
# CHRD 2022: Abstract & Poster Submission Form

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**Presenter Status**

○ Undergraduate Students

○ Masters Student

◉ PhD Student

○ Post-Doctoral Fellows

○ Residents

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**Research Category**

◉ Basic Science

○ Clinical

○ Community Health / Policy

**Role in the project**

☑ Design

☑ Perform Experiments

☑ Analyze Data

☑ Write Abstract

☐

**Title**

Oxidized Phosphatidylcholine Promotes β2-Adrenoceptor Desensitization in Airways: Implications for Bronchodilator Insensitivity

**Background**

Many asthmatics are refractory to β2-adrenergic-receptor (β2AR) mediated-bronchodilator therapies. Understanding of mechanisms for β2AR-insensitivity is incomplete. We showed that oxidized-phosphatidylcholine (OxPC) accumulates in the lungs after inhaled allergen challenge. OxPC associates with airway hyperresponsiveness, induces airway-contraction, and triggers cytokine release by ASM-cells. We hypothesized that OxPC impairs bronchodilator responses, potentially contributing to β2AR-insensitivity.

**Objective**

We hypothesized that OxPC impairs bronchodilator responses, potentially contributing to β2AR-insensitivity.

**Methods**

Isometric contractile-force in murine tracheal rings (n=5-6, BALB/c) and airway narrowing in murine thin-cut-lung slices (TCLS, 12-15 airways) was measured after incubating (24-hrs, 37ºC) with OxPC (oxidized 1-palmitoyl-2-arachidonoyl-sn-phosphatidylcholine, 80 μg/mL). The relaxation dose-response to β2AR agonist, isoproterenol (Iso), or adenylyl-cyclase (AC) activator, forskolin was assessed in rings or TCLS pre-constricted with methacholine. Using cultured human ASM-cells (5-donors), we assessed effects of OxPC (5-80 μg/mL) on Iso-induced cAMP signaling (1 nM), by tracking phosphorylation of the Protein Kinase-A substrate, VASP, using immunoblotting (VASP-shift assay). Real-time cAMP production (rate*steady state) was measured using a transfected cADDis sensor in cells. Data analysis included nonlinear-curve-fit to establish EC50, and one-way ANOVA with Dunnett's post-hoc test.

**Results**

In tracheal rings, OxPC pre-exposure significantly increased EC50 of the Iso relaxation dose-response curve (17.8 nM), compared to control (3.3 nM); this also reduced maximum relaxation by 12%. Conversely, the forskolin dose-response curve, EC50 and maximum response, was unaffected by OxPC. Similarly, in TCLS, OxPC significantly increased Iso EC50 (0.38 μM) compared to vehicle (0.09 μM), with maximum airway dilation reduced by 34%. OxPC pre-treatment significantly reduced intracellular cAMP-signalling in ASM cells: (1) VASP-shift assay revealed that Iso induced only 29.8% phosphorylation of VASP at OxPC (80-μg/mL) vs. 63.4% that of control, and (2) cAMP-kinetic assays, OxPC pre-treatment reduced 49.6% cAMP signalling (rate*steady-state= 0.071 at OxPC-80-μg/mL vs. 0.141 in control).

**Conclusion**

OxPC impairs β2AR-agonist mediated bronchodilation associated with reduced cAMP signaling, without affecting AC activity. This implicates OxPC in mechanisms that target β2-Adrenoceptor to elicit bronchodilator insensitivity.

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# Authors

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