CHRD 2022: Abstract & Poster Submission Form

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

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

Role in the project
- ☑ Design
- ☑ Perform Experiments
- ☑ Analyze Data
- ☑ Write Abstract
- ☐

Title
Understanding the mechanism underlying 19-HETE’s bronchodilating effect

Background

Asthma is the most common chronic disease in Canadian children. Airway smooth muscle (ASM) contraction is a hallmark of the disease. Bronchodilators are used to relax ASM and ease breathing, but these drugs are rendered ineffective in severe disease. Therefore, alternative bronchodilators are needed.19-HETE is a lipid signalling molecule that is abundant in the lungs. We have recently shown that 19-HETE relaxes ASM. However, the mechanism by which 19-HETE induces ASM relaxation is unclear.

Objective

To establish an understanding of the signalling network leveraged by 19-HETE to relax ASM.

Methods

Human ASM cells were exposed to 19-HETE and molecules known to inhibit key signaling proteins. Changes in cAMP production, vasodilator-stimulated phosphoprotein (VASP) phosphorylation, p21-activated kinase (PAK1) phosphorylation, and myosin light chain (MLC) phosphorylation were measured as indicators of specific signaling pathways. All data is presented as mean percent activity relative to control. Significance set at $p<0.05$.

Results

19-HETE significantly increased cAMP production (+156%, n=4), a change that was significantly reversed with the addition of a prostacyclin receptor antagonist (+6%, n=4). 19-HETE significantly increased VASP phosphorylation, an indicator of PKA activation downstream of cAMP (+70%, n=3). 19-HETE also promotes PAK1 phosphorylation, which may be an indicator of EPAC activation downstream of cAMP (+49%, n=3). Lastly, histamine induced MLC phosphorylation, a key molecular indicator of ASM contraction, is significantly decreased in the presence of 19-HETE (-48%, n=2). This change in MLC phosphorylation is ablated by incubation with a prostacyclin receptor (+2%, n=2), PKA (+6%, n=1), and EPAC2 (+82%, n=1) inhibitor.

Conclusion

19-HETE promotes ASM relaxation through the prostacyclin receptor and a signaling network that depends on PKA, EPAC2, and possibly PAK1. Understanding the mechanism for 19-HETE's bronchodilatory effect provides a foundation for research into the role this molecule has in asthma and future potential therapies for asthma.

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Authors

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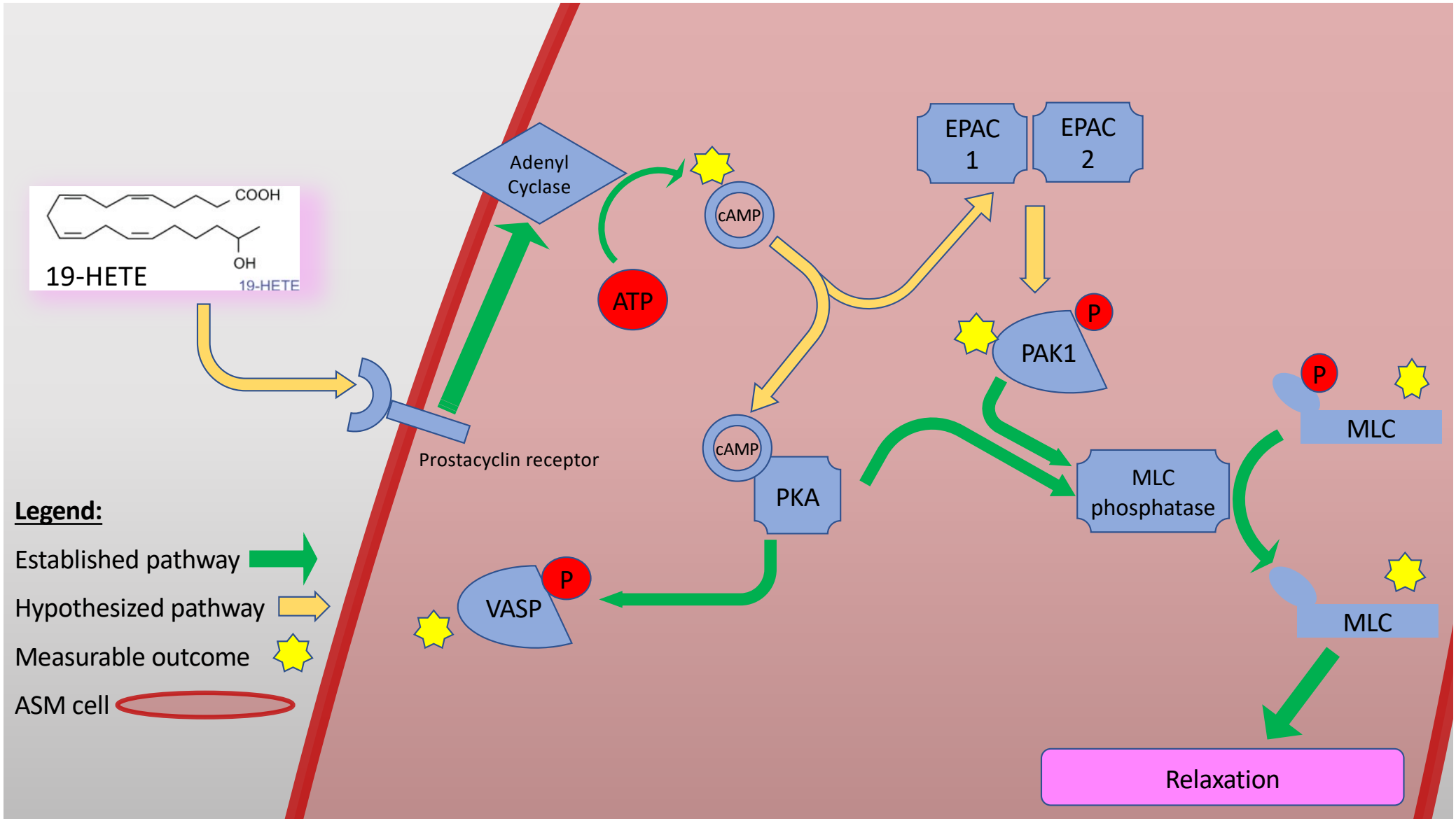
COOH
OH
19-HETE
19-HETE
Adenyl Cyclase
ATP
cAMP
EPAC 1
EPAC 2
P
PAK1
Prostacyclin receptor
cAMP
PKA
MLC phosphatase
P
MLC
MLC
P
VASP
Relaxation
Legend:
Established pathway
Hypothesized pathway
Measurable outcome
ASM cell