Rhinovirus (RV) C15, but not A16, induces airway hyper-responsiveness in human small airways and airway smooth muscle (HASM) through modulation of calcium and actin dynamics

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Abstract

Rhinovirus induces airway hyper-responsiveness and inflammation

- Viruses induce wheezing and airway hyper-responsiveness in normal individuals and those with underlying respiratory disorders like asthma.
- In murine models of virus-induced respiratory infection and exacerbations of allergic airway disease, viral exposure elicits airway hyper-responsiveness.
- Direct effects of a viral mimetic in airway smooth muscle whilst mediator production, even in the absence of increased extracellular contraction.
- Rhinovirus serotypes A and C induce more severe symptoms than B serotypes. Rhinovirus C serotypes are known to be associated with the most severe respiratory symptoms observed, as well as the most severe exacerbations of underlying airways diseases, than A or B serotypes.

Hypothesis

Rhinovirus-induced hyper-responsiveness modulates calcium - dependent and - independent pathways in HASM.

METHODS

PHENOTYPING - Viral-mediated respiratory infections, a leading cause of morbidity, result in increased airway reactivity and inflammation in normal and asthmatic subjects. The study is to examine the role of virus-induced calcium signaling and actin cytoskeleton rearrangement in airway smooth muscle.

RESULTS - Human primary small airway smooth muscle (HASM) were exposed to an agonist (carbachol) with or without rhinovirus (RV) and calcium signaling and actin cytoskeleton rearrangement were measured using fluorescence microscopy. HASM stimulation was also performed with RV and calcium signaling and actin cytoskeleton rearrangement were measured using fluorescence microscopy. HASM stimulation was performed with RV and calcium signaling and actin cytoskeleton rearrangement were measured using fluorescence microscopy.

CONCLUSIONS - These data suggest that differences in contractile responses lead to a model of changes in calcium dynamics and actin cytoskeleton rearrangement. Further study is needed to assess definitive mechanisms by which RV alone or viral co-infection of HASM.

Summary

- Exposure of RV to A16, but not A16, augments calcium-induced bronchoconstriction by affecting the sensitivity of the airways as well as affecting the integrated response following contractile agonist stimulation.
- Co-infusions of A11-differentiated epithelial cells (HACE) showed enhanced responsiveness of HASM cells to calcium-induced calcium flux following exposure to RV but not A16.
- RV exposure of HACE/HASM co-cultures augments calcium-induced phosphorylation of actin cytoskeleton-associated proteins (vimentin and HSPB1).

Significance

Defining mechanisms by which rhinovirus modulates contractility of smooth muscle will provide novel therapeutic targets to abrogate exacerbations of asthma.

References

Figure 1 – RV/C15 exposure of A11-differentiated epithelial cells induces increased calcium transients in co-cultured HASM, with RV/C15 having little effect on calcium transients. Epithelial cells were exposed to RV/C15 (100, 10, 40, 0) culture adhered above HASM (A). Bulk calcium transients were measured using Fura-2 over 120 sec (B). Exposure to RV alone did not induce calcium flux. Area under the curve (S1) and maximal calcium (D) relative fluorescein units) were calculated and plotted as a standard error. *p<0.05, n=3 distinct donor cell culture experiments.

Figure 2 – RV/C15 exposed A11-differentiated epithelial cells induce increased calcium transients in co-cultured HASM, with RV/C15 having little effect on calcium transients. Epithelial cells were exposed to RV/C15 (100, 10, 40, 0) cultured adhered above HASM (A). Bulk calcium transients were measured using Fura-2 over 120 sec (B). Exposure to RV alone did not induce calcium flux. Area under the curve (S1) and maximal calcium (D) relative fluorescein units) were calculated and plotted as a standard error. *p<0.05, n=3 distinct donor cell culture experiments.