Physiology

Sheet Slide

number 5

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In the previous lectures we talked about secretion, secretion by salivary gland, its mechanism and the function of saliva. We have 2 types of cells, Acinar cells (production of the primary saliva) and Duct cells (modification process).

Also, we said that there is a difference in PH and the composition of the final saliva between secretion at low and high rate.

Aldosterone (hormone) is related to sodium absorption and has no control over salivary glands secretion (some reference books say it has some effect on it, ignore it). The only controller is the autonomic nervous system. After that we talked about esophageal secretion.

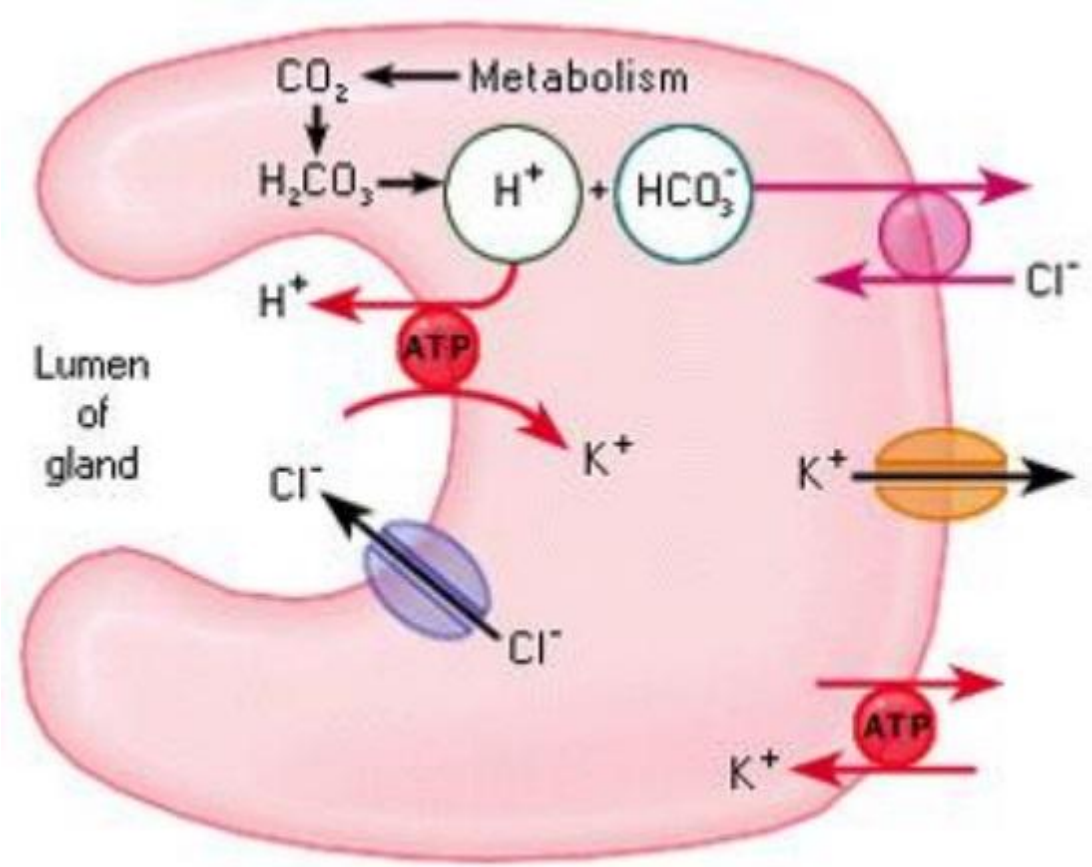
We started talking about gastric secretion. We have Oxyntic glands (gastric pits). There are many types of secretory cells like oxyntic cells or parietal cells (which secrets substances in their canaliculi like HCl and Intrinsic factor, which is important for the absorption of vitamin B12).

The mechanism of hydrochloric acid (HCl) secretion:

In the oxyntic cells we have transport (active secretion) of Cl- into the canalicus. The increase of Cl- concentration in these canaliculi will create tans- cellular potential which induces passive diffusion of K+ and Na+ (mainly K+).

To release H+ protons we have to synthesis carbonic acid (H_2CO_3) inside these cells from water and CO_2 in presence of carbonic anhydrase enzyme.

