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First Author: Jane McHowat
Saint Louis University 1402 S Grand St Louis, MO 63104
United States
Phone: 3143236118
jane.mchowat@health.slu.edu

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First Author is a member of: The American Physiological Society
First Author Degree: PhD, DSc, or equivalent

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Sponsor: Jane McHowat
Sponsor Phone: 3143236118
jane.mchowat@health.slu.edu
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Chlorinated lipids mediate small airway epithelial dysfunction

Jane McHowat[1], Carolyn Albert[2], Celine Hartman[2], Daniel Pike[2], David Ford[2]. [1]Saint Louis University, St Louis, MO, [2]Biochemistry and Molecular Biology, Saint Louis University, St Louis, MO

Neutrophil myeloperoxidase is a major mediator of microbicidal activity, catalyzing the conversion of hydrogen peroxide to hypochlorous acid (HOCl), a potent oxidant that reacts with both microbial and host molecular targets. HOCl targets the vinyl ether bond of plasmalogen lipids, resulting in the production of 2-chlorofatty aldehyde, which is in turn metabolized to 2-chlorofatty acid (2-ClFA). Recently, we have shown that free 2-ClFA levels are significantly associated with acute respiratory distress syndrome (ARDS) in sepsis patients. Lung endothelial cells treated with 2-ClFA showed increased permeability, surface expression of adhesion molecules, and neutrophil and platelet adherence. These data indicate that plasma 2-ClFA is a predictor for ARDS, likely through effects on the lung microvasculature. In this study, we determined the effect of 2-ClFA on human small airways epithelial cell (SAEC) function. Incubation of SAEC with 2-ClFA (100 nM-10 μM, up to 24 hours) resulted in a concentration- and time-dependent decrease in electrical resistance, with no change in resistance noted when SAEC were incubated with non-chlorinated fatty acid (FA). Our recently published studies published recently by us show that 2-ClFA (1 μM) treatment of lung microvascular endothelial cells resulted in a 2-fold increase in cell surface expression of intercellular adhesion molecule 1 (ICAM-1) and a 1.7-fold increase in vascular cell adhesion molecule 1 (VCAM-1) after a 4-hour incubation. We now show that incubation with 2-ClFA for 4 hours resulted in a 3.3-fold increase in cell surface expression of ICAM-1 and a 4.4-fold increase of VCAM-1 in SAEC. No increase in adhesion molecules was observed with FA incubation. 2-ClFA treatment resulted in neutrophil adherence to SAEC and enhanced transmigration across the SAEC monolayer after 2-ClFA treatment. Neutrophil transmigration across SAEC was 3-fold greater in a basolateral-to-apical direction when compared to apical-to-basolateral. Taken together, these data suggest that 2-ClFA mediates small airways epithelial dysfunction and neutrophil transmigration that may contribute to fluid accumulation and inflammation observed in ARDS patients.

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