بسم الله الرحمن الرحيم

PHARMACOLOGY

FINAL | Lecture 1

Peptic Ulcer Treatment

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﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

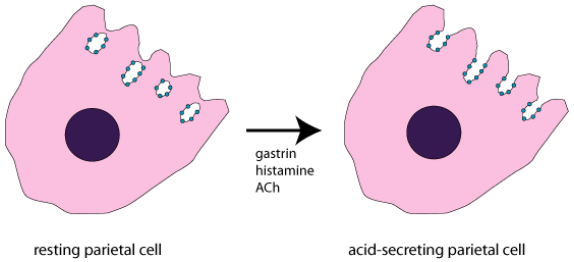
اللهم استعملنا ولا تستبدلنا

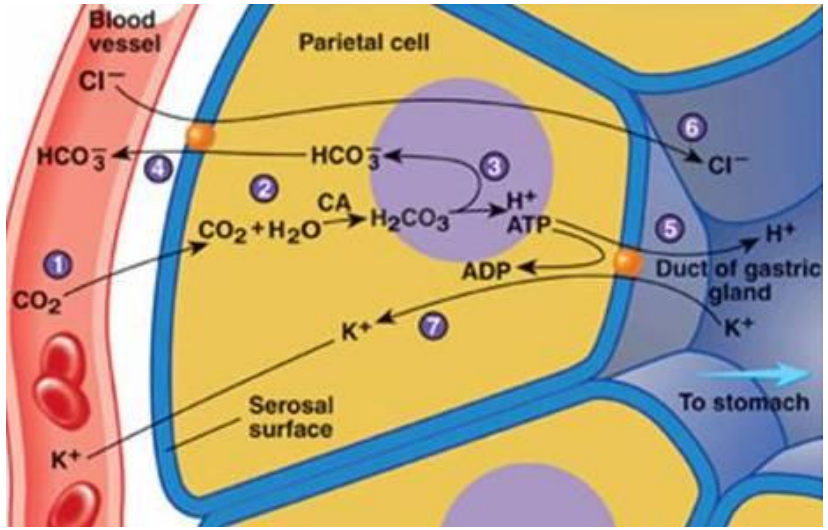
Drugs Used in the Treatment of Gastrointestinal Diseases.

Manar Zraikat

Physiology of gastric Secretion

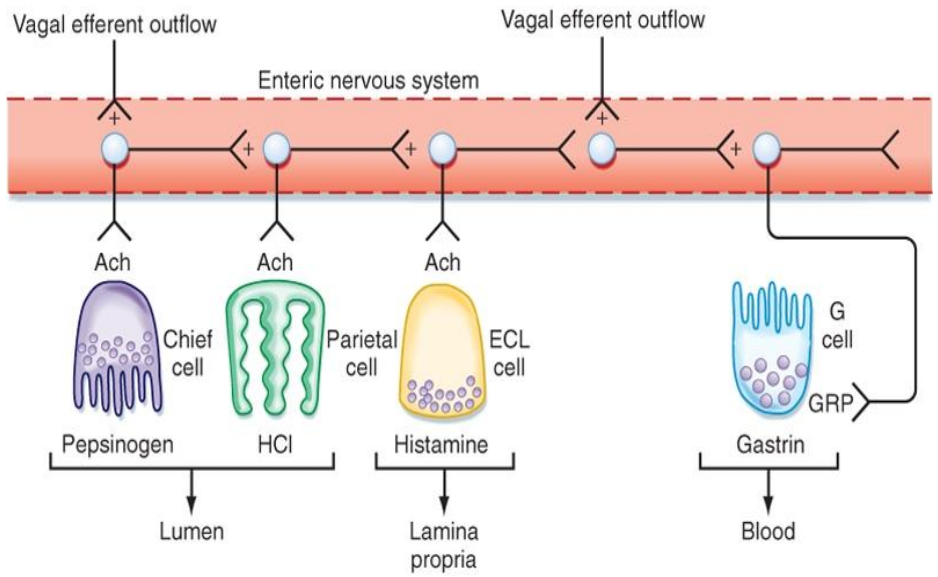
- Parietal cells secrete 2 liters of acid/day; a huge amount that aids in digestion.
- Optimal pH (between 1.8-3.5) for the function of the digestive enzyme pepsin.
- Stimulation of acid secretion from the parietal cells involves translocation of H+/K+-ATPase to the apical membrane of parietal cell.
- H+/K+-ATPase (proton pump) uses the energy derived from ATP hydrolysis to pump H+ into the lumen of stomach in exchange for potassium ions.
- Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi (lumen).