Carbonic acid dissociates forming H+ protons and bicarbonate HCO_3- (Which is transported toward interstitial fluid in exchange for Cl- at the basolateral membrane). H+ protons are pumped into the canaliculi.



Ulcers:

There are some drugs which can block the activity of proton pumps (they are called proton pump inhibitors). Some ulcers (mainly the duodenal ulcer) may be the result of high HCl- secretion. These drugs can help in this case.

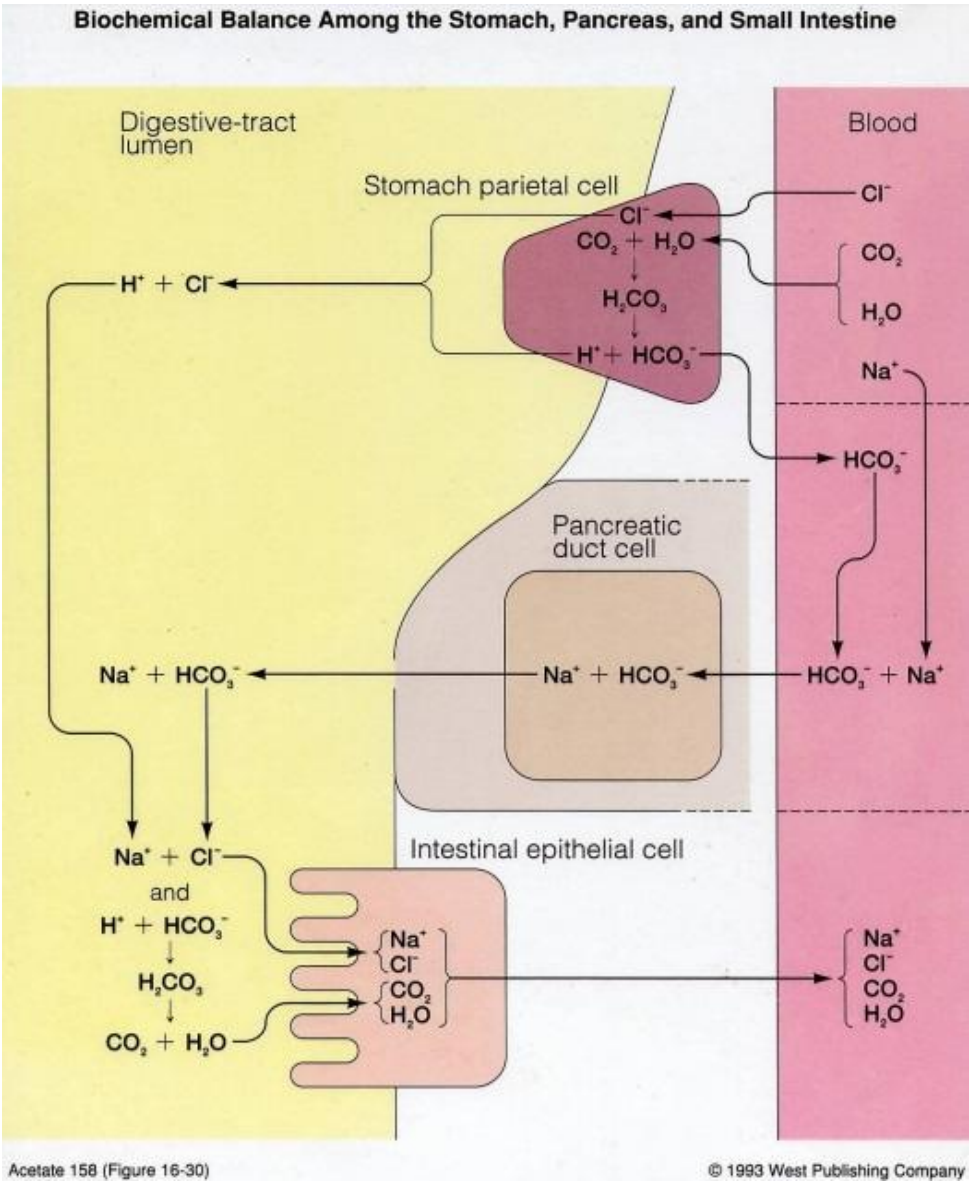
Aspirin is contraindicated in ulcers. People at high risk of developing ulcers can't take Aspirin or other anti-inflammatory drugs.

