 exhibits superior anti-inflammatory effects.

Keywords: Guinea pig; Inflammation mediators; Nasal mucosa; Polyethylene glycols

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INTRODUCTION

Allergic rhinitis (AR) is a chronic inflammatory disorder of the upper airway, characterized by sneezing,

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nasal congestion, rhinorrhea, and nasal itching in response to otherwise harmless environmental allergens such as pollen, dust mites, and animal dander. The immunopathogenesis of AR is primarily mediated by a type I hypersensitivity reaction, which involves a dysregulated adaptive immune response and a shift toward T helper 2 (T_H2) cell dominance.[1,2]

The pathophysiological process of AR unfolds in three main phases: sensitization, early-phase response, and late-phase inflammation. During sensitization, inhaled allergens are captured by antigen-presenting cells (APCs), predominantly dendritic cells within the nasal epithelium, which then process and present antigenic peptides to naïve $CD4^+$ T cells in regional lymph nodes. Under the influence of interleukin-4 (IL-4), these T cells differentiate into T_H2 cells, which secrete IL-4, interleukin-5 (IL-5), and interleukin-13 (IL-13). IL-4 plays a central role in promoting B cell class switching to produce allergen-specific immunoglobulin E (IgE). These IgE antibodies bind to high-affinity FcεRI receptors on mast cells, priming them for rapid activation upon subsequent allergen exposure.[3–5]

Upon re-exposure to the same allergen, cross-linking of IgE on mast cell surfaces triggers degranulation and the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins—driving the acute symptoms of AR. This is followed by a late-phase response, typically 4–12 hours later, marked by the recruitment of eosinophils, basophils, and T_H2 lymphocytes to the nasal mucosa. These cells release additional cytokines and chemokines that sustain inflammation, promote epithelial damage, and increase mucosal sensitivity to nonspecific stimuli.[6,7]

Epidemiological data indicate that the global prevalence of AR is rising, affecting up to 25% of children and 40% of adults worldwide, thereby representing a growing public health concern.[8,9] Beyond its clinical burden, AR significantly impacts patients' quality of life and contributes to substantial economic costs due to healthcare utilization and reduced productivity.[10]

Current AR treatments include allergen avoidance, pharmacotherapy, immunotherapy, and surgical interventions. Among these, intranasal corticosteroids and antihistamines are commonly used for symptom control, while allergen-specific immunotherapy offers the potential for long-term disease modification. However, therapeutic efficacy is often limited by incomplete symptom control, adverse effects, or patient non-adherence. These limitations underscore the need for novel, targeted, and well-tolerated treatment strategies.[11–13]

Polyethylene glycol (PEG) is a biocompatible, non-immunogenic polymer widely used in biomedical applications. Its activated derivative, NHS-PEG-NHS, contains reactive N-hydroxysuccinimide (NHS) groups that readily form covalent amide bonds with primary amines on mucosal proteins under physiological conditions, enabling strong and sustained tissue adhesion. This functionalization makes NHS-PEG-NHS a promising candidate for mucosal barrier reinforcement. Clinically approved PEG-based hydrogels, such as Coseal, have demonstrated rapid adhesion and controlled degradation profiles.[14,15] Importantly, the degradation rate of PEG conjugates can be modulated by adjusting pH, molecular weight, and ester bond composition, allowing for tunable retention and drug release.[16]

Building upon these physicochemical and biological properties, we hypothesize that NHS-PEG-NHS can serve as a topical, mucosa-adherent barrier that prevents allergen entry and mitigates local immune activation in AR. In this study, we employed animal models to evaluate the efficacy of NHS-PEG-NHS with varying molecular weights and concentrations in reducing nasal mucosal inflammation and preserving epithelial integrity. Additionally, we assessed its biocompatibility and explored its potential to act as a non-pharmacologic intervention targeting the early stages of allergen exposure. These findings aim to establish a theoretical foundation for future clinical translation of PEG-based barrier therapies in the management of AR.

MATERIALS AND METHODS

Animals

Forty-eight healthy guinea pigs (half male and half female), weighing 250–300 g, were purchased from the Experimental Animal Center of Hangzhou Normal University (supplier: Jiashanshengwang Farm, China) and housed at the same facility for experimentation. The animals were in good general condition, showing no signs of nasal scratching, sneezing, nasal discharge, or wheezing, with normal activity and feeding behavior.