Stimulants of acid secretion:

1. Ach from enteric neurons that results in the secretion of pepsinogen.
2. Histamine from ECL (enterochromaffin - like) cells.
3. Gastrin released by G cells.



Gastrin releasing peptide (**GRP**)

Somatostatin in **D cells inhibits acid secretion.**

Gastric pH < 3 --> gastric D cells release somatostatin
It inhibits acid secretion and keeping the balance where PH < 3.

By:

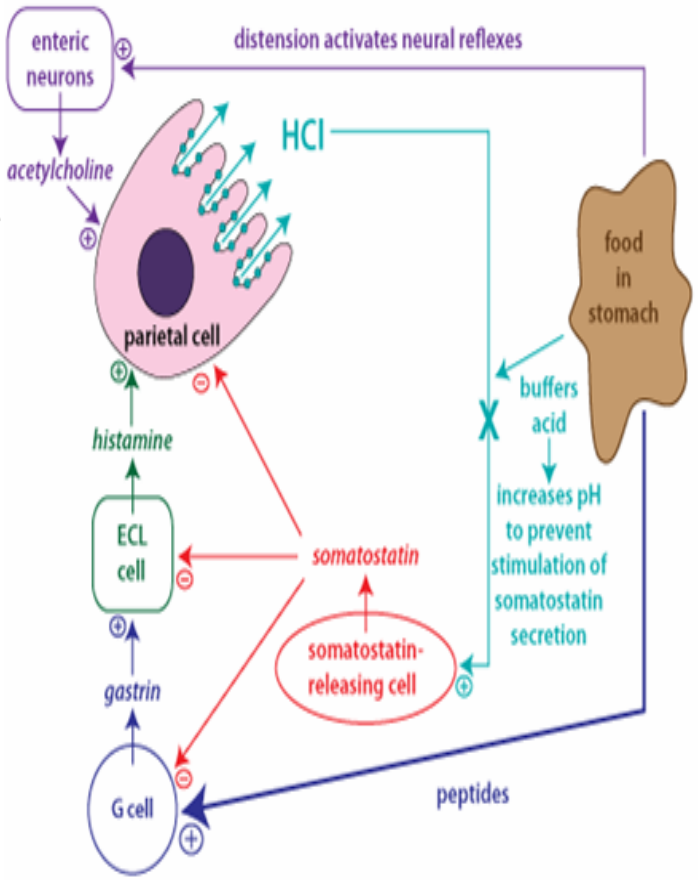
1- direct effects on parietal cells and inhibiting their functions.

2- inhibiting release of histamine & gastrin or both.

Three phases in gastric acid secretion.

❖ Cephalic Phase:

- sight, smell, taste or thought of food, activate enteric neurons that induce the Ach to be secreted and induce parietal cells to work.
- In humans, the major effect of **gastrin** is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.



❖ Gastric Phase:

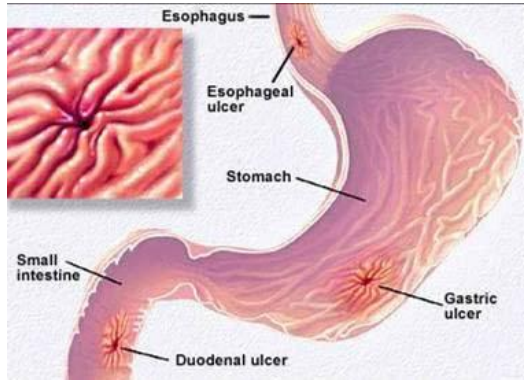
- Food stretch stomach walls activating a neural reflex to stimulate acid secretion.
- Peptides & amino acids stimulate G cells to release gastrin leading to induce the ECL cells and the PH will decrease.
- Food acts as a buffer, raising the pH & thus removing the stimulus for somatostatin secretion, then somatostatin inhibits the secretion of HCl, the food act as a buffer that will increase the PH which will inhibit somatostatin secretion.

❖ Intestinal Phase:

- Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion.

Peptic ulcer

- A defect in the lining of the stomach or the duodenum.



