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Title: Budesonide reverses IL-13–induced airway hyper-responsiveness but has little effect on β2 agonist response in human small airways

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Body: IL-13 modulates airway smooth muscle sensitivity to contractile stimulus. Steroids and β2 adrenoceptor (AR) agonists decrease inflammation and inhibit airway hyper-responsiveness (AHR) in asthma. We postulate that steroids decrease AHR after IL-13 stimulation, and IL-13 alters bronchodilation of small airways. Precision cut lung slices (PCLS) from disease-free donors were incubated with 100 ng/mL IL-13 (18 h) and examined for carbachol (Cch)-induced bronchoconstriction, and formoterol- (Form) or forskolin (Fsk)-induced bronchodilation. To assess the effect of steroids, slices were preincubated with budesonide (Bud) for 1 h prior to IL-13. Data shown are mean % change of baseline luminal area ± sem. IL-13 significantly increased bronchoconstriction to a maximal effective concentration (100 μM) of Cch (Control (C): -80 ± 4, IL-13: -89 ± 3, p=0.02) and decreased the bronchodilation to 0.3 nM Form (C: 54 ± 8, IL-13: 20 ± 4, p<0.01). 10 nM Bud significantly decreased the AHR to Cch following IL-13 (IL-13: -89 ± 3, IL-13/Bud: -80 ± 3, p=0.01), but had little effect on IL-13-induced impairment of the Form response (IL-13: 20 ± 4, IL-13/Bud: 28 ± 7, p=0.2). In contrast, bronchodilation to 100 μM Fsk was rescued by Bud (IL-13: 42 ± 8, IL-13/Bud: 82 ± 8, p<0.01; C: 76 ± 5, IL-13/Bud: 82 ± 8, p=0.6). These data suggest that pretreatment with budesonide completely prevents the effects of IL-13 on both airway contractility and adenylyl cyclase-mediated bronchodilation but does not prevent the IL-13-induced impairment of β2AR agonist-mediated bronchodilation. Further studies will define the underlying mechanisms by which IL-13 attenuates β2AR-mediated bronchodilation.