Table 1. Reagent list for nasal treatment and sensitization studies

Reagent name	Molecular weight	Supplier	Purpose
NHS-PEG-NHS-600	600	Shanghai Aladdin Biochemical Technology Co., Ltd.	For nasal treatment studies
NHS-PEG-NHS-3400	3400	Shanghai Aladdin Biochemical Technology Co., Ltd.	For nasal treatment studies
Ovalbumin (OVA)	–	Sigma-Aldrich	For allergen sensitization in AR models
Aluminum hydroxide [$Al(OH)_3$] powder	–	Shanghai Yuanye Biotechnology Co., Ltd.	Used as an adjuvant
Guinea pig IgE, IL-4, and IFN-γ ELISA kits	–	Quanzhou Ruixin Biotechnology Co., Ltd.	For serological analysis

ELISA: enzyme-linked immunosorbent assay; Ig: immunoglobulin; IFN-γ: interferon-gamma; IL-4: interleukin 4.

Table 2. List of laboratory equipment used in the study

Equipment name	Model	Manufacturer
ELISA plate reader	CMaxPlus	MD Company
Low-temperature high-speed centrifuge	Micro17R	Thermo Fisher Scientific Company
Dehydrator	TP1020	Leica Microsystems Inc.
Embedding machine	BMJ-IB	Tianjin Tiantali Company
Histopathology slide maker	RM2235	Leica Microsystems Inc.
Brightfield optical microscope	Nikon Eclipse Ci-L	Nikon Corporation
Imaging system	Nikon DS-Fi2	Nikon Corporation

ELISA: enzyme-linked immunosorbent assay.

Model Establishment, Grouping, and Administration

Model establishment: After completing a 7-day acclimatization phase with standardized dietary regimens, 40 guinea pigs were randomly selected and allocated from the initial cohort of 48 animals to develop an ovalbumin (OVA)-sensitized experimental model. The sensitized group received intraperitoneal injections of a precisely formulated OVA suspension (20 mg OVA combined with 30 mg aluminum hydroxide in 1 mL of physiological saline) every other day for a total of eight doses over the 15-day treatment period. On day 16, the allergen challenge phase commenced through intranasal administration of 10% OVA solution (0.5 mL per nasal cavity, twice daily) for 10 consecutive days. For comparative analysis, an additional control group comprising eight guinea pigs was included, which received identical intraperitoneal and intranasal administrations of physiological saline throughout the experimental duration.

Grouping: Among the 8 guinea pigs in the control group, the weight of 2 guinea pigs was significantly different from that of the others. A total of 40 guinea pigs were initially subjected to OVA sensitization, of which 34 were successfully sensitized. To ensure randomization and minimize selection bias, 30 animals were randomly selected using a computer-generated sequence for subsequent experimental procedures. The remaining 4 animals were maintained under identical housing conditions as reserve subjects. In the event of

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unexpected mortality or data loss, reserve animals were used as replacements according to the predefined randomization order. Unused reserves were humanely euthanized following the approved institutional animal care protocol. All experimental procedures were approved by the Animal Ethics Committee of Hangzhou Normal University (Approval No. HSD-20240329-01). Therefore, we selected 6 guinea pigs as a group for the experiment. After successful establishment of the animal model, the subjects were randomly allocated to 6 experimental groups.[17]

Table 3. Experimental group design

Group name	Treatment drugs and concentrations
Group 1	Control group
Group 2	Sham group
Group 3	600-5% (NHS-PEG-NHS-600, 5 wt%)
Group 4	600-15% (NHS-PEG-NHS-600, 15 wt%)
Group 5	3400-5% (NHS-PEG-NHS-3400, 5 wt%)
Group 6	3400-15% (NHS-PEG-NHS-3400, 15 wt%)

Administration Protocol: Both experimental, sham, and control groups-initiated treatment on day 2 post-intranasal sensitization. The experimental cohort received sequential bilateral nasal administrations as follows: First, 0.5 mL/side of activated PEG solution was delivered, followed 10 minutes later by 0.05 mL/side of 2% OVA in physiological saline. This therapeutic regimen was meticulously repeated once daily over a 14-day period, totaling 14 standardized administrations. The sham group underwent identical temporal scheduling with modified treatment parameters: Initial bilateral administrations consisted of 0.5 mL/side physiological saline, succeeded 10 minutes later by 0.05 mL/side of 2% OVA in physiological saline. The treatment paradigm mirrored the experimental group's frequency and duration (14 daily administrations). Throughout the 14-day study period, the control group received strictly sham therapy. Initial bilateral administrations consisted of 0.5 mL/side physiological saline, succeeded 10 minutes later by 0.05 mL/side physiological saline.

