CHRD 2021: Abstract & Poster Submission Form

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Research Category:

- ◉ Basic Science
- ○ Clinical
- ○ Community Health / Policy

What was your role in the project?

- ☐ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Presenter Status:

- ○ Undergraduate Students
- ○ Masters Student
- ◉ PhD Student
- ○ Post-Doctoral Fellows
- ○ Residents
- ○ Non-Trainee

Title

19-HETE causes airway smooth muscle relaxation via cAMP production

Background

Affecting over 850,000 children in Canada, asthma is the most common chronic disease among children. β-agonists are first-line medications for alleviating asthma exacerbations but can be rendered ineffective through β-adrenergic receptor desensitization. Hydroxyeicosatetraenoic acids (HETEs), an abundant class of lipid mediators (oxylipins) in the airways, have not been effectively studied in the context of airway smooth muscle (ASM) physiology and asthma. We hypothesize that 19-HETE causes ASM relaxation by promoting cAMP production in ASM cells.

Objective

To investigate the role of 19-HETE in regulating ASM contractility.

Methods

HETE production in primary cultured ASM cells (non-smokers, no lung disease, n=3) was quantified with HPLC-MS/MS. Murine trachea (BALB/c female, n=3) were pre-contracted with 1μM methacholine and cumulative relaxation dose-response was generated using isoproterenol (10pM to 3.2μM) and 19-HETE (1nM to 10μM). Serum-deprived ASM cell lines (n=3) were pre-exposed to forskolin (10μM), isoproterenol (10μM), and 19-HETE (0.01, 0.1, 1, and 10μM) and cAMP production was measured using colorimetric assay. A three-parameter dose-response curve was constructed to determine EC50 for 19-HETE induced relaxation and cAMP generation. Data presented as mean±SD.

Results

19-HETE is the most abundant HETE produced by ASM cells (5.5ng/mL). 19-HETE relaxed methacholine contracted trachea by 56.3±7.9% (1μM) and 71.1±12.6% (10μM). The EC50 dose for 19-HETE was 200nM, compared to 1.6nM for isoproterenol. Furthermore, 19-HETE induced a dose-dependent increase in cellular cAMP with a maximal fold induction of 3.8±0.4 at 10μM. However, forskolin and isoproterenol yielded 11±4.5 and 8.7±2.7 folds cAMP at 10μM respectively.

Conclusion

Our results reveal that 19-HETE is produced by ASM cells and causes profound bronchodilation through cAMP dependent mechanism. 19-HETE may signal through prostacyclin receptor to promote cAMP production, although more research is necessary. These outcomes establish a role for 19-HETE in regulating ASM contractility in the context of asthma.

Authors

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