Student's question: Aspirin can cause ulcer and H+ pump inhibitors can heal ulcer, so can I give them with Aspirin as a protective mechanism?

No, now there is Aspirin with other compounds (like calcium) which can provide some protection against generation of ulcers. You can give aspirin to normal people (small amount) without problems. Not all who take Aspirin will develop ulcer, some people are at higher risk than others. Ulcers have other causes too.

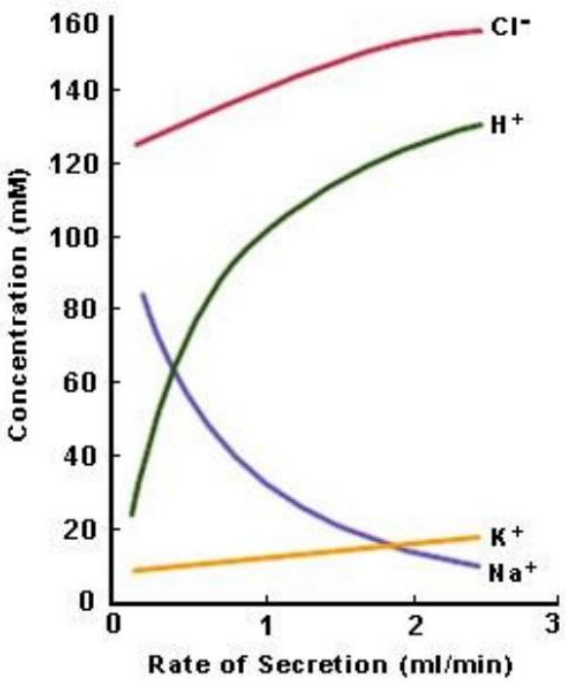
The mucosa is protected by mucus. Sometimes the amount of mucus (which is lining the whole mucosa) is reduced, so we have other causes of ulcer.

Actually ulcer formation happens all the time but high vascularization causes a fast healing process. Some people who are at risk (at stress) develop ulcer more because of lower vascularization (because the high sympathetic tone decreases vascularization of the stomach).



You can see in the picture above the activity of oxyntic cells. Also, we have other types of cells (at pancreas we have other mechanism to secrete water and electrolytes). We will see this slide again later to differentiate between them.

•The composition of gastric juice differs according to the rate of stimulation (secretion).



At low rate: the proton concentration is much lower with high rate of sodium.

At high rate: the sodium is lower and we have high amount of protons in the gastric juice.

So usually we don't release high amount of H+, instead we secrete sodium. (Sodium chloride -NaCl- rather than HCl).

Some people who release high amount of HCl between meals when there is no food in the stomach (as a result of some kind of stimulation) are subjected to developing ulcer.

Aspirin changes prostaglandin release, so we have reduction of protection at the level of mucosa.

00:00-10:05

Some drugs which are stimulating the release of HCl are recommended to be taken with a stomach full of food, so that most of HCl will be used on the food rather than acting on the stomach walls and causing ulcers in case of empty stomach (actually the effect on the duodenum is more than that on the stomach).

So these people with hyperacidity develop more duodenal ulcer rather than gastric ulcer because the protection of the duodenum is much less than that of the stomach.

Potassium in the GI tract is moving according the electrochemical potentials. Some literature talk about the exchange through Na-K

pumps, but also we have H+ pumps (we take potassium from the lumen and release H+ into it). So the concentration and the potential determine potassium movement. Its movement is a passive movement. There isn't much change in the concentration of K+ between high and low rate of gastric juice secretion.

Functions of HCl:

1) Increase the acidity of the media, which is important for the Conversion of pepsinogen to pepsin, and it is the optimal conditions for pepsin activity (in the duodenum the media becomes more alkaline so pepsin is not active anymore), we need more proteolytic enzymes which can be released from the pancreas.

2) HCl work as dissolvent, it helps in the decomposition and liquefying of food, mainly connective tissue, meat …etc. They will be dissolved by the low PH of the stomach.