Behavioral Assessment Metrics

Quantitative behavioral evaluations were performed at the conclusion of the experimental induction phase and on the final treatment administration day (Days 25 and 39) to evaluate model efficacy and therapeutic outcomes. Observable clinical indicators were systematically quantified using a validated scoring protocol:[18]

Sneeze Frequency:
1–3 episodes: 1 point
4–10 episodes: 2 points
≥11 episodes: 3 points

Nasal Rubbing Intensity:
1–4 contacts: 1 point
> 4 contacts: 4 points

Nasal Discharge Severity:
Mild flow (anterior nares only): 1 point
Moderate overflow (exceeding anterior nares): 2 points

Severe profusion (copious drainage): 3 points

Behavioral scoring data collection commenced immediately following intranasal allergen challenge and continued for a standardized 30-minute observation period per trial session. Cumulative scores were calculated through sequential summation of individual metric values. A total score exceeding 5 during the induction phase was established as the threshold for successful AR model development.

Serological Analysis Protocol

Following the final intranasal drug administration,

blood samples were collected through abdominal aortic puncture in anesthetized guinea pigs. Serum specimens were prepared by allowing blood to coagulate at room temperature for 20 minutes, followed by centrifugation at 3500 rpm for 15 minutes. The resultant supernatants were cryopreserved at−80°C until analyzed for serum IgE, IL-4, and IFN-γ levels using ELISA kits.

Histopathological Observation

Following blood sample collection, nasal tissues were excised and processed to isolate the nasal mucosa. Specimens were fixed in 10% formalin solution for 24

hours at room temperature, subsequently underwent dehydration through a graded alcohol series (70%, 80%, 90%, and 100% ethanol), then were paraffin-embedded, and finally were sectioned into 4-μm-thick slices. Histopathological evaluation was conducted through hematoxylin-eosin (HE) staining, with subsequent microscopic examination to evaluate histological changes and eosinophil infiltration in the nasal mucosa of AR models.

Histological Evaluation

Nasal mucosal tissue sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope at ×400 magnification. Quantification of inflammatory cell infiltration was independently performed by two blinded investigators, with results expressed as the number of cells per mm² or per high-power field (HPF). Six sections were randomly selected from each experimental group for analysis. The cell counting method was based on previously established protocols:[19,20]

Infiltration was graded per HPF:

0-4 cells = score 0

5-10 cells = score 1

11–30 cells = score 2

>30 cells = score 3

Mucosal edema:

Intact mucosa with normal architecture; no edema or erosion = score 0

Mild edema or slight surface irregularity; overall mucosal structure well preserved = score 1

Moderate edema, mild mucosal erosion, or irregular mucosal folds = score 2

Marked mucosal erosion, atrophy, or architectural distortion with focal defects = score 3

Epithelial damage:

Intact and continuous epithelium with no detachment or necrosis = score 0

Mild epithelial swelling and slight disorganization, but continuity is preserved = score 1

Moderate injury with focal epithelial loss or mild detachment = score 2

Marked epithelial detachment, degeneration, or large areas of necrosis = score 3

The final score is the sum of the three dimensions.

Statistical Analysis

Data were analyzed using SPSS 20.0. For normally distributed data with homogeneity of variances, one-way analysis of variance (ANOVA) was applied, followed by Tukey's test for pairwise comparisons. Non-normal data or unequal variances were analyzed using the Kruskal-Wallis H test or Dunnett's T3 test, respectively. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Behavioral Scores

The results demonstrated that on day 26, 34 of the 40 allergen-sensitized guinea pigs exhibited scores exceeding 5 points, with a statistically significant difference compared to the control group ($p<0.01$), thereby confirming the successful establishment of the experimental model. Subsequently, animals were randomized into 6 groups of 6 animals each. Following random allocation, all subjects received standardized drug treatment regimens over a 14-day period. Statistical analysis revealed significant differences in behavioral scores between PEG-600 experimental groups and the sham group ($p < 0.05$). And there was no difference between the PEG-3400 experimental groups and the sham group ($p>0.05$). Details are provided in Table 4.

Serological Markers

The levels of serum IgE, IL-4, and IFN-γ did not show statistically significant differences among the groups ($p>0.05$). Details are provided in Figure 1.

