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Treatment of allergic rhinitis with intranasal infusion of botulinum toxin type A in mice

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ABSTRACT

Aims: To determine whether intranasal infusion of botulinum toxin type A (BTX-A) relieves symptoms of ovalbumin (OVA)-induced allergic rhinitis (AR) and reduces nasal inflammation in mice.
Main methods: AR was induced via intraperitoneal injection of OVA followed by daily intranasal challenge with OVA. Five weeks after the initiation of OVA sensitization, nasal cavities were exposed to a single intranasal infusion of BTX-A. The behavior of mice was observed before and 1, 3, 5, 7, 14, 21, and 28 days after infusion. Mice were sacrificed after 28 days and late histological findings were examined. PBS was administered to control mice.
Results: On Day 3, the frequency of typical AR symptoms, including sneezing and nose scratching, significantly decreased in the BTX-A-treated group ($n = 6$) compared to the control group ($n = 6$). Although the AR-inhibiting effects of BTX-A persisted until Day 21, AR symptoms re-appeared in response to daily OVA stimulation. Histological findings of the nasal mucosa also improved following BTX-A administration. Although capillary dilatation and eosinophil infiltration decreased by Day 3, these effects disappeared by Day 28. In contrast, the number and size of the secretary glands in the nasal mucosa did not change following BTX-A administration. PBS had no effect on nasal symptoms or histology.
Conclusions: Topical treatment with BTX-A efficiently and temporarily ameliorates AR symptoms. Intranasal infusion does not cause pain or bleeding, and the effects of a single infusion of BTX-A last for at least three weeks. This treatment might be a promising therapeutic strategy for the treatment of AR.

1. Introduction

Allergic rhinitis (AR) is an IgE-mediated disease of the nasal mucosa that usually occurs after exposure to allergens such as cedar pollen, house dust mites, and animal hair. In Japan, the incidence of AR was approximately 39.4% in the 2008 Practical Guidelines for the Management of Allergic Rhinitis in Japan [1]. Current treatment of this disease involves the avoidance of allergens when possible, which is often difficult and impractical. To prevent or reduce the symptoms of AR, various medications have been developed such as corticosteroids, antihistamines, decongestants, anticholinergics, and leukotriene receptor antagonists. Few of these, however, enable the complete relief of symptoms without complications. Further, these medications usually require frequent administration once- or twice-daily for a relatively long period of time, thus deteriorating the quality of life (QOL) of patients.

Botulinum toxin type A (BTX-A) is a neurotoxin produced by the bacterium *Clostridium botulinum*. According to Burgen et al., BTX-A blocks signal transmission at the neuromuscular and neuroglandular junctions by decreasing acetylcholine release from presynaptic nerve endings [2]. BTX-A is now widely used to treat various neuromuscular disorders, such as strabismus, blepharospasm, achalasia, and facial spasm [3]. BTX-A has also been applied to cosmetics [4,5] and the prevention of gustatory sweating [6]. Due to this anticholinergic activity, BTX-A is considered a promising treatment for the attenuation of AR symptoms. Various application procedures have been proposed, including injection into the nasal turbinate or septum [7–11], placement of a BTX-A-containing cotton or gauze on the nasal mucosa [12,13], and placement of gel formula on the nasal turbinate [14]. Nasal drip infusion is considered the most convenient way to administer BTX-A into the nasal cavity without causing pain or bleeding. To our knowledge, however, this procedure has not been reported for BTX-A.

Here, we investigated whether nasal drip infusion of BTX-A could attenuate the nasal symptoms and reduce inflammatory responses of the

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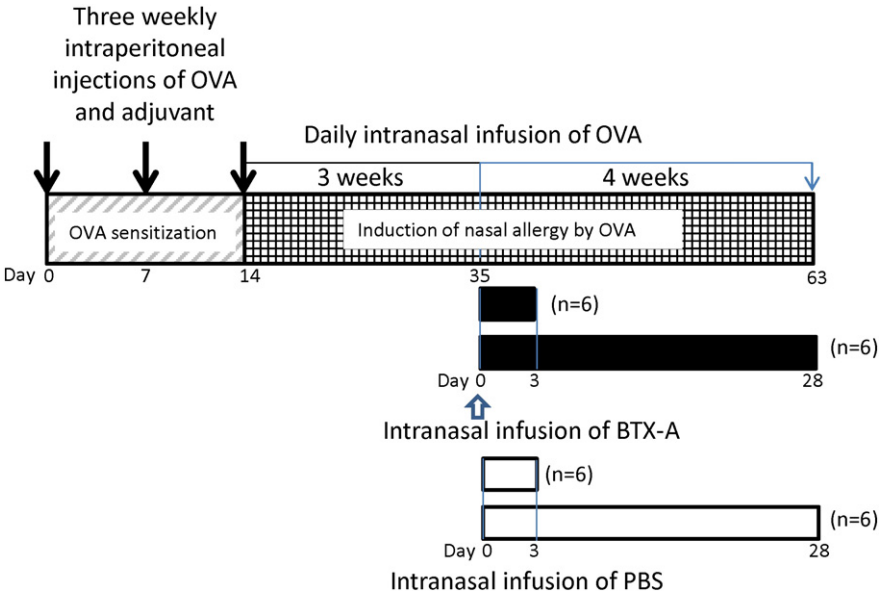

