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 airways of humans *ex vivo* remains poorly understood. Other demonstrated heterogeneity of symptoms in response to depending on the strain of rhinovirus the patient was exposed to. Therefore, we hypothesized that there would be differential responses observed between serotypes dependent upon how closely or distantly they are related at a sequence level.

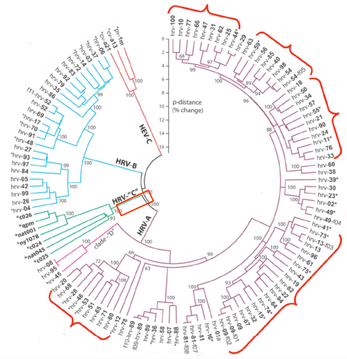
METHODS: Human precision cut lung slices (PCLS), each containing a small airway, were exposed to the following rhinovirus strains or control buffer for 48 hr at 33°C (10^5-10^7 Pfu): RVA 75, 9, 18, 34, 59, 85, 66, 62, 51, 16, or RVC15. Bronchoconstriction to carbachol (10-8 – 10-8 M) was measured and compared to no contractile agonist, with maximal bronchoconstriction, area under the curve, and log EC50 of contractile agonist measured from the sigmoidal dose response curves and compared.

RESULTS: Airway responsiveness following stimulation with RVA and RVC strains modulated AHR, but the RVA strains were not significantly different compared to control. However, exposure to RVC15 resulted in a significant increase in AHR (AUC ANOVA p=0.04; control vs 10^7 Pfu, 165 vs 226, p=0.01).

CONCLUSIONS: These data suggest that differences in contractility following rhinovirus exposure may be a function of serotype rather than close sequence similarity. Therefore, attenuation of AHR following rhinovirus exposure will require targeted therapeutic approaches to abrogate specific RV strain effects on AHR.

Rhinovirus modulates airway hyper-responsiveness and inflammation

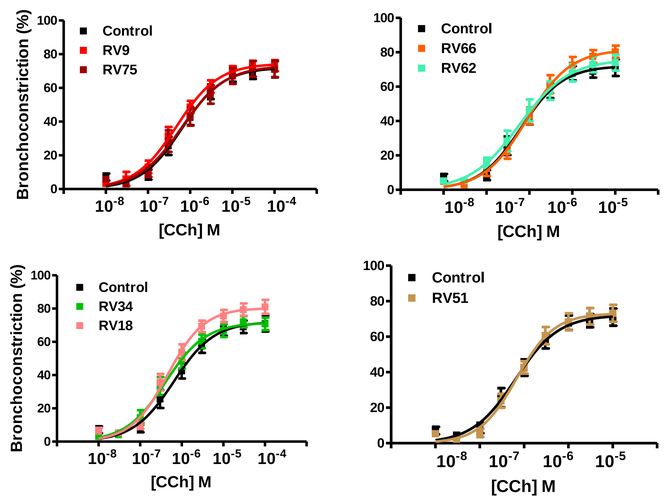
- Viruses induce wheezing and airway hyper-responsiveness in normal individuals and those with underlying respiratory disorders like asthma. Mechanisms underlying the increased responsiveness of the airways following viral exposure are unclear.
- In murine models of virus-induced respiratory infection 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 airways diseases, than A or B serotypes.

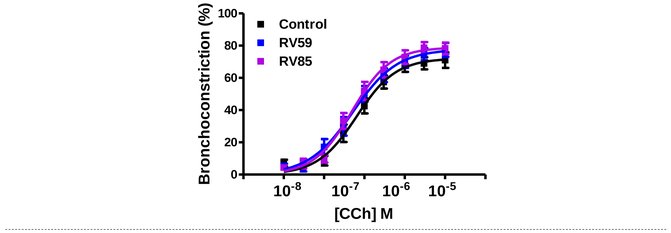


Hypothesis

Rhinovirus serotypes induce differential responses, which are dependent upon 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





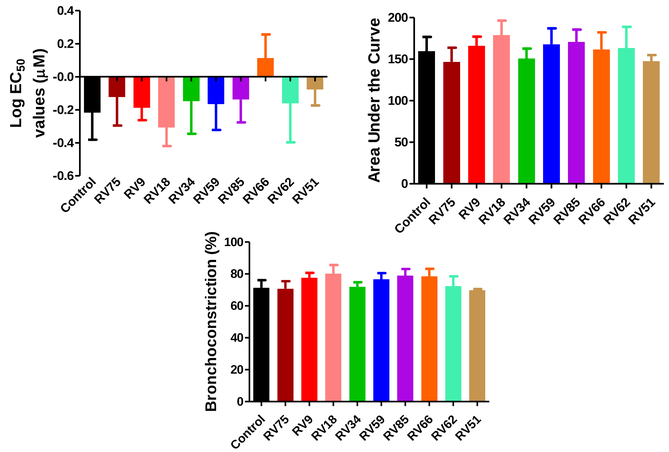


Figure 1 – Human precision cut lung slices (hPCLS) were incubated for 48 hr in the presence of increasing concentrations of RVA serotypes (10^5 Pfu), and then contracted to a dose response of carbachol. Dose response curves for control and each RVA strain, log EC_{50} values, and E_{max} values are shown. Data shown is representative of at least eight independent experiments. * p≤0.05 as compared to control