Histomorphological Analysis

As shown in Figure 2, all experimental groups exhibited statistically significant differences compared with the control group (score=0), confirming the successful establishment of the AR model. Compared with the control group, the sham group displayed marked mucosal edema, extensive inflammatory cell infiltration, and disrupted tissue architecture, consistent with typical histopathological features of AR ($p<0.001$). Scores for inflammatory cell infiltration, mucosal edema, and epithelial damage all followed a similar trend: the PEG-600-treated groups consistently showed lower scores than the PEG-3400-treated groups. Within the PEG-600 cohort, the higher concentration group exhibited lower scores than the lower concentration group, with both groups showing statistically significant improvements compared to the sham group. In contrast, no clear dose-dependent trend was observed within the PEG-3400 groups. These findings were corroborated by the H&E-stained sections. In the low molecular weight PEG-600-treated groups, epithelial cell alignment

appeared more regular, and both inflammatory cell infiltration and epithelial damage were markedly reduced compared to the model group. Conversely, the high molecular weight PEG-3400 groups exhibited disorganized epithelial cell arrangements, more pronounced inflammatory cell infiltration, and greater epithelial tissue damage.

Table 4. Comparison of nasal allergy symptom scores in each group of guinea pigs after modeling and drug administration

Groups	Post-modeling	*p* vs control	14 days after administration	*p* vs sham
Control group	0.833 ± 0.753		0.667 ± 0.816	
Sham group	5.833 ± 0.753[a]	<0.0001	5.333 ± 1.033	
PEG-600-5%	5.833 ± 0.753[a]	<0.0001	3.667 ± 1.033[b]	0.0190
PEG-600-15%	6.000 ± 0.894[a]	<0.0001	3.667 ± 0.816[b]	0.0112
PEG-3400-5%	6.167 ± 0.753[a]	<0.0001	5.000 ± 1.095[ns]	0.5995
PEG-3400-15%	6.000 ± 0.894[a]	<0.0001	4.333 ± 1.033[ns]	0.1245

p<0.0001 vs the control group, *p*<0.05 vs the sham group, ns: not significant vs the sham group

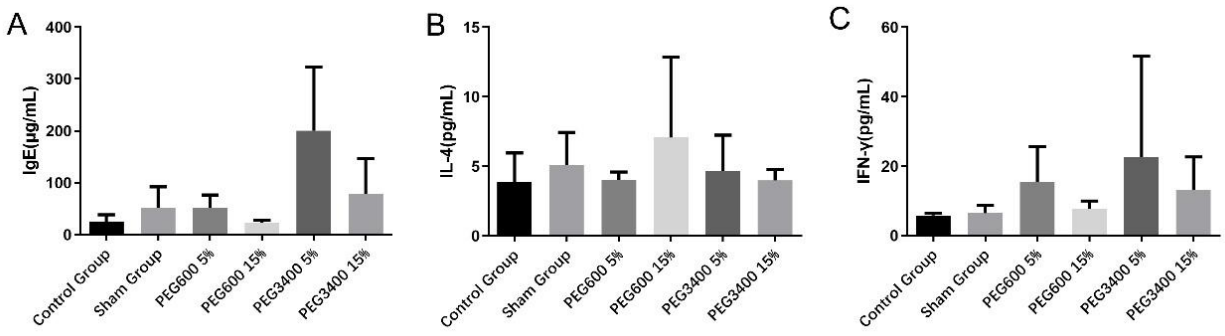
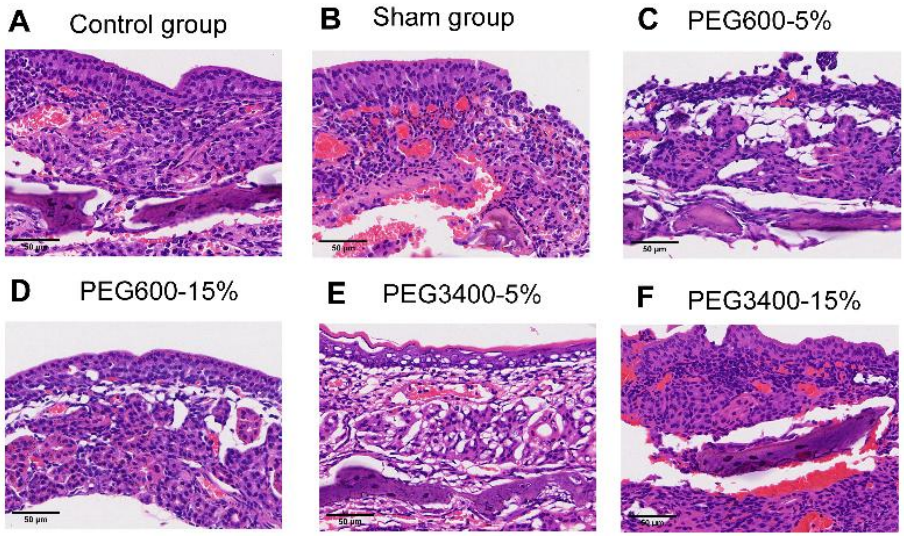


Figure 1. Serum levels of immunoglobulin E (IgE, A), interleukin-4 (IL-4, B), and interferon-gamma (IFN-γ, C) in guinea pigs (mean±SD, n=6).



