› FASEB J. 2021 Apr;35(4):e21514. doi: 10.1096/fj.202002555R.

25-Hydroxycholesterol metabolism is altered by lung inflammation, and its local administration modulates lung inflammation in mice

Pauline Bottemanne [1], Adrien Paquot [1], Hafsa Ameraoui [1], Owein Guillemot-Legris [1], Mireille Alhouayek [1], Giulio G Muccioli [1]

Affiliations + expand

PMID: 33734509 DOI: 10.1096/fj.202002555R

Abstract

Inflammation is a critical component of many lung diseases including asthma and acute lung injury (ALI). Using high-performance liquid chromatography-mass spectrometry, we quantified the levels of oxysterols in two different murine models of lung diseases. These are lipid mediators derived from cholesterol and known to modulate immunity and inflammation. Interestingly, 25-hydroxycholesterol (25-OHC) was the only oxysterol with altered levels during lung inflammation, and its levels were differently affected according to the model. Therefore, we sought to assess how this oxysterol would affect lung inflammatory responses. In a model of lipopolysaccharide (LPS)-induced acute lung inflammation, 25-OHC levels were increased, and most of the hallmarks of the model (eg, leukocyte recruitment, mRNA expression, and secretion of inflammatory cytokines) were decreased following its intratracheal administration. We also found that, when administered in the lung, 25-OHC is metabolized locally into 25-hydroxycholesterol-3-sulfate and 7α,25-dihydroxycholesterol. Their administration in the lungs did not recapitulate all the effects of 25-OHC. Conversely, in a model of allergic asthma induced by intranasal administration of house dust mites (HDM), 25-OHC levels were decreased, and when intranasally administered, this oxysterol worsened the hallmarks of the model (eg, leukocyte recruitment, tissue remodeling [epithelium thickening and peribranchial fibrosis], and cytokine expression) and induced changes in leukotriene levels. Ex vivo, we found that 25-OHC decreases LPS-induced primary alveolar macrophage activation while having no effect on neutrophil activation. Its sulfated metabolite, 25-hydroxycholesterol-3-sulfate, decreased neutrophil, but not macrophage activation. Taken together, our data support a differential role of 25-OHC in ALI and allergic inflammation models.

Keywords: 25-HC; ARDS; cholesterol-25-hydroxylase; corticosteroid; leukotrienes; pneumonia.

© 2021 Federation of American Societies for Experimental Biology.