CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR DYSFUNCTION IN VIP KNOCKOUT MICE.

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Abstract

Vasoactive intestinal peptide (VIP), a neuropeptide, controls multiple functions in exocrine tissues, including inflammation, and relaxation of airway and vascular smooth muscles, and regulates CFTR-dependent secretion, which contributes to mucus hydration and local innate defense of the lung. We had previously reported that VIP stimulates the VPAC1 receptor, PKCε signaling cascade, and increases CFTR stability and function at the apical membrane of airway epithelial cells by reducing its internalization rate. Moreover, prolonged VIP stimulation corrects the molecular defects associated with F508del, the most common CFTR mutation responsible for the genetic disease cystic fibrosis. In the present study, we have examined the impact of the absence of VIP on CFTR maturation, cellular localization, and function in vivo using VIP knockout mice. We have conducted pathological assessments and detected signs of lung and intestinal disease. Immunodetection methods have shown that the absence ofVIP results in CFTR intracellular retention despite normal expression and maturation levels. A subsequent loss of CFTR-dependent chloride current was measured in functional assays with Ussing chamber analysis of the small intestine ex vivo, creating a cystic fibrosis-like condition. Interestingly, intraperitoneal administration of VIP corrected tissue abnormalities, close to the wild-type phenotype, as well as associated defects in the vital CFTR protein. The results show in vivo a primary role for VIP chronic exposure in CFTR

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