Causes of Peptic Ulcer:

- *Helicobacter pylori* (most common).
- Drugs such as aspirin & other NSAIDs

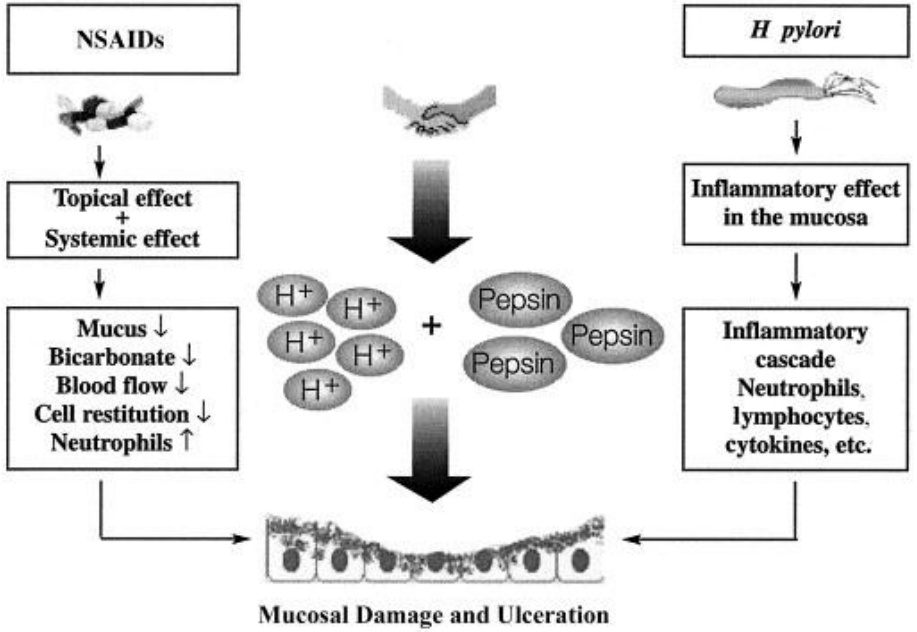
Other factors:

Smoking, Stress, alcohol.

➢ **Gastrinomas** (Gastrinomas are neuroendocrine tumors in the stomach characterized by the secretion of gastrin with resultant excessive gastric acid production causing severe peptic ulcer disease and diarrhea, a combination referred to as the Zollinger-Ellison syndrome (ZES)

➢ **Zollinger Ellison syndrome**

- a rare gastrin-secreting tumors.

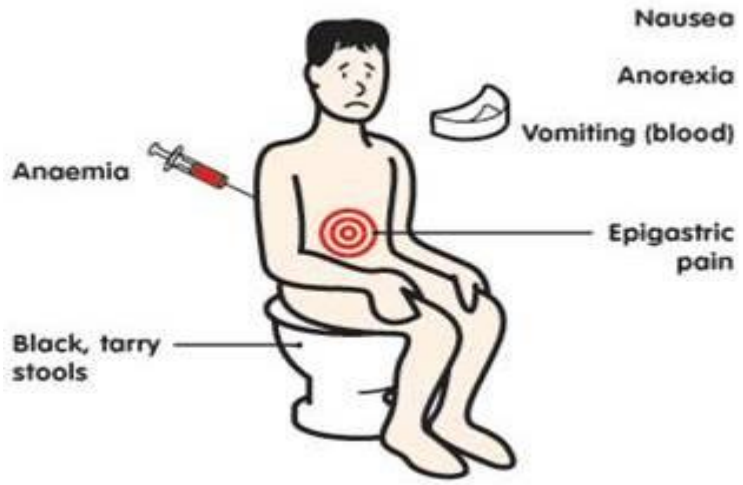


Symptoms:

- burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.

In severe cases, symptoms include:

- Dark or black stool (due to bleeding)
- Vomiting blood because of the high bleeding in the stomach.
- Weight loss & severe pain
- in the mid to upper abdomen.

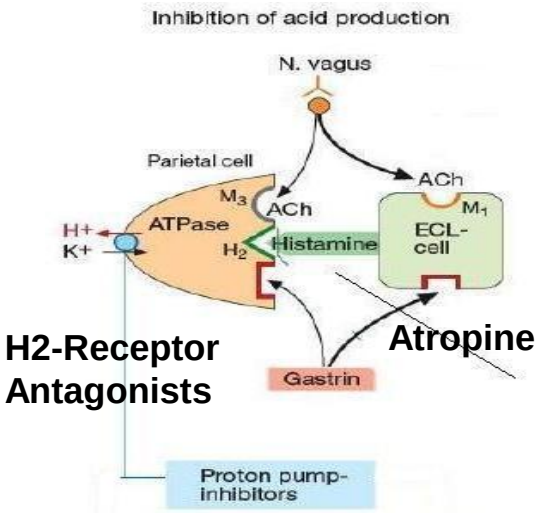


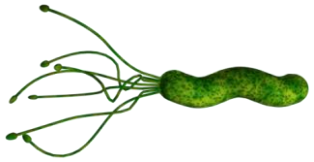
Complications of peptic ulcer

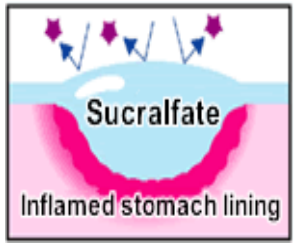
- Gastrointestinal bleeding. (Sudden large bleeding can be life threatening).
- Cancer (Helicobacter pylori as the etiological factor)
- Perforation (hole in the wall) Penetration (this case is life-threatening)

