

Public Abstract

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Degree:

Degree Program:

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Graduation Term:

Graduation Year:

Title:

Bicarbonate (HCO_3^-) secretion by the duodenum plays an important role in protecting the epithelium from acidic chyme entering from the stomach. This secretory process involves the apical membrane activities of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride (Cl^-) channel, the protein defective in cystic fibrosis (CF), and $\text{Cl}^-/\text{HCO}_3^-$ exchangers. Under basal (unstimulated) conditions, studies of CF patients and mouse models indicate that HCO_3^- secretion by $\text{Cl}^-/\text{HCO}_3^-$ exchange predominates. In addition, HCO_3^- secretion is reduced in the CF duodenum, but the specific pathophysiology for this deficiency has yet to be elucidated. Therefore, studies were performed to determine the role of CFTR and $\text{Cl}^-/\text{HCO}_3^-$ exchangers in duodenal HCO_3^- secretion under basal conditions using the CF mouse model. These studies revealed that Cl^- channel activity by CFTR facilitates apical membrane $\text{Cl}^-_{\text{in}}/\text{HCO}_3^-_{\text{out}}$ exchange by providing a Cl^- 'leak' and is responsible for the reduced rate of $\text{Cl}^-/\text{HCO}_3^-$ exchange in the CF upper villus of the duodenum. Using mice with gene-targeted deletions of the apical membrane $\text{Cl}^-/\text{HCO}_3^-$ exchangers putative anion transporter-1 (PAT-1), down-regulated in adenoma (DRA), and anion exchanger isoform 4 (AE4), PAT-1 was shown to be the major $\text{Cl}^-/\text{HCO}_3^-$ exchanger of the upper villus of the duodenum. These studies also revealed a novel role for PAT-1 as a HCO_3^- -importer whereby it interacts with carbonic anhydrase II (CAII) to regulate intracellular pH during the absorption of peptides, which are generated during protein digestion. Thus, PAT-1 plays an important role in duodenal HCO_3^- secretion as well as nutrient absorption.