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

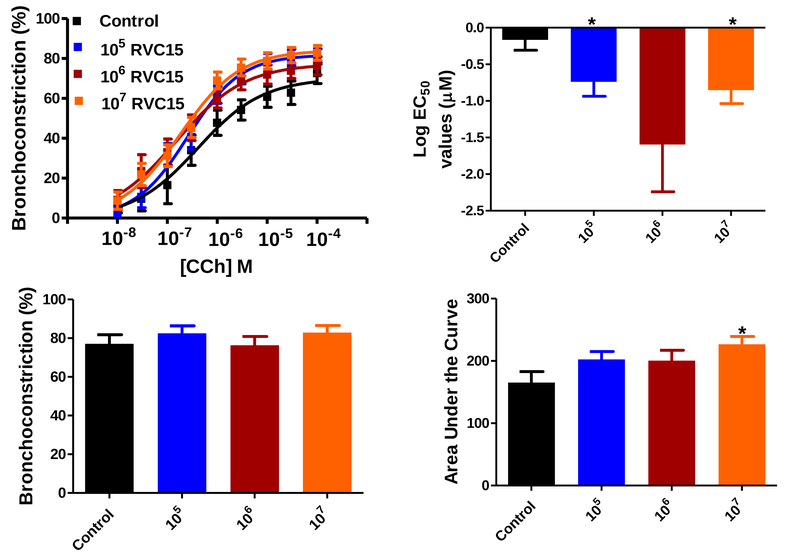


Figure 2 – Human precision cut lung slices (hPCLS) were incubated for 48 hr in the presence of increasing concentrations of RVC15 (10^5-10^7 Pfu), and then contracted to an increasing dose response of carbachol. Dose response curves for control and each dose of RV16, log EC_{50} values, and E_{max} values are shown. Data shown is representative of at least five independent experiments. * p≤0.05

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

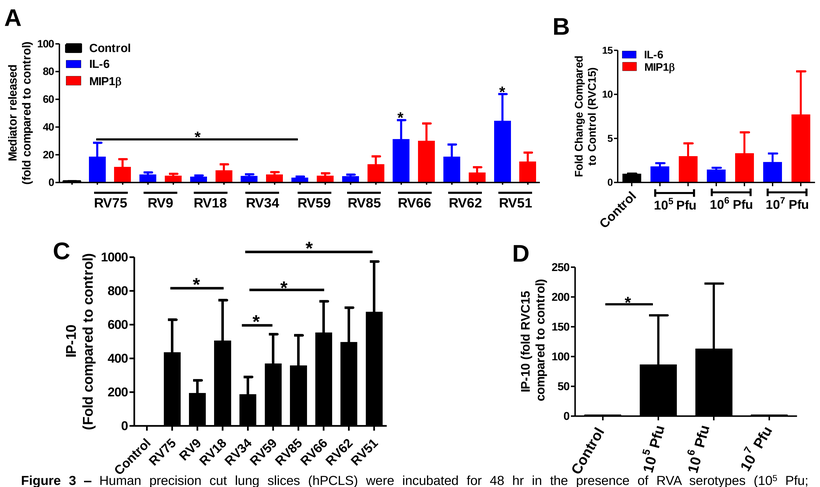


Figure 3 – Human precision cut lung slices (hPCLS) were incubated for 48 hr in the presence of RVA serotypes (10^5 Pfu: RV75,9,18,34,59,85,66,62,51) or RVC15 (10^5 Pfu) and inflammatory mediator release measured (IL-6 and MIP1β in A and B, IP-10 in C and D) in media collected from RV incubation with the slices by single analyte ELISA. Data shown is representative of ≥ five independent donors, where mediator release is expressed as fold compared to control. *p=0.05. In A, * above 66 and 51 represent statistical significance vs all other serotypes listed. All mediators are significantly induced compared to control.

Summary

- Little differences exist in ability to alter agonist-induced contractility following exposure to RVA strains. However, incubation with increasing concentrations of RVC15 enhances sensitivity to contractile agonist stimulation.
- Exposure of airways to RVA serotypes shows some heterogeneity in inflammatory responses between serotypes, but does not appear to be dependent on sequence similarity/divergence. All serotypes induce significant mediator release compared to control buffer stimulation.
- 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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