NITRIC OXIDE AND CERAMIDE PATHWAY INTERACTION: A NEW TARGET IN ALLERGIC ASTHMA

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Reactive oxygen and nitrogen species (ROS and RNS respectively) are environmental pollutants affecting lung epithelial cell functions by modulating inflammation, cell proliferation, growth or apoptosis. Because ceramide is a second messenger molecule modulating cell apoptosis and oxidative stress, we hypothesized that ceramide upregulation contributes to airway hyperreactivity and inflammation during asthma. In fact, epithelial cell apoptosis, chronic inflammation and hyperreactivity define asthma a chronic inflammatory disease confined to the airways of the lungs. The availability of ceramide is fine-tuned by the rate of generation involving sphingomyelinases, the de novo synthesis from sphingosine and the rate of degradation catalyzed by ceramidases. Therefore a number of pathways can account for altered ceramide levels in pathophysiological situation.

In models of allergic bronchospasm in actively sensitized guinea-pigs, the aerosol administration of the antigen determined an increase in ceramide levels in the airway epithelium. Ceramide increased concurrently with markers of oxidative stress (3-nitrotyrosine, PARP and 8-OHdG) and apoptosis (caspase 3 activity), and was associated with a profound deactivation of MnSOD in lung tissues. In addition, ceramide upregulation was associated with the development of an inflammatory response characterized by eosinophil and neutrophil infiltration in the lung tissue, as well as elevation of cytokines in bronchoalveolar lavage. These effects were associated with bronchial hyperreactivity. The treatment of the animals with nitric oxide (NO) donors increased cellular ceramide levels without any apoptotic response. Inhibition of the enzymes controlling de novo ceramide synthesis prevented alveolar cell apoptosis, oxidative stress and inflammation. These effects were amplified when inhibitors of ceramide synthesis were given together with NO donors.

These results suggest that the interaction between NO and the sphingomyelin/ceramide pathway could be a novel therapeutic target for inflammation and airway hyperreactivity in allergic asthma.