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Neuropeptide regulation of secretion and inflammation in human airway gland serous cells

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ABSTRACT Airway submucosal gland serous cells are sites of expression of the cystic fibrosis transmembrane conductance regulator (CFTR) and are important for fluid secretion in conducting airways. To elucidate how neuropeptides regulate serous cells, we tested if human nasal turbinate serous cells secrete bicarbonate (HCO_3^-), important for mucus polymerisation and antimicrobial peptide function, during stimulation with cAMP-elevating vasoactive intestinal peptide (VIP) and if this requires CFTR. Serous cells stimulated with VIP exhibited a ~15–20% cAMP-dependent decrease in cell volume and a ~0.15 unit decrease in intracellular pH (pH_i), reflecting activation of Cl^- and HCO_3^- secretion, respectively. HCO_3^- secretion was directly dependent on CFTR and was absent in cells from CF patients. In contrast, neuropeptide Y (NPY) reduced VIP-evoked cAMP increases, CFTR activation, and Cl^-/HCO_3^- secretion. Culture of primary serous cells in a model that maintained a serous phenotype confirmed the activating and inhibiting effects of VIP and NPY, respectively, on fluid and HCO_3^- secretion. Moreover, VIP enhanced antimicrobial peptide secretion and antimicrobial efficacy of secretions while NPY reduced antimicrobial efficacy. In contrast, NPY enhanced cytokine release while VIP reduced cytokine release through a mechanism requiring CFTR. As levels of VIP and NPY are up-regulated in diseases like allergy, asthma, and chronic rhinosinusitis, the balance of these two peptides in the airway may control mucus rheology and inflammatory responses in serous cells. Furthermore, the loss of CFTR conductance in serous cells may contribute to CF pathophysiology by increasing serous cells inflammatory responses in addition to directly impairing Cl^- and HCO_3^- secretion.