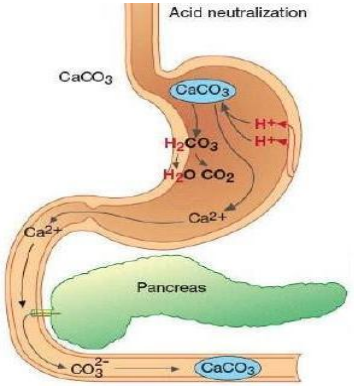
Treatment options

1. **Reduce** acid secretion by agents such as H2 receptor antagonists.
2. **Neutralize** acid in the lumen by antacids.
3. **Protect** the mucosa from acid destruction.
4. **Antibiotics** to eradicate *Helicobacter pylori.* If this is successful then the ulcer should begin to heal on its own.









Neutralization of acid (Antacids)

- Nonprescription remedies which don't need prescription for treatment of **heartburn & dyspepsia.**
- Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.
  - The doctor mistakenly said that the drug should be taken before meals

AL(OH)3 + HCl -----> ALCl3 + H2O
2HCl + **Mg(OH)2** ----> MgCl2 + 2H2O

As seen here, they combine with HCL and reduce its concentration.

Aluminum antacids cause constipation, interfere with absorption of many drugs.

Magnesium antacids have laxative action; diarrhea.
ionic magnesium stimulates gastric release (acid rebound)

Magnesium trisilicate slow-acting antacid, thereby increasing the duration of action of the drug.

Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation). This combination decrease the amount of aluminum hydroxide, thereby reducing its interference with the absorption of other drugs.

Antacids

Magnesium Hydroxide	Aluminum Hydroxide
React slowly and without gas formation.	
Metabolic alkalosis is also uncommon.	
Magnesium salts cause diarrhea.	Aluminum salts cause constipation.
Usually given in combination, to avoid the problem of constipation caused by aluminum salts and diarrhea caused by magnesium salts.	
Contraindicated in renal failure, because these drugs are primarily excreted by the kidneys.	

Neutralization of acid (Antacids)

1. **Calcium carbonate (associated with "acid rebound“)**

   with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate, urea, nitrogen, creatinine & bicarbonate levels, so it should be given with caution, ensuring adherence to the prescribed dose.

$$2HCl + CaCO3 \text{ ---> } CaCl2 + \mathbf{CO2} + H2O$$

This reaction decreases acid secretion by binding to HCl, producing calcium chloride and carbon dioxide.

