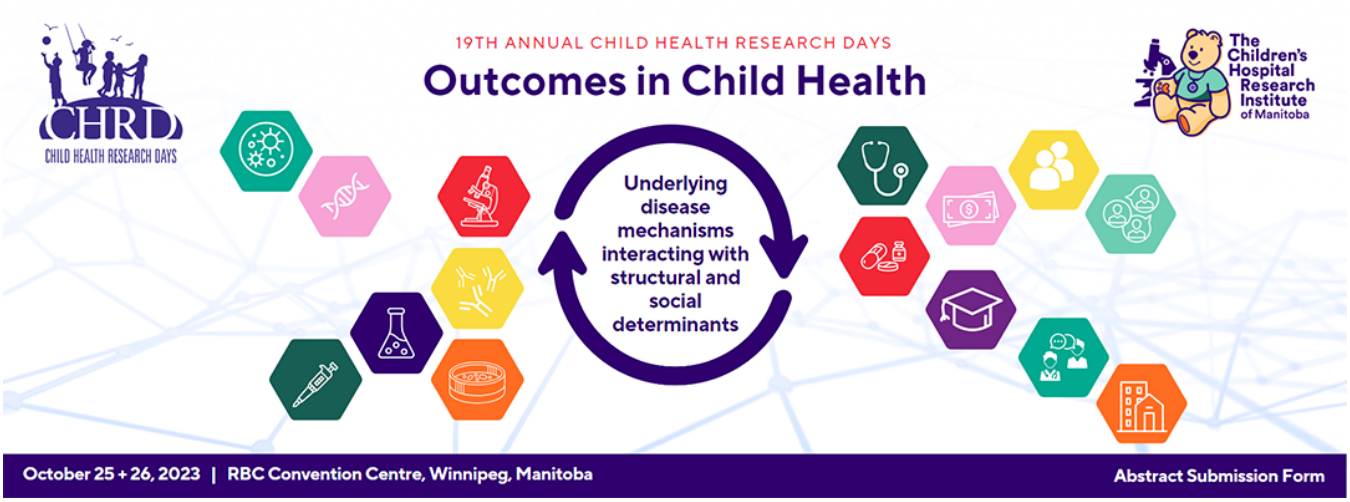

CHRD 2023: Abstract Submission Form

Submitter Name
Dina Mostafa

Presenter Name
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Presenter Status
Non-Trainee

Research Category
Basic Science

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Title
Arachidonic Acid Metabolite 19-HETE Induces bronchodilation through Prostacyclin receptor (IP) in airway smooth muscle.

Background
Lipidomics studies have provided insight into oxylipin profiles in asthma and lung health. But little is known about the function of specific oxylipins beyond the classical prostaglandins and leukotrienes. Hydroxyeicosatetraenoic acids (HETEs) are a class of oxylipins that are abundant in the lung and may play a role in lung physiology and pathophysiology. 19-HETE is the most prevalent HETE produced in the lung, while previous studies have shown that 19-HETE can induce vasorelaxation, little is known about its ability to regulate airway smooth muscle (ASM) contractility.

Objective
To examine whether 19-HETE promotes bronchodilation via the prostacyclin receptor and cyclic-AMP (cAMP) signaling.

Methods
Murine trachea and human ASM cells were exposed to increasing concentrations of 19-HETE (0.1-10μM) to measure relaxation and cAMP production. cAMP signaling was monitored via Western blotting for phospho-vasodilator-stimulated-phosphoprotein (pVASP) and phospho-myosin light chain (pMLC2). Inhibitors for the prostacyclin receptor, protein kinase A (PKA), and exchange protein activated by cAMP (EPAC1/2) were used and changes in pMLC measured. Changes in cellular forces to 19-HETE in the presence of specific inhibitors were monitored with traction force microscopy (TFM). Sample size n=3-5.

Results
19-HETE caused dose-dependent relaxation of murine trachea (maximum of 90%). 19-HETE (1μM) significantly decreased ASMC force by 30% and increased cAMP accumulation by 3-fold. Pre-treatment with a prostacyclin receptor inhibitor attenuated this response (2-fold). 19-HETE increased VASP phosphorylation, which indicates PKA signaling. Histamine-induced contraction was reduced by 19-HETE (2-fold). This was prevented by pre-treatment with inhibitors for prostacyclin receptor, PKA, and EPAC2, but not EPAC1.

Conclusion
19-HETE signals through the prostacyclin receptor to promote bronchodilation, a process that depends on cAMP induced signaling via both PKA and EPAC2. Understanding the mechanism for 19-HETE's bronchodilatory effect provides information crucial for understanding lipidomics results in asthma and a framework for exploring its therapeutic potential, particularly unresponsive patients to available bronchodilators.

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