Rhinovirus strains differentially affect airway hyper-reactivity (AHR) in a model of human precision cut lung slices (hPCLS)

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Abstract

RATIONALE: Viral-induced respiratory infections, a leading cause of asthma exacerbations, are primarily evoked by rhinovirus. Direct effects of virus on small basilar airways of humans are not fully understood. Other denominator respiratory viruses, such as parainfluenza virus and respiratory syncytial virus, also induce bronchoconstriction. One potential mechanism may be through virus-induced mediator release. We examined the mediators released in response to rhinovirus and parainfluenza virus.

METHODS: Human precision cut lung slices (hPCLS) were incubated in a closed chamber at 37°C for 24 hr with 10^6 plaque forming units (PFU) of various rhinovirus serotypes. The release of mediators, including cytokines and chemokines, was measured using a multiplex cytokine assay. The effect of rhinovirus infection on airway smooth muscle contractility was assessed using a multi-channel isometric tension transducer.

RESULTS: Rhinovirus infection resulted in the release of pro-inflammatory cytokines and chemokines, including interleukin-6 (IL-6) and macrophage inflammatory protein-1 beta (MIP-1 beta). The release of these mediators was dependent on the serotype of the rhinovirus used. The release of mediators was also dependent on the dosage used.

CONCLUSIONS: Our findings indicate that rhinovirus infection induces the release of pro-inflammatory mediators, which may contribute to the pathogenesis of respiratory infections.

Rhinovirus modulates airway hyper-responsiveness and inflammation

- Virus induces 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 elicits mediator production, even in the absence of increased excitation/contraction coupling.
- 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 airway diseases, than A or B serotypes.

Hypothesis

Rhinovirus serotypes induce differential responses, which are dependent on how closely or distantly they are related at the sequence level.

Ex vivo exposure to RVA serotypes does not significantly enhance agonist-induced small airway constriction

- Control
- RVA

Ex vivo exposure to RVC15 induces airway hyper-responsiveness to carbachol in human small airways

- Control
- RVC15

Ex vivo exposure to RVA and C serotypes induces production of inflammatory mediators from small airways

- Control
- RVA
- C

Summary

- Little differences exist in ability to elicit agonist-induced constriction following exposure to D or RVA strains. However, alteration in mediator concentrations of RVC15 enhanced response to carbachol.

- Exposure of airway to RVA serotypes show more mediator release compared to RVC15 or RV51. The release of mediators was dependent on the dosage used.

RVC15 induces mediator release similarly to that induced by RVA strains.

Significance

Defining shared mechanisms underlying virus-mediated AHR and mediator release will provide novel therapeutic targets for intervention in prevention or abrogation of exacerbations of underlying lung diseases.

References


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