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Intranasal simvastatin reverses the allergen-induced lung inflammation and dysfunction in a chronic murine model of allergic asthma

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Background:

Asthma is the leading cause of school absenteeism and hospitalization among children. At the time of diagnosis, pathological features of asthma are already established resulting in recurrent attacks. Thus, an ideal asthma therapy should prevent the future episodes and reverse the established features. Previously we showed the preventive benefits of intranasal simvastatin (S_{in}) against the 'allergic asthma' in mice.

Objective:

For the current study, we tested the hypothesis if S_{in} can reverse the established allergic lung inflammation, remodelling, and dysfunction in mice.

Methods:

Balb/c mice (6-8wks, female, n = 12) received House Dust Mite (HDM) challenge for 5wks (5days/wk). From wk-3, 50% mice received treatment with S_{in} (30mg/kg) once daily. 48hrs post final challenge we assessed: lung function using a small animal ventilator; airway inflammation by immune cell counting and cytokine array in bronchoalveolar lavage (BAL); and, lung histology for tissue remodelling. Data were analyzed using univariate analysis (SPSS20.0).

Results:

S_{in} (30mg/kg) significantly reversed all indices of the lung inflammation established by chronic HDM challenge- 38% reduction ($p<0.01$) in total immune cells with over 60% reduction ($p<0.05$) in eosinophils and neutrophils along with proinflammatory Th2 cytokine Il-5. The marker of lung remodelling, goblet cells, was almost entirely reversed by S_{in} treatment to 0.6±0.1/µm basement membrane compared to the 7.7±0.7/µm basement membrane established by chronic HDM challenge ($p<0.001$). Most importantly, lung function test revealed that intranasal simvastatin significantly reversed the total respiratory resistance (airway hyperreactivity) ($p<0.05$) to methacholine challenge established by chronic HDM-challenge.

Conclusion:

Our results suggest that i.n. simvastatin can reverse the established features of asthma in the mouse that includes lung inflammation, remodelling, and dysfunction. The dose used in the current study is clinically relevant and could be extrapolated for first-in-human trials for both adults and children. Thus, our study is an important step towards bringing the i.n. simvastatin closer to the clinic.