# Therapeutic effects of interleukin-1 receptor antagonist on allergic rhinitis of guinea pig[1]

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**KEY WORDS** interleukin-1 receptors; perennial allergic rhinitis; histamine; IgE

## ABSTRACT

**AIM:** To determine the effect of interleukin-1 receptor antagonist (IL-1ra) on allergic rhinitis. **METHODS:** Allergic rhinitis was induced by toluene-2,4-diisocyanate (TDI). At the end of the treatment, the pathological changes in the nasal mucosa were observed. The concentrations of hitamine in the nasal mucosa and IgE in the blood were determined as well. **RESULT:** Symptoms of allergic rhinitis were remarkably relieved after IL-1ra treatment. Hematoxylin and eosin staining demonstrated that less edema was found in the nasal mucosa and small vessel was normal after IL-1ra application, but edema, vasodilation, and inflammatory cell infiltration were discovered in the model group. The concentrations of hitamine in the nasal mucosa and IgE in the blood were less than those in the control group. **CONCLUSION:** IL-1ra im administration selectively and non-traumaticly alleviated nasal congestion, rhinorrhea, and sneezing.

## INTRODUCTION

Allergic rhinitis has been described as an inflammatory disorder of the upper airway mucosa, characterised by a local influx of eosinophils[1]. Exposure of allergic patients to their specific allergens produces a biphasic physiological response[2]. The early phase response results in an itching or tingling sensation in the nose within 1 to 2 min after allergen challenge, the late phase response, although poorly understood, may reflect the inflammatory response to allergen exposure characterized by sustained nasal congestion. Airway allergic inflammation is set in motion in genetically predisposed individuals at the first exposure to a novel antigen. This sensitization step likely depends on differentiation of Th2 lymphocytes and subsequent cytokine released. Among Th2-derived cytokines, IL-4 potently enhances B-lymphocyte generation of immunoglobulin E antibodies. IgE was specifically associated with allergic rhinitis[3]. Symptoms of allergic rhinitis are produced by inflammatory mediators that are released upon activation of mast cells by antigen-IgE interaction. These mediators target the end organs directly or indirectly. Stimulation of sensory nerves by histamine, for example, leads to the symptoms[4]. These mast cell-derived mediators collectively produce acute-phase clinical symptoms by enhancing vascular leakage, bronchospasm, and activation of nociceptive neurons linked to parasympathetic reflexes.

Simultaneously, some mast cell mediators up-regulate expression of adhesion molecules on endothelial cells for leukocytes (not only eosinophils, but also basophils and lymphocytes), which are key elements in

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the late-phase allergic response[5]. And sensitization increases the number of histamine H1 receptor. Increased number of H1 receptor in nasal mucosa in sensitized guinea pigs may be one of the causes of nasal hyperrespon-siveness to antigen[6]. Increase in IL-4 in sera might be at least partly involved in the seasonal increase in specific IgE in sera. Immunotherapy's inhibitory effect on IL-4 production and specific IgE response might be one of its working mechanisms[7]

IL-1 is actually a family of 3 proteins, IL-1α, IL-1β, IL-1ra. IL-1 has significant biologic properties related to its proinflammatory activity. A prominence of $CD4^+$ T cells and eosinophils, synthesis and release of T(H)2 cytokines, and the coordinate expression of chemokines and adhesion molecules are all characteristics of the allergic response observed in rhinitis[8]. In type I immediate hypersensitivity, IL-1 has been shown to be involved in generating enhanced basophil-histamine release either directly or indirectly through intermediate induction of IL-1 as well as chemokines. Allergic rhinitis represents a persistent inflammation in terms of an activation of eosinophils and constant upregulation of proinflammatory cytokine IL-1beta[9]. IL-1ra is thought to modulate the potentially deleterious effects of IL-1 in the natural course of inflammation, and has been used experimentally as an anti-inflammatory agent. Its physiologic role in inflammation and pathologic role in systemic inflammatory states are increasingly recognized. Major anti-inflammatory cytokines include interleukin (IL)-1 receptor antagonist[10].

