Veterinary Bioscience: Digestive System

LECTURE 16
MECHANISMS OF GASTRIC ACID SECRETION AND THEIR CONTROL

LECTURER

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INTENDED LEARNING OUTCOMES

At the end of this lecture, you should be able to:

- Describe the structure of the gastric mucosa, recognise the layers of the stomach wall and the cell types of the gastric gland in tissue specimens, and explain how the structure and ultrastructure of gastric mucosal cells relates to their function.
- List the secretory components of gastric juice and describe the cellular and biochemical mechanism of HCl secretion from gastric parietal cells, and of pepsinogen from chief cells.
- Describe the mechanisms that control gastric secretion during the cephalic, gastric and duodenal phases of gastric secretion.
- Describe the mechanism of action of different classes of drugs that modulate gastric acid secretion and explain the circumstances in which they may be used.

KEY WORDS

Gastric gland, gastric pit, surface mucous cell, mucous neck cell, chief cell, parietal cell, enterochromaffin cell, hydrochloric acid, pepsinogen, pepsin, secretory canaliculus, gastrin, histamine, acetylcholine, prostaglandin, vagus nerve, carbonic anhydrase, hydrochloric acid, proton pump, H/K ATPase, cephalic phase, gastric phase, intestinal phase, H2 receptor antagonist, proton pump inhibitor, cytoprotective drug, cimetidine, omeprazole, misoprostol, sucralfate, antacid.

LECTURE OVERVIEW

Digestive secretions of the stomach

Along with mechanical digestion that is the consequence of gastric motility, chemical digestion continues in the stomach as a result of secretions from gastric mucosal cells.

The stomach wall is comprised of the same tissue layers found throughout the gut tube - mucosa, submucosa, circular and longitudinal muscle layers and peritoneum. With the exception of the region around the cardiac sphincter of some species, the gastric mucosa is a single layer of cells thick, that is folded into glands that empty their secretions into gastric pits and from there into the lumen of the stomach. Secretion of digestive enzymes is from specialized cells located in the fundic region of the mucosa: pepsinogen secreted by chief cells, that is cleaved to the active protease pepsin in the presence of hydrochloric acid (HCl), HCl secreted from gastric parietal cells, and mucus released from both surface mucous and mucous neck cells. The structure of each of these cell types reflects its specialized function.

The gastric parietal cell: a cell specialised for secretion of HCl

The gastric parietal cell is a wonderful example of a cell specialized for its function- the secretion of HCl by active transport against a concentration gradient. The active transport mechanism- a H/K ATPase, is located membrane bound on the luminal border of the cell. The surface area of this luminal border is greatly expanded by a deep infolding of the surface to form an intracellular secretory canaliculus. During periods of active secretion this surface is further expanded by translocation of intra cellular tubules and vesicles to form microvilli on the canalicular border. The energy for active transport and also for membrane cycling is provided by large numbers of mitochondria in parietal cells. Generation of hydrogen ions in parietal cells is catalysed by the enzyme carbonic anhydrase. Chloride secretion is also active, by a separate membrane bound mechanism. Chloride ions enter the cell in exchange for bicarbonate ions generated in the carbonic anhydrase reaction.

Control mechanisms in HCl secretion

The secretion of HCl is a rate-limiting step in gastric digestion- without HCl pepsinogen remains inactive. As a consequence, understanding the factors controlling acid release is fundamental to managing gastric digestion, and in particular to managing medical situations such as gastric ulceration.

Control of acid release from parietal cells can be considered at a macro or at a cellular level. Acid release is observed in response to the sight or smell of a meal, and when food is chewed in the mouth even before swallowing. This is the so-called cephalic phase of secretion and involves extrinsic nerves. Acetylcholine released from vagal efferents binds to muscarinic receptors on the basal surface of parietal cells. Vagal efferents also stimulate the release of the enterogastrone gastrin from G cells in the pylorus, that circulates to the fundic region and binds to its receptor on parietal cells. Finally, vagal stimulation of enterochromaffin cells, stimulates local release of histamine that binds to H2 histamine receptors on parietal cells in close proximity, stimulating acid release.

Once food enters the stomach (in the gastric phase of secretion), mechano- and chemo- receptors (sensitive in particular to intra gastric protein levels) activate local intrinsic neural and neuro-endocrine pathways to further augment both acid and pepsinogen release. Binding of neurotransmitter or hormone to the parietal cell activates an intracellular pathway involving the second messenger cAMP. Acid secretion is inhibited by prostaglandins binding to cell surface PG receptors, that results in decreased intracellular cAMP levels.

Just as gastric motility is inhibited by the presence of increasingly fatty, acidic or hyperosmotic chyme in the duodenum, gastric secretion is similarly inhibited. This is the intestinal phase of secretion and involves local intrinsic (gastro-enteric) nerve reflexes, enterogastrones- secretin, CCK and GIP.

Anti-ulcer drugs: drugs used to inhibit gastric acid secretion

Understanding the cellular mechanism of acid secretion provides receptor targets for inhibiting acid release. Classes of drugs used to reduce acid secretion include:

Histamine (H2) receptor antagonists: for example, cimetidine, ranitidine. As the histamine receptor is the dominant receptor on parietal cells, these drugs can reduce acid release by up to 70%. Whilst they are

relatively free of side effects, they share metabolic pathways with several other classes of drugs, so drug interactions can be important.

Proton pump inhibitors: for example, omeprazole. These drugs are very potent inhibitors of acid release because they irreversibly bind and block the active transport protein. Their effect persists even after drug is detectable in the blood stream. They are used in the treatment of unresponsive ulcer.

Anti-ulcer drugs: cytoprotective drugs

Prostaglandin analogues: for example, misoprostol. These drugs mimic the effect of endogenous prostaglandins (PG's) to decrease acid release. In addition, PG's protect against gastric ulceration and aid ulcer repair by increasing mucosal blood flow, stimulating mucosal cell turnover, and stimulating mucus secretion. Their role in the maintenance of the gastric mucosa will be discussed further in the upcoming lecture on 'mucosal barrier'.

Sucralfate has sometimes been described as an ulcer bandaid- it dissociates in the gastric lumen to octosulfate, that forms a sticky sucrose gel, and aluminium hydroxide, that neutralizes gastric acid.

Anti-ulcer drugs: antacids

Act to neutralise hydrochloric acid, bind bile acids and decrease pepsin activity. They provide only symptomatic relief. Antacids generally contain AlOH, $CaCO_3$, $Mg(OH)_2$, $NaHCO_3$. Magnesium salts lead to increase bowel motility, aluminium salts to a decrease in bowel activity. As a consequence, antacids often include both Mg and Al salts. Antacids are used only in human medicine.

FURTHER READING

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