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Title: Endothelin-1-mediated contraction of mouse small airways is resistant to salbutamol, but sensitive to rosiglitazone

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Body: Introduction: In vitro investigations of bronchodilator efficacy routinely examine large airways and utilise methacholine (MCh) as a constrictor agent. However, small airway reactivity can be assessed in situ in lung slices, and increased levels of endothelin-1 (Et-1) detected in steroid-resistant asthma support its use as a clinically relevant alternative constrictor. We have identified rosiglitazone (RGZ) as a novel bronchodilator opposing small airway contraction to methacholine (MCh), but its efficacy against Et-1 is yet to be determined. Methods: Changes in airway lumen area in response to Et-1, MCh, RGZ and the β_2-adrenoceptor agonist salbutamol (SALB) were visualized in lung slices from Balb/C mice. The effects of ET_A- and ET_B-selective antagonists (BQ123, BQ788) on contractions to Et-1 were also assessed. Results: Mouse small airways were >10-fold more sensitive to Et-1 than trachea or bronchi. Et-1 was ~20-fold more potent than MCh in small airways (pEC_{50} 8.5±0.1, 7.1±0.1, $p<0.05$), with contraction mediated predominantly by ET_B-receptors. In reversing submaximal Et-1 contractions, RGZ had lower potency but greater efficacy than SALB (max %relaxation: RGZ 71±4%, SALB 51±14%). Relaxation to RGZ, but not SALB, was maintained in maximally contracted airways, and the development of Et-1-induced reductions in lumen area was inhibited by RGZ only. Conclusion: Et-1 is a potent bronchoconstrictor of mouse small airways. Contraction to Et-1 is relatively resistant to β_2 -adrenoceptor-mediated relaxation. Characterisation of the mechanism underlying the greater efficacy of RGZ in this setting may identify novel approaches targetting small airways for asthma treatment.