THE ROLE OF CERAMIDE PATHWAY IN ASTHMA

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Although the mechanisms involved in the pathogenesis of asthma remain unclear, a role for inflammation, oxidative/nitrative stress and epithelial cell apoptosis has been documented. These observations, taken together with our current understanding of the ceramide metabolic pathway, have lead to our hypothesis that increased formation of the biologically active lipid ceramide contributes to the development of airway hyperreactivity in part through the induction of oxidative/nitrative stress. Using a well characterized *in vivo* model of allergic bronchospasm in ovoalbumin (OA) actively sensitized guinea-pigs [1,2] we found that aerosol administration of OA increased ceramide levels in the airway epithelium.
The increase in ceramide levels was associated with inflammation, deactivation of MnSOD, nitrotyrosine formation, PARP activation and epithelial cell apoptosis. Finally, ceramide *up-regulation* was associated with several histopathological abnormalities and bronchoconstriction in response to OA challenge. Inhibition of *de novo* ceramide synthesis with fumonisin B1 (FB1), a competitive and reversible inhibitor of ceramide synthase and thus of *de novo* ceramide synthesis, attenuated oxidative/nitrative stress, lung cell apoptosis and the deactivation of MnSOD. FB1 also reduced the inflammatory response and the associated respiratory and histopathological abnormalities.
Taken together, our results suggest that ceramide contributes to the development of airway hyperreactivity through the induction of oxidative/nitrative stress and activation of downstream pathways. Therefore, strategies aimed at reducing the levels of ceramide should yield promising novel anti-asthmatic agents and as such this pathway needs to be explored comprehensively.

[1] Suzuki Y., Masini E., Marzocca C., Cuzzocrea S., Ciampa A., Suzuki H. and Bani D. (2004) J. Pharmacol. Exp. Ther. 311:1241-1248.
[2] Masini E., Bani D., Vannacci A., Pierpaoli S., Mannaioni P.F., Comhair S.A.A., Xu W., Muscoli C., Erzurum S.C. and Salvemini D (2005) Free Rad. Biol. Med. 39:520-531.