Bidirectional Regulation Of Bronchial Epithelial Function By PKA And PKC In Organic Dust-Induced Airway Injury

T. A. Wyatt[1], J. H. Sisson[2], J. DeVasure[2], D. Yanov[2], A. Heires[2], D. J. Romberger[2]

[1]University of Nebraska Medical Center /, Omaha, NE, United States of America, [2]University of Nebraska Medical Center, Omaha, NE, United States of America

Corresponding author's email: lrichard@unmc.edu

Bidirectional regulation of signal transduction by protein kinase C (PKC) and the cAMP-dependent protein kinase (PKA) have been observed in neuronal and inflammatory cells. Bronchial epithelial cell functions such as cilia beating and wound repair are enhanced by PKA-activating agents and diminished by PKC-activating agents. Previously, we have shown that organic dusts from confined animal feeding operations stimulate airway epithelial cell proinflammatory cytokine release via a PKC-dependent manner. We hypothesized that a mechanism of bidirectional regulation of airway epithelial function exists that is driven by the net balance of PKA/PKC activity. Primary bovine bronchial epithelial cells were grown in culture and assayed for PKA and PKC activity using a direct specific substrate radiolabeled-phosphate incorporation assay. Kinase activities were compared to measurements of organic dust-stimulated increases in interleukin-8 release. We observed that pretreating bronchial epithelial cells with beta agonists, forskolin, or cell-permeable cAMP analogs blocked organic dust-induced PKC epsilon activation. Likewise, alcohol pretreatment under conditions of cAMP elevation and PKA activation resulted in the inhibition of organic dust-stimulated PKC epsilon activity. Organic dust-induced release of interleukin-8, a process dependent upon PKC activation, was significantly diminished in response to PKA activating agents. These data provide evidence for PKA as a negative regulator to PKC-driven signaling inflammatory events in airway epithelium and suggests that PKA plays an anti-inflammatory role in the lung.

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