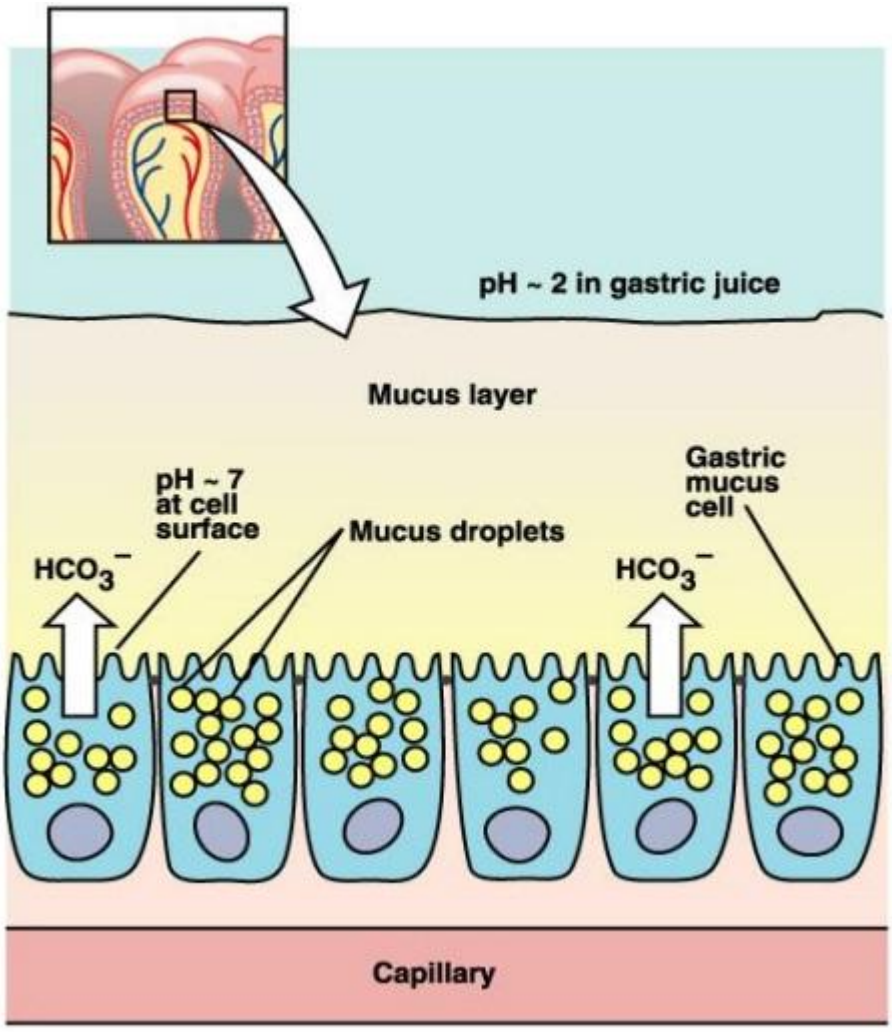
3) HCl plays a role in Defense mechanism; the food we ingest contains a lot of bacteria, some of which are pathogenic. Most of these bacteria are not resistant to the low PH of the stomach. So we decrease the amount of pathogens that reach the small intestine and can be harmful to the body.

Pepsinogen:

Secreted by peptic (chief) cells (main secretion), some mucus cells also secret it.

Peptic cells = chief cells = zymogenic cells (all names refer to the same type of cells).

The optimal activity of this enzyme is at the low PH (1.8-3.5). That's why we need the acidic media. Pepsinogen has one function which is to start the process of digestion (but it does not finish here) by cleaving longer polypeptides (cuts at a certain places in the middle) into smaller peptides.



Mucus:

We have another mean of protection by releasing huge amount of mucus the forms barrier between the lumen and the tissue (the line of epithelial cells). The mucus protects the tissues from the activity of enzymes (like pepsinogen {its active form is pepsin}) and the activity of HCl. The PH of the mucus is around 7 (neutral towards alkaline). Any amount of protons that trys to diffuse toward the tissue is neutralized by the alkaline component.

Some people get ulcer by reduced release of mucus.