Fig. 1. Experimental protocol. Nasal allergy was induced by three intraperitoneal injections of OVA and aluminum hydroxide over the course of two weeks, followed by daily nasal challenge with OVA. Five weeks post-OVA sensitization, a single intranasal infusion of BTX-A was administered to reduce allergic responses induced by OVA.

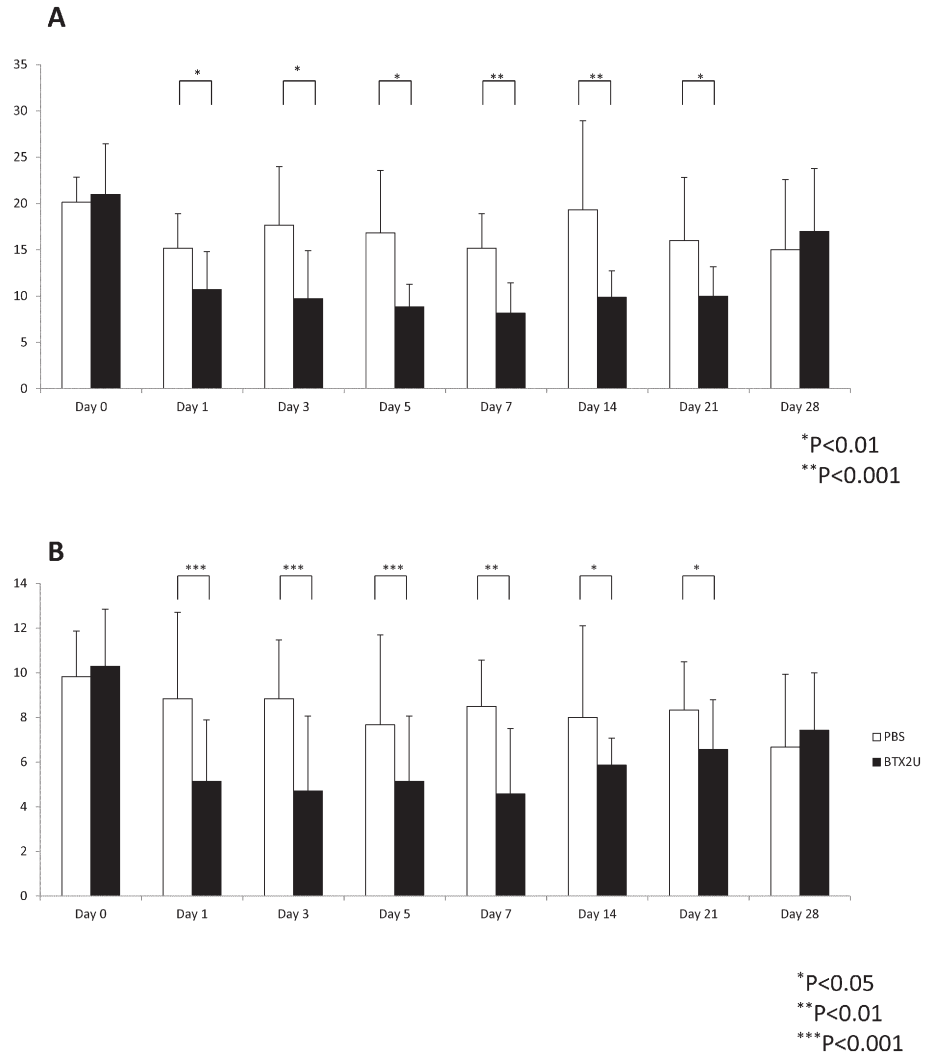

Fig. 2. Sequential changes in OVA-induced nasal symptoms after nasal drip infusion of BTX-A. A, Number of sneezes per 10 min and B, number of nose scratches per 10 min. Incidence of sneezing and nose scratching significantly decreased until 3 weeks post-BTX-A administration.