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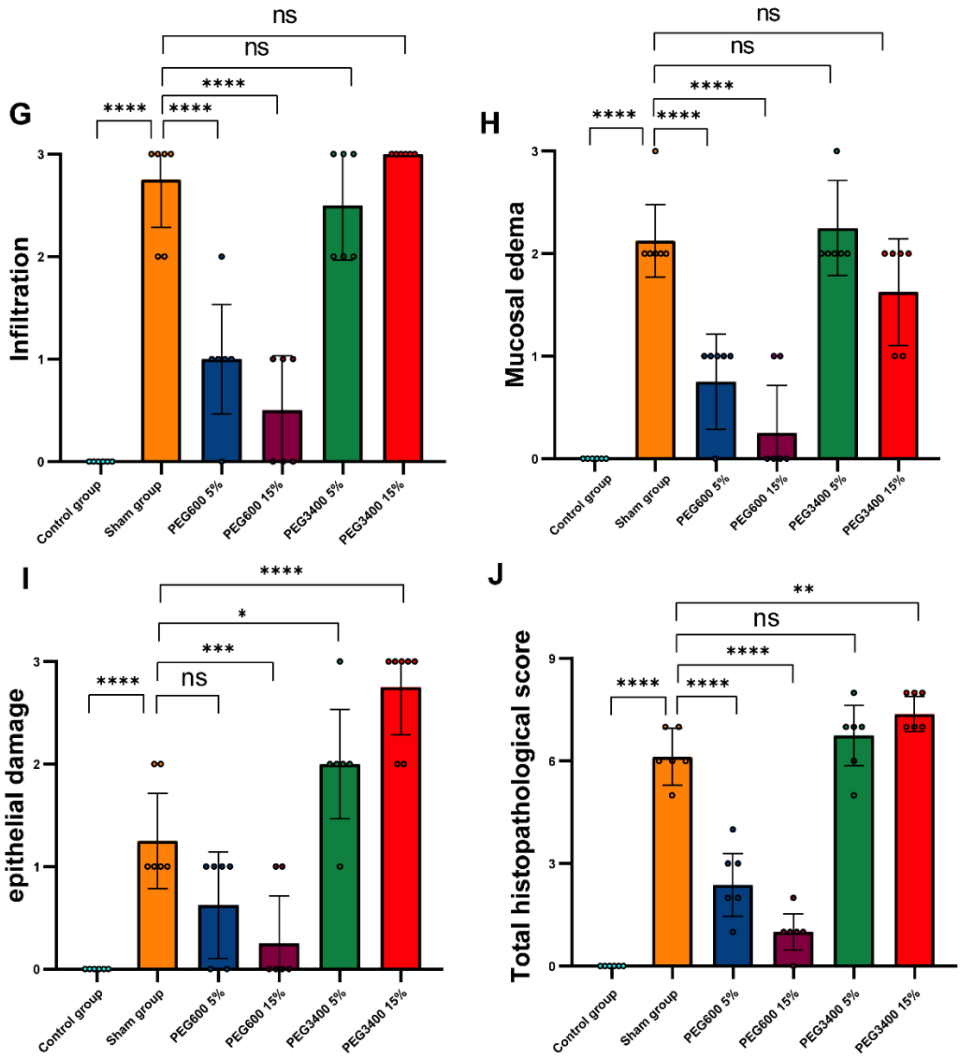

Figure 2. A. H&E-stained histological images of control group; B. H&E-stained histological images of sham group; C. H&E-stained histological images of activated PEG-600 (5%) group; D. H&E-stained histological images of activated PEG-600 (15%) group; E. H&E-stained histological images of activated PEG-3400 (5%) group; F. H&E-stained histological images of activated PEG-3400 (15%) group; G. quantitative comparison of inflammatory cell infiltration scores in the pathological sections after HE staining of the 6 groups (n = 6 per group); H. comparison of mucosal edema scores in the pathological sections after HE staining of the 6 groups (n = 6 per group); I. comparison of epithelial tissue damage scores in the pathological sections after HE staining of the 6 groups (n = 6 per group); J. comparison of total histopathological scores in the pathological sections after HE staining of the 6 groups (n = 6 per group).