Interleukin-1 receptor antagonist (IL-1ra) is an antagonist that has no agonist activity compared with other 2 family members IL-1α and IL-1β. IL-1α and IL-1β are not only potent enhancers of immune responses but also very potent inducers of acute phase responses and inflammation. They have a wide variety of effects in immunity. The identification of IL-1ra as a potential antagonist leads to some very interesting possibilities for clinical intervention with cytokine antagonists that have only begun to be explored in terms of their efficacy[11]. Based on the characteristics of the IL-1ra, we want to know theraputical effects of IL-1ra on the allergic rhinitis of guinea pig challenged by TDI.

## MATERIALS AND METHODS

**Animals** Guinea pigs of either sex (350-450 g), conventional animals,were provided by Experimental Animal Center of Yangzhou University. Certificate No 93104.

**Drugs** Toluene-2, 4-diisocyanate (TDI) and Olive oil were supplied by Shanghai Chemical Company. Interleukin-1 receptor antagonist (IL-1ra) were supplied by the Biopharmaceutical Company of Peking University

**Experimental protocol** Forty-eight adult guinea pigs were randomly divided into six groups ($n$=8): vehicle (Olive oil), model, dexamethasone (Dex) group; IL-1ra 1, 2, 4 mg/kg group. Guinea pig was sensitized following the procedures with some modification[12]. Vehicle group received an intranasal instillation of 5 μL of Olive oil. The other group received intranasal instillation of 5 μL of 10 % TDI (vehicle was Olive oil) once a day for 7 d.

After 7 d, Dex 2.2 mg/kg was given im once a day. IL-1ra 1, 2, and 4 mg/kg was injected im. All the drugs were administered 30 min before TDI administration for 14 d.

Within 30 min after the sensitization, nasal itching, sneezing, and rhinorrhoea were observed to monitor the effects of IL-1ra. Performance severity was assessed by use of numerical scores: itching, light and occasional smear, 1 point; severe and continuous smear, 2 points; sneezing: 1-3 times, 1 point; 4-10 times, 2 points; over 10 times, 3 points. Rhinorrhoea: within the nasal cavity, 1 point; outside the nasal cavity, 2 points; on the face, 3 points. In the end scores for itching, sneezing, and rhinorrhoea were added together.

After the drugs were im administered for 30 min on the last day, the blood was withdrawn from the carotid artery. The concentration of IgE in blood was measured by ELISA. The guinea pigs were sacrificed, and the septum nasi was dissected, routinely processed, and embedded in paraffin for histopathological observation. The nasal mucosa was stained with hematoxylin and eosin (HE). The infraturbinal, middle turbinate, and supraturbinal were taken from the basal layer, and nasal mucosa 100-150 mg was obtained. Total histamine content was assayed by Shore's method[13].

**Statistic analysis** All data were shown as mean±SD and analyzed with $t$-test.

## RESULTS

**Effect of IL-1ra on the performance of guinea pig induced by TDI** In the first week, no significant differences in the scores between groups were found, although the scores were higher than before. In the following two weeks, changes in performance were

significantly different among groups ($P$<0.05), IL-1ra 1-4 mg/kg ameliorated the TDI-induced increase in the scores ($P$<0.05 *vs* model group). The effect of IL-1ra 4 mg/kg is better than others (Fig 1).

**Effect of IL-1ra on histology changes** The nasal mucosa of Olive oil group was normal. In the model group, the lesions were characterized by edema, congestion, and the infiltration of numerous inflammatory cells into nasal mucosa, especially the eosinophils. Some increase in number of lymphocyte was also noticed. IL-1ra 1, 2, and 4 mg/kg protected nasal mucosa against morphological damage by TDI. Effect of IL-1ra 4 mg/kg was the best among 3 doses. In Dex treated group, the mucosa lesions were qualitatively similar but significantly less severe than IL-1ra 4 mg/kg group (Fig 2).

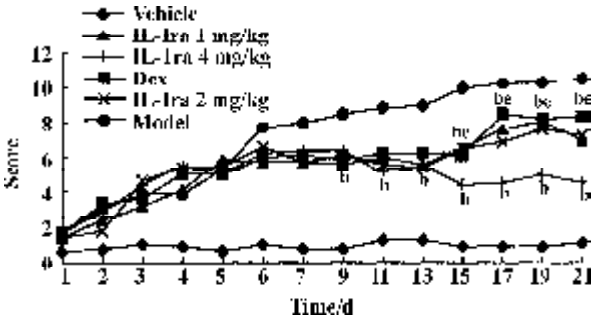


**Fig 1. Effect of IL-1ra on the performance of guinea pig induced by TDI. $n$=8. Mean±SD. $^{b}P$<0.05 *vs* model group. $^{e}P$<0.05 *vs* IL-1ra 4 mg/kg group.**

**Effect of IL-1ra on histamine** TDI induced a profound increase in histamine ($P$<0.05) in model group. Dex, IL-1ra 1, 2, and 4 mg/kg reduced the TDI-induced histamine increase in ($P$<0.05) (Fig 3).

