

NASPGHAN Physiology Education Series

Exocrine Pancreas Physiology

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Introduction

Fat digestion is a particularly complex process that occurs in the digestive tract. This is so because a water insoluble substance needs to be converted into small enough particles to be transported into cells, and then delivered to the rest of the body, all within different aqueous compartments. This can only be accomplished via well-orchestrated events that package water-insoluble molecules within water-soluble delivery particles both within the intestinal lumen and in the lymphatic system. The purpose of these physiology modules is to describe how this is accomplished, and provide insights on normal and abnormal physiology, with special attention to pediatrics.

Pancreatic Overview (slides 5-7)

The exocrine pancreas is responsible for providing the intestine with the enzymes necessary for the bulk of carbohydrate, protein, and fat intraluminal digestion AND for providing the liquid milieu that optimizes these reactions– namely a neutral pH. It is interesting and important to note that the pancreas in newborns is not fully mature– meaning that enzyme secretion is low for the first several months of life. We will explore this in more detail in the coming slides.

Please see Dr Christine Waasdorp's slides on embryology and anatomy to understand how the ventral and dorsal segments give rise to the major and minor papillae respectively.

The exocrine pancreas consists of glandular **acinar cells**, which synthesize, store and release digestive proenzymes, enzymes, and certain enzyme inhibitors. Cells contain zymogen granules near the apical pole, which contain the digestive enzymes that are released when the cells receive the appropriate signals. **Ductules**, which convey pancreatic fluid in larger and larger channels to the main pancreatic duct, are lined with cells that modify the primary secretions, most importantly by secreting significant amounts of bicarbonate and fluid- in effect, 'washing' the enzymes out of the pancreas.

Pancreatic Secretion (slides 8-18)

Acinar cell secretion is regulated primarily by the hormone CCK. CCK is released from I cells in the duodenum when contact occurs with fatty acids and certain amino acids. There are additional mechanisms for prompting CCK release: a complex interaction with a pancreatic-derived monitor peptide and a local mucosa-derived peptide called CCK-

releasing peptide--- simply an example of redundancy and mechanism for feedback inhibition. **Ductular secretion** is under the control of secretin, produced in the duodenum by enteroendocrine S cells.

It is appropriate to think of the I cells in the duodenum as 'food sensor's and the S cells as 'pH sensors'. The I cells respond to nutrient molecules and provoke the secretion of pancreatic enzymes and the release of concentrated bile from the gall bladder through the Sphincter of Oddi. The S cells sense the acidic chyme from the stomach and provoke fluid and bicarbonate secretion in the pancreatic and biliary ductules.

As secretion in pancreatic ducts increase under the influence of secretin, more and more sodium and water accumulate in the lumen, while the same is not true for chloride: it is effectively increasingly exchanged for bicarbonate via the mechanism described in the next slide. Hence, as secretin-stimulated pancreatic secretion increases, the fluid composition changes from close to plasma to a bicarbonate rich, Cl- poor fluid, aptly designed to neutralize gastric chyme.

Cellular mechanisms for bicarbonate and fluid secretion in the duct cell are reasonably well understood, and contextualize understanding a very well known channel- CFTR. Secretin uses cAMP to induce cytosolic events resulting in the opening of chloride channels in duct apical membranes. CFTR results in increased Cl- flux out of cells. Adjacent bicarbonate/Cl- antiporters then increases its activity, resulting in vectoral accumulation of bicarbonate in the duct lumen. Water and sodium follow paracellularly, in response to the electrochemical gradient across the epithelium set up by CFTR being open.

Cystic fibrosis is used as a robust example of the negative consequences of having poorly functional CFTR.

Pancreatic Enzymes (slides 19-27)

What are the organic constituents in pancreatic juices? 80% of secreted proteins are proteases. Human pancreatic juice contains 3 isoforms of trypsinogen. On the basis of their relative electrophoretic mobility, these are commonly referred to as cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and mesotrypsinogen. Cationic trypsinogen is the predominant isoform, followed by anionic and then mesotrypsinogen.

The majority of enzymes released by the pancreas are synthesized and stored in zymogen granules as inactive **proenzymes** (e.g., trypsinogen, chymotrypsinogen). Trypsinogen is the first **proenzyme** activated after it reaches the lumen of the duodenum. Trypsinogen is converted to trypsin upon release into the intestinal lumen by the action of the membrane bound brush border endo-protease **enterokinase**. Activated trypsin then serves to activate all other pro-forms of pancreatic proteases (including itself!). The secretion of proteases in pro-form serves to protect the pancreas from auto-digestion. Additional protection comes from a trypsin inhibitor that is co-packaged in the zymogen granules. This serves to largely inhibit any small amounts of trypsin that get activated prematurely. To learn more about protein digestion, please refer to the NASPGHAN physiology slide set 'Protein Digestion'.

Recurrent pancreatitis because of PRSS1 mutation is used as clinical correlation to understand the relevance of enzymes being activated in the right and wrong places.

It is important to remember that there is physiologic pancreatic insufficiency in infancy; compensation occurs from influence of gastric enzymes and unique features of breast milk.