Student question: mucus isn't continuous because where the gland opens toward the lumen there shouldn't be any mucus because we want to release the content in the lumen, so how can this be?

We have a plenty of cells at the surface to release mucus also we have some cells along the canaliculi (mucus neck cells), this provides more protection to the gland from the effect of acids so, if acids try to go back to the gland it will be neutralized.

So with time and continuous secretion you will have high amount in the lumen of the organ, the glands secrete small amount but with time a huge amount will accumulate in the lumen of the organ.

SO the functions of the mucus can be summarized in:

1) Lubrication functions

2) Protect the mucosa from chemical injury by:

A) Preventing the activity of proteolytic enzymes (like pepsin) on the mucosa

B) Neutralizing HCl by its alkaline character.

10:05-20:00

Gastrin Secretion:

Gastrin is released by G cells-entercendocrine cells- (in the oxyntic glands), stimulated by:

1) Gastric distension.

2) Presence of proteins in chyme.

3) Vagal stimulation (vagal reflexes; fortifying the process).

Functions of gastrin include hormonal control (stimulates the secretion of pepsinogen), secretion of HCl, and trophic effect on gastric mucosa. The trophic effect of gastrin is like that of supportive cells of the nervous system which release trophic factors to maintain the survival of the neuronal cells as long as possible. So, gastrin helps to maintain growth

and survival of mucosal cells as long as possible (but not long as neurons because this tissue is exposed to many harmful products and high acidity).

Secretion of Intrinsic factor:

It is secreted by parietal cells (oxyntic cells). It is essential for vitamin B12 absorption.

In atrophic gastritis, the amount of mucosa and the cells inside it is much less, so the secretion of intrinsic factor is lesser leading to the development of pernicious (with failure of RBC maturation) anemia in these people.

Usually we don't have deficiency of b12 in our diet, there is plenty of it, the main problems occur in its absorption (less absorption).

Control of Gastric Secretion:

Neural control:

ENS

The secretion of the stomach is well controlled, we have neural control achieved enteric nervous system ENS (local distension…..etc.), Ach neurons stimulate parietal and peptic cells.

ANS

Also, we have control of the ANS (Parasympathetic): vagal activation during cephalic and gastric phases (via long arc reflex). ANS can change the activity of the secretory cells directly or indirectly.

So the ANS can stimulate some enteric neurons which release Ach for example, we have its receptors on the secretory cells (effector cells). So we can increase their activity. Or the ANS can activate some enteric neurons to activate another type of cells called enterochromaffin-like

cells to release Histamine (which is involved in the paracrine-cells act on nearby cells- control).

In addition the ANS can activate enteric neurons to release GRP (Gastrin Releasing Peptide) which stimulate G cells to release gastrin (activation of hormonal control).

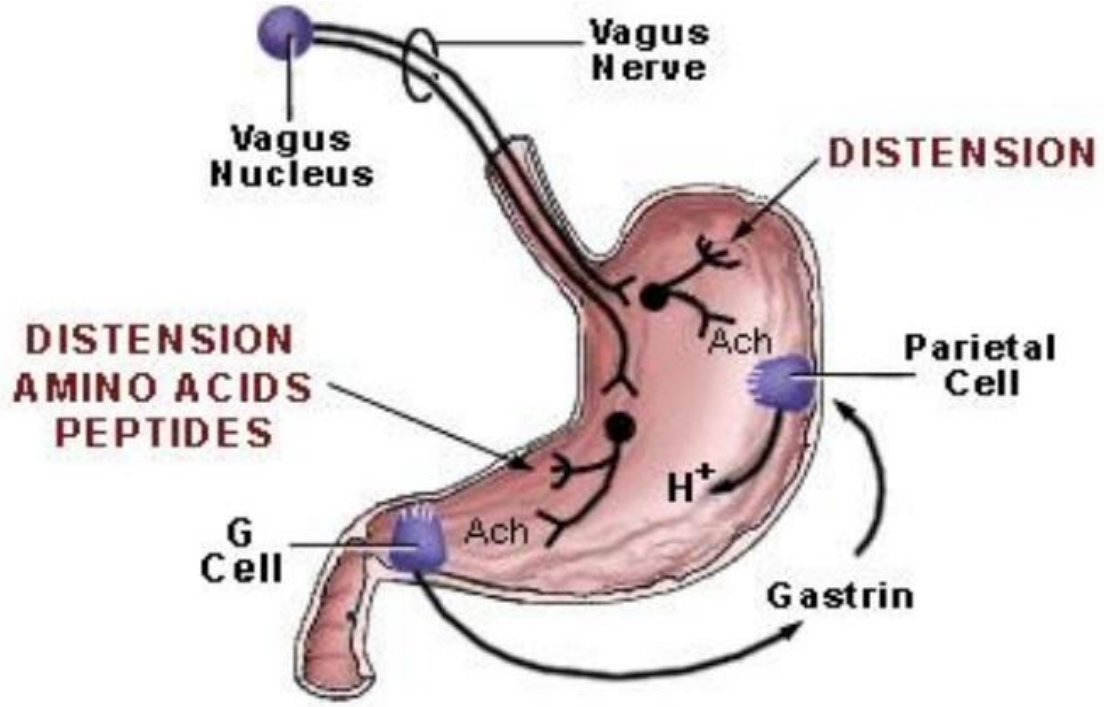
So ANS can stimulate:

1) Neural control by enteric nervous system.

2) Paracrine control by stimulating the release of histamine.

3) Hormonal control by stimulating the release of gastrin.

All of these are done through ENS (some enteric neurons release these peptides which are involved in the control).



Hormonal control:

Gastrin has receptors on secretory cells which are called cholecystokinin B receptors CCK-B. We can tell from their name that also cholecystokinin can bind to these receptors, but the stimulation by binding of gastrin is

much higher. High release of gastrin increases the secretory activity of the stomach, whereas high release of cholecystokinin prevent the binding of gastrin and its effect on the secretory cells, so apparently the activity of the stomach is inhibited.

The cholecystokinin is released from intestinal mucosa (the duodenal mucosa not the gastric mucosa). So, during intestinal phase, the secretion of the stomach is inhibited, and this is achieved through CCK-b receptors.

Remember: cholecystokinin is a hormone. That means it is released in the blood, and it reaches the stomach through it. It can also reach and act on the nervous system and have a lot of effects.

20:00-30:02

Paracrine control:

Histamine (released by enterochromaffin-like cells) can act on secretory cells (like parietal cells) through H2 receptors. There are some drugs -H2 blockers- which can block H2 receptors –histamine receptors type 2-, so by blocking them we prevent Histamine from binding and acting on cells, resulting with the reduction of HCl secretion.

Note: histamine also acts in the respiratory system but the type of receptor there is H1.

When histamine binds to H2 receptor on parietal cells, it activates carbonic anhydrase enzyme causing more production and release of H+ protons.

Somatostatin (SS) is usually a hormone, but it is released by paracrine cells in the mucosa and acts on other nearby cells to reduce HCl secretion, by binding to SS receptors on parietal cells to decrease cAMP.

Role of HCl in controlling secretion:

HCl itself inhibit HCl secretion (negative feedback mechanism). High rate of HCl secretion activates a lot of reflexes which reduce gastrin release

or Initiation of inhibitory reflexes to reduce HCl secretion. This maintains the pH from falling very low (below 3) which is harmful.

HCl acts indirectly by initiating enteric reflexes that cause an increase in pepsinogen secretion by peptic cell.

Summary of Control:

Cephalic phase: gastric activity increase (via parasympathetic NS).

Gastric phase: gastric activity increase

Distension and the presence of proteins stimulate local and long reflexes which result with increased gastric secretion. Caffeine and alcohol also stimulate acid secretions via ENS, ANS and Hormones.

Intestinal phase: we have enterogastric reflex (inhibitory), release of some hormones like (cholecystokinin, secretin and GIP [–gastric inhibitory peptide - which is released from duodenal mucosa and can inhibit gastric activity]).

So in general intestinal phase is inhibitory but in some literature it is written that in the beginning of the intestinal phase we have some excitatory effect. The upper part of the duodenum contains also G cells so through their stimulation we increase the release of gastrin which can increase the activity of the stomach.