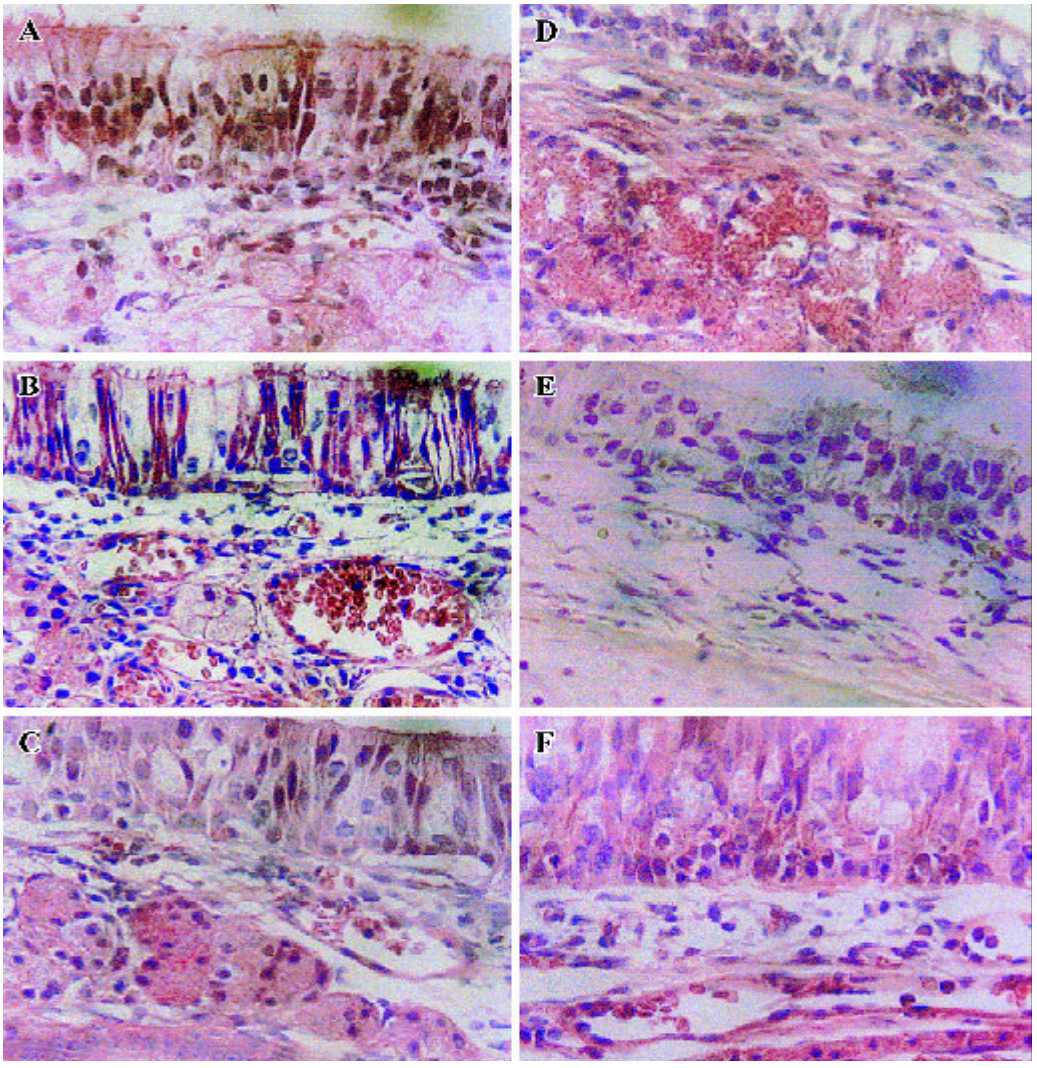


**Fig 2. Representative photomicrographs of mucosa in nasal tissue after administration of IL-1ra for 14 d. A: Vehicle group. B: Model group. C: Dex group. D, E, F: IL-1ra-treated group at a dose of 1, 2, and 4 mg/kg, respectively. HE stain, ×40.**