DISCUSSION

The present study demonstrates that topical administration of activated polyethylene glycol (PEG) formulations, particularly PEG-600, can effectively ameliorate nasal symptoms and reduce local inflammatory responses in a guinea pig model of AR. Behavioral scoring revealed a notable reduction in clinical symptoms-including sneezing frequency, nasal rubbing, and watery nasal discharge-in the PEG-600 treatment groups relative to the sham cohort. Although the differences in total symptom scores between the PEG-3400 treatment groups and the sham group did not reach statistical significance (p>0.05), the PEG-600-treated animals consistently exhibited a trend toward greater symptomatic relief compared to the PEG-3400 group, suggesting a potential dose- and molecular weight-dependent effect.

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Histopathological analysis further substantiated these findings. The PEG-600 groups showed significantly attenuated eosinophilic infiltration (p<0.05), improved preservation of mucosal epithelial architecture, and a notable decrease in local inflammatory cell accumulation. In contrast, the PEG-3400 group exhibited only partial histological improvement, characterized by persistent epithelial disruption and moderate inflammatory infiltration. These data indicate that PEG-600, owing to its lower molecular weight and likely superior mucosal adhesion, may provide more effective local protection against allergen-induced epithelial disruption and subsequent immune activation.

From an immunological perspective, AR is primarily driven by a T_H2-skewed immune response. Upon allergen exposure, antigen-presenting cells such as dendritic cells activate naïve $CD4^+$ T cells, promoting their differentiation into T_H2 effector cells under the influence of IL-4.[21,22] These T_H2 cells secrete a range of cytokines—most notably IL-4, IL-5, and IL-13—that collectively mediate hallmark features of AR, including IgE class switching in B cells, eosinophil recruitment, and mucus hypersecretion.[23] In contrast, T_H1 cytokines such as interferon-γ (IFN-γ) act in opposition to this pathway by downregulating IL-4 expression and limiting T_H2 cell expansion.

Although systemic measurements of IgE, IL-4, and IFN-γ did not show significant differences between the PEG-600 and sham groups in our study (p>0.05), the local histological findings suggest that PEG-600's primary therapeutic effects are localized to the nasal mucosa. This supports the hypothesis that activated PEG-600 acts primarily as a physical barrier, preventing allergen access to immune cells within the nasal epithelium and thereby limiting downstream T_H2-mediated inflammation without inducing broad systemic immunomodulation. This dissociation between local and systemic responses highlights an important therapeutic distinction. While systemic cytokine levels remain unchanged, the substantial reduction in local immune activation suggests that PEG-600 may offer a non-pharmacologic, topical approach to mitigate allergic inflammation at its site of initiation. As such, PEG-600 presents a promising candidate for development as a barrier-enhancing, polymer-based therapy for AR. Future investigations should explore synergistic strategies combining PEG-based formulations with anti-inflammatory or immunomodulatory agents to achieve more comprehensive control of both local and systemic immune responses in allergic airway diseases.

This study systematically investigated the potential therapeutic effects of activated PEG (NHS-PEG-NHS) with varying molecular weights and concentrations in local nasal treatment for AR using a guinea pig AR model. Through multi-dimensional evaluation, including behavioral scoring, serological analysis, and pathological histological examination, we comprehensively assessed the intervention efficacy of activated PEG on AR. The experimental findings revealed significant therapeutic potential for activated PEG compounds in mitigating localized nasal inflammation, with the low molecular weight formulation (PEG-600) demonstrating superior therapeutic efficacy compared to its high molecular weight counterpart (PEG-3400).

However, the serological results obtained in this study did not reflect a significant effect of activated PEG-600. To further validate our findings, we will examine local inflammatory markers-including IL-4, IL-5, IFN-γ, as well as high-affinity receptor for IgE (FcεRI) and IgE expression in nasal tissues. These additional data are expected to offer stronger experimental support for the therapeutic efficacy of activated PEG in AR.

STATEMENT OF ETHICS

Animal studies (ethics approval number: HSD-20240329-01) were approved by the Animal Ethics Committee of Hangzhou Normal University, Zhejiang, China.

FUNDING

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

DATA AVAILABILITY

Data are available upon reasonable request from the corresponding author via wuhonglin205961@163.com.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation, writing, or editing of this manuscript.

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