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The severity of airway inflammation and goblet cell hyperplasia in a murine model of atopic asthma are directly related to allergen dose and are reduced by treatment with a glucocorticoid

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Introduction: Using a model of atopic asthma in ovalbumin (OA)-sensitized male Balb/c mice, which reproduces many of the characteristic features of the disease in man (Blyth et al 1996), we have studied the relationships in the absence and presence of a glucocorticoid between the dose of allergen and the degree of cell infiltration into lung tissue or airway lumen, and that of goblet cell hyperplasia (GCH) in airway epithelium.

Methods: Accurate delivery of known amounts of OA to the pulmonary airways was achieved by non-surgical intratracheal (i.t.) instillation (Blyth et al 1998). Mice (groups of 5) were challenged i.t. with 0, 1.25, 5, 20 or 80μg OA in 10μl endotoxin-free saline on each of three occasions, each three days apart. The mice were treated for 8 days by the intraperitoneal injection of either saline or dexamethasone (1mg/kg/day), beginning on the day before the first OA challenge. They were killed 24h after the third challenge. The cellular content of the airway lumen was assessed by total and differential counting of cells present in bronchoalveolar lavage (BAL) fluid. The lungs were inflated *in situ* with buffered neutral formalin, removed into the fixative for 24h, and processed to paraffin wax. 3-4 μm sections were stained with haematoxylin and eosin for general morphology, or Alcian Blue–Periodic Acid Schiff (with α-amylase predigestion to remove glycogen) for the detection of mucins and identification of GC. Semi-quantitative 6-point scoring systems were used to assess the degrees of inflammation and GC hyperplasia (GCH).

Results: In the airway lumen, numbers of eosinophils (eos), neutrophils (neu) and lymphocytes (lym) increased progressively as the dose of OA increased. Responses (cells $\times 10^{-4}$ per mouse) to 0, 1.25, 5, 20 and 80μg OA respectively were: 0, 10.2, 7.1, 29.0 and 76.6 (eos); 0.3, 0.2, 0.3, 5.5 and 7.7 (neu); 0.1, 1.0, 0.6, 2.4 and 4.5 (lym). Increases in the numbers of macrophages, the normal intraluminal population of non-inflamed airways, were not as clearly dose-related as those of other cell types.

In the lung tissue, similar dose-related increases in numbers of eos, lym, plasma cells, macrophages and GC were seen. Systemic treatment with dexamethasone reduced all these increases, the suppression of intraluminal numbers of recruited cells (eos response to top dose of OA reduced by 99.3%; neu by 80.8%; lym by 97.8%) being more complete than that of cells in the lung tissue. Importantly, dexamethasone-induced reductions in the numbers of inflammatory cells (and GC) in the lung tissue, but not the lumen, were overcome by increasing the dose of OA.

Discussion: These results show that analysis limited only to that of cell numbers in BAL fluid (and particularly to a single time-point) can be misleading. It can underestimate the degree of allergen-induced pathology in lung tissues and overestimate the response to suppressive therapy.

This study demonstrates that the degrees of asthma-like cellular infiltration and GCH in the airways of mice were directly related to the amount of allergen to which the airways were exposed. Treatment with dexamethasone, at a dose which completely suppressed cell recruitment into the airway lumen, only partially suppressed cell influx and GCH in lung tissue. Suppression in the lung tissue, but not in the lumen, was overcome by exposure of the airways to higher concentrations of allergen.

References:

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