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Title: The muscarinic M_3 receptor regulates allergen-induced airway remodeling in mice

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Body: RATIONALE Asthma is a chronic obstructive airway disease, characterized by inflammation and remodeling. Acetylcholine (ACh) contributes to asthma symptoms by inducing bronchoconstriction via the muscarinic M_3 receptor. Recent evidence suggests that ACh also regulates airway inflammation and remodeling. Therefore, we studied the contribution of the M_3 receptor to allergen-induced inflammation and remodeling using M_3 receptor subtype deficient ($M_3R^{-/-}$) mice. Wild type (WT), $M_1R^{-/-}$ and $M_2R^{-/-}$ mice were used as controls. METHODS Female C57Bl/6 mice (n=8-10) were sensitized and challenged with ovalbumin (twice weekly, for 4 weeks). Control animals were challenged with saline. Lungs were collected for analyses. RESULTS Allergen exposure induced goblet cell metaplasia, airway smooth muscle thickening, pulmonary vascular smooth muscle remodeling and increased deposition of collagen I and fibronectin in the airway wall of WT mice. These effects were partly to fully prevented in $M_3R^{-/-}$ mice, whereas $M_1R^{-/-}$ and $M_2R^{-/-}$ mice responded similar to WT mice. In addition, airway smooth muscle mass and pulmonary vascular smooth muscle mass were lower in saline-challenged $M_3R^{-/-}$ mice compared to WT mice. Interestingly, allergen-induced airway inflammation, measured as eosinophil infiltration and cytokine release (IL-4, IL-5, IL-13 and IL-17), was similar in all strains. CONCLUSION Our data indicate that ACh contributes to allergen-induced remodeling and smooth muscle mass via the M_3 receptor, and not via M_1 or M_2 receptors. Surprisingly, no role for individual muscarinic receptor subtypes in allergic inflammation was observed, suggesting that the role of ACh in remodeling is independent of the allergic inflammatory response.