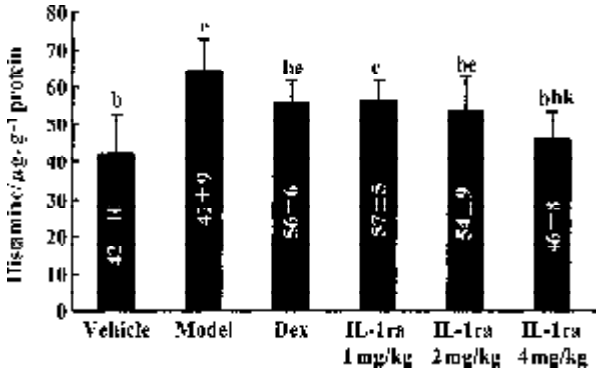


**Fig 3. Effect of IL-1ra on histamine in allergic nasal mucosa of guinea pig induced by 10 % TDI. *n*=8. Mean±SD. $^{b}P<0.05$ *vs* model group. $^{e}P<0.05$ *vs* vehicle group. $^{h}P<0.05$ *vs* Dex group. $^{k}P<0.05$ *vs* IL-1ra 1 mg/kg group.**

**Effect of IL-1ra on IgE in serum** Dex, IL-1ra 1, 2, and 4 mg/kg inhibited the TDI-induced increase in IgE ($P<0.05$), but significant differences between these groups were found (Fig 4).

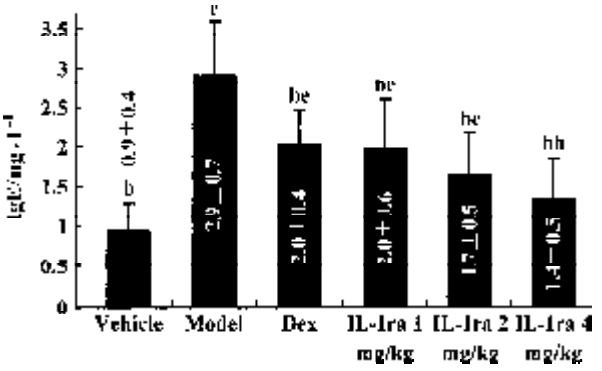


**Fig 4. Effect of IL-1ra on IgE in allergic nasal mucosa of guinea pig induced by TDI. *n*=8. Mean±SD. $^{b}P<0.05$ *vs* model group. $^{e}P<0.05$ *vs* vehicle group. $^{h}P<0.05$ *vs* Dex group.**

## DISCUSSION

Our experiments demonstrated that IL-1ra can alleviated the rhinitis symptoms effectively, inhibited the pathological processes of the nasal mucosa, and prevented the infiltration of lymphocytes and eosinophils. The ameliorating mechanism was perhaps due to the breakdown of the balance of the inflammation cytokines and anti- inflammation cytokines *in vivo*. Histamine may influence several functions of lymphocytes, monocytes, basophils, and macrophages to modulate the release of inflammatory mediators and cytokines[14]. Mast cells are recognized as a new type of immunoregulatory cells capable of producing different cytokines[15]. Taking our observations into account, there was no significant difference between the Dex, IL-1ra 1, 2, and 4 mg/kg group. Perhaps it was related to the complicated net among the cytokines, which indicated multiple facters influenced histamine and IgE secretion.

But there were other reports about the contrary sense that IL-1ra was in great molar excess in the secretions or the serum[16,17]. But our experiment indicating that IL-1ra could treat allergic rhinitis *in vivo* induced by TDI alleviating the symptoms and the pathological processes suggests that IL-1ra has protective effects against allergic rhinitis. Preventing the increase in histamin and IgE may serve as one of the mechanisms. Thereby. IL-lra may have a bright future in the therapy of allergic rhinitis. Further study, such as whether there is a common base between IL-lra and Dex, and whether there is difference between the IL-1ra *in vivo* and *in vitro*, will be investigated.

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