

A selective H₄R antagonist prevents antigen-induced asthma-like reaction and airway inflammation in guinea pigs

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Introduction

Although the mechanisms involved in the pathogenesis of asthma remain unclear, roles for oxidative/nitrosative stress, epithelial cell apoptosis and airway inflammation have been documented [1]. Besides the classical allergen-dependent pathways, reactive oxygen and nitrogen species, produced during airway inflammation, activate neutrophils, eosinophils and mast cells to release histamine, prostaglandins and cytokines, which exacerbate the response and directly participate in the pathogenesis of asthma [2]. The inflammatory responses resulting from the release of histamine have long been thought to be mediated by histamine H₁-receptor, and H₁-receptor antagonists have been used for the treatment of allergies for many years. Recently, accumulating evidence suggest that histamine has roles in inflammation and immune function through the activation of histamine H₄-receptor, a novel G-protein coupled receptor, expressed on dendritic and inflammatory cells [3].

Here, we report the effect of compound JNJ 777120, a selective H₄-receptor antagonist, on antigen-induced asthma-like reactions in sensitized guinea pigs.

Materials and methods

Male albino guinea pigs (Harlam, Milan, Italy) were used and the experimental protocol was similar to that previously utilized [4]. It complied with the recommendations of the European Economic Community (86/609/CEE) for the care and the use of laboratory animals and was approved by the Animal Care Committee of the University of Florence (Florence, Italy). The guinea pigs

were sensitized with ovalbumin (OA 100 mg/kg b.wt. i.p. plus 100 mg/kg b.wt s.c.) and eight animals were left unsensitized (group 1). After 18–21 days, the sensitized guinea pigs were divided in 2 groups, at least 8 animals each. Group 2 was treated for 4 days with an i.p. injection of 1 ml PBS, group 3 was treated with compound JNJ 777120 5 mg/kg b.wt. i.p. for 4 days. Sixty min after the last treatment, the guinea pigs were placed, one by one, in the whole respiratory chamber and challenged with OA aerosol, as previously described [4]. The changes in the respiratory activity of PBS- and JNJ 777120-treated animals were recorded for 10 min after aerosol administration and the following parameters evaluated: latency time (sec) for the appearance of respiratory abnormalities; cough severity score and occurrence of dyspnea. At the end of the experiments, guinea pigs were killed by lethal i.p. injection of sodium thiopental (Abbott, Latina, Italy), the thorax was opened and tissue specimens from the middle and lower lobes of the right lung were excised and processed for histopathological and morphometric analyses.

Compound JNJ 777120 was kindly provided by Johnson & Johnson Pharmaceutical Research & Development, San Diego CA, USA.

The experimental data are mean ± SEM of at least 8 animals per group. Statistical comparison of differences was carried out by one-way ANOVA and post-hoc test, as appropriate. $P \leq 0.05$ was considered significant.

Results and discussion

The values of the respiratory parameters assayed are reported in Fig.1, panels A and B. There were no substantial abnormalities in the unsensitized control guinea pigs after inhalation of OA aerosol (group 1), apart from sporadic

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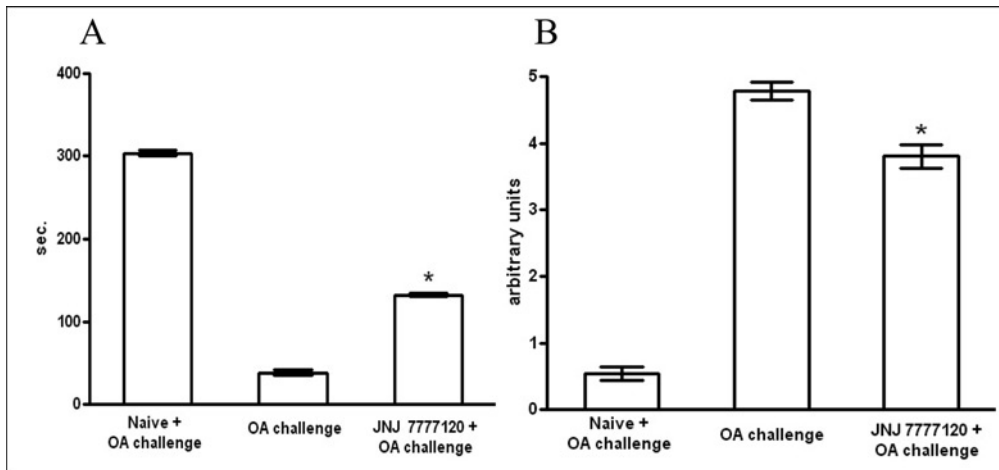


Fig.1. Occurrence of respiratory abnormalities in guinea pigs of the different experimental groups. **A:** latency for the onset of cough; **B:** severity of cough. * $p < 0.01$ vs OA-challenged animals

cough strokes arising approximately 2 min after the onset of aerosol.

Aerosol administration of OA in sensitized guinea pigs produced a significant reduction of cough latency and of onset of dyspnea and a significant increase in cough severity (Fig.1). Conversely, pretreatment with JNJ 777120 of sensitized guinea pigs before antigen inhalation (group 3) resulted in a marked, statistically significant reduction of respiratory abnormalities compared with those in the sensitized PBS-treated animals (group 2). In particular, the latency for cough increased and the cough severity decreased (Fig.1, panels A and B). No clear-cut signs of dyspnea were detected in JNJ 777120-treated animals. The improvement of functional parameters were objectified by morphometric analysis, in JNJ 777120-treated group there was a significant decrease in the mean surface area of alveolar air spaces and a significant increase in the mean surface area of bronchial lumina (data not shown). These findings provide evidence that a H_4 -receptor antagonist counteracts allergic asthma-like reaction in sensitized guinea pigs. In fact, H_4 -receptor expression and function on mast cells, eosinophils, basophils, dendritic and T cells [5, 6] suggest that this receptor may play a role in the asthmatic response, and in the fu-

ture, H_4 -receptor antagonists could provide beneficial for the relief of asthma symptoms.

References

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