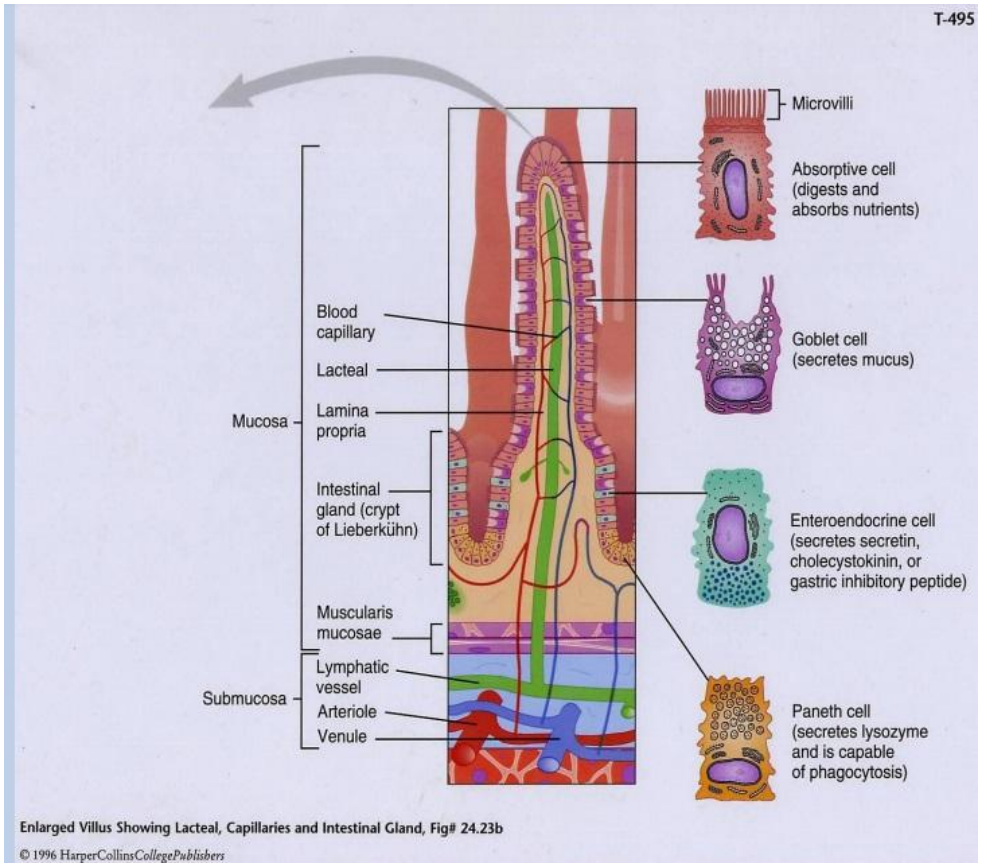
But in general, it is considered inhibitory, once the content of the stomach is emptied you don't need its activity anymore.

Intestinal Secretions:

We have many types of secretory cells; Cells of mucosal epithelium secrete mucus, water and electrolytes. Most of the secretion at the level of the small intestine is serous secretion (about 1.5 L) but there are some mucus secreting cells. Small intestine secretion is alkaline.

There are Tubular glands in submucosa of duodenum (duodenal glands). These invaginations of epithelium known as crypts of Leiberkuhn empty their content into the lumen of duodenum (serous secretion). These glands secrete serous secretion. We also have enteroendocrine cells which release secretin, cholecystokinin and GIP).

Release of secretin is stimulated by the presence of acidic content in the chyme while the release of cholecystokinin is stimulated by fat content in chyme. Once gastric content is emptied into the duodenum, you have the acidic chyme which can stimulate the release of secretin to release alkaline media to neutralize these acids.



30:02-40:33

Regulation:

We have also the ANS and ENS. The main neurotransmitters which are involved are Ach and VIP (Vasoactive intestinal peptide increases blood flow to small intestine which means more available water and electrolytes for secretion).

Hormonal control is by secretin which acts over cells to increase water and electrolytes secretion.

Colonic secretions:

It is Mostly mucus secretion and Small amount of serous secretions which is rich in K+ and HCO3-. We have high reabsorption of sodium. The potassium movement (absorption or release) is according to the electrochemical gradient. In the small intestine, we have reabsorption of K, and in the colon we have secretion.

The end