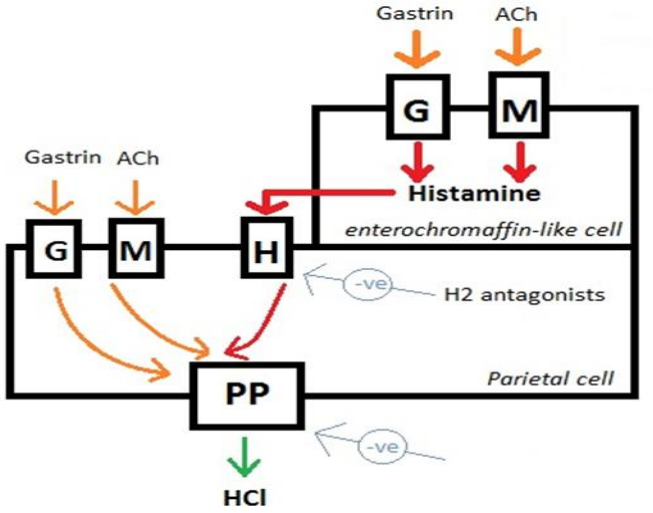
2. **Sodium bicarbonate**

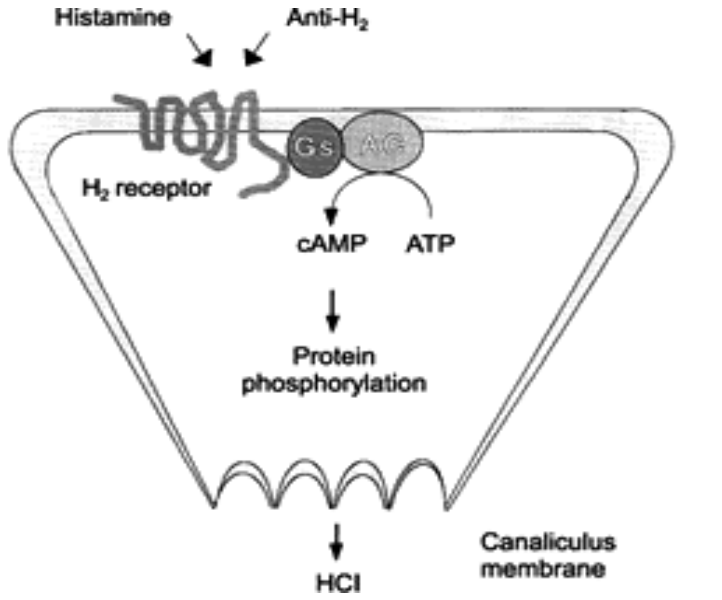
- Should be avoided as it counteracts diuretic therapy for hypertension, thus people with hypertension **shouldn’t** be given this drug.
- Short duration of action, followed by acid rebound.
- Highly absorbed, potentially causing **metabolic alkalosis.**
- CO2 results in **belching**.

$$NaHCO3 + HCl \rightarrow NaCl + H2O + \mathbf{CO2}$$

H_2- Receptor Antagonists

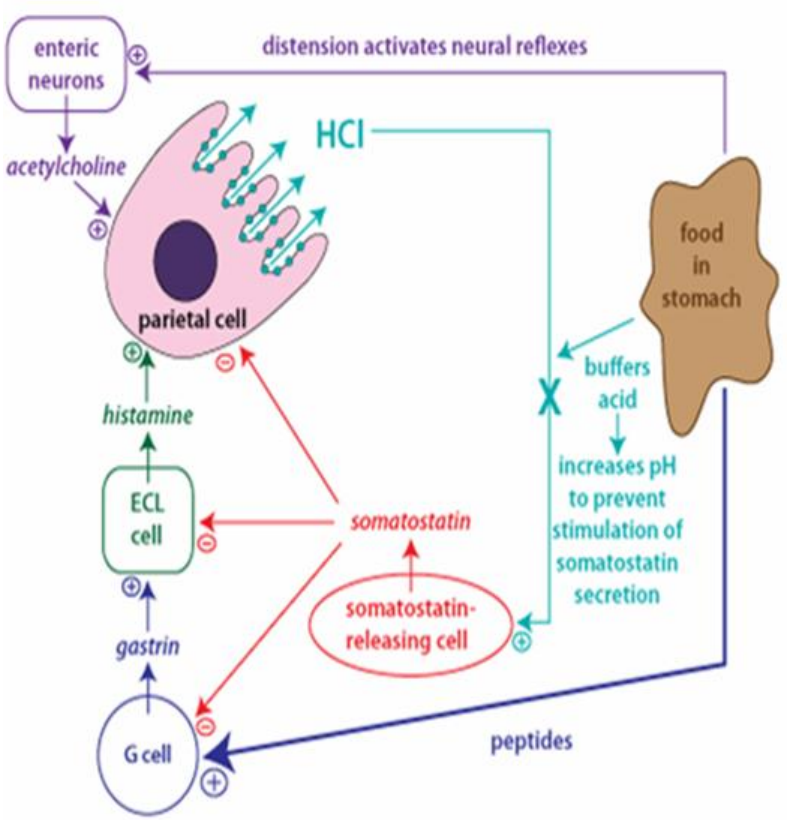
- In the normal situation, acetylcholine and gastrin induce the release of Histamine, which bind to H2 receptors and activate the proton pump (K+/H+) to produce HCl.
- When H2 receptor antagonists are used, they block the action of histamine, thereby preventing activation of the proton pump and reducing HCl production.
- H2 receptor antagonists block the action of histamine, interrupting the downstream signaling pathway, particularly protein phosphorylation, which ultimately stops HCl production.





H_{2-} Receptor Antagonists

- Selective competitive inhibitors of the parietal cell H2 receptor suppress basal and meal-stimulated acid secretion in a dose-dependent manner.
- They also decrease volume of secretion and pepsin concentration.
- Remember, Histamine works on H2 receptors, so blocking them counteracts its function (acid secretion), so no secretion.



H_{2-} Receptor Antagonists (1970s-1990s)

Were the most commonly prescribed drugs in the world, **proton pump inhibitors are considered the alternative of these drugs.**

Examples:

- **Cimetidine**

  Prototype drug – associated with many problems.

- **Ranitidine.**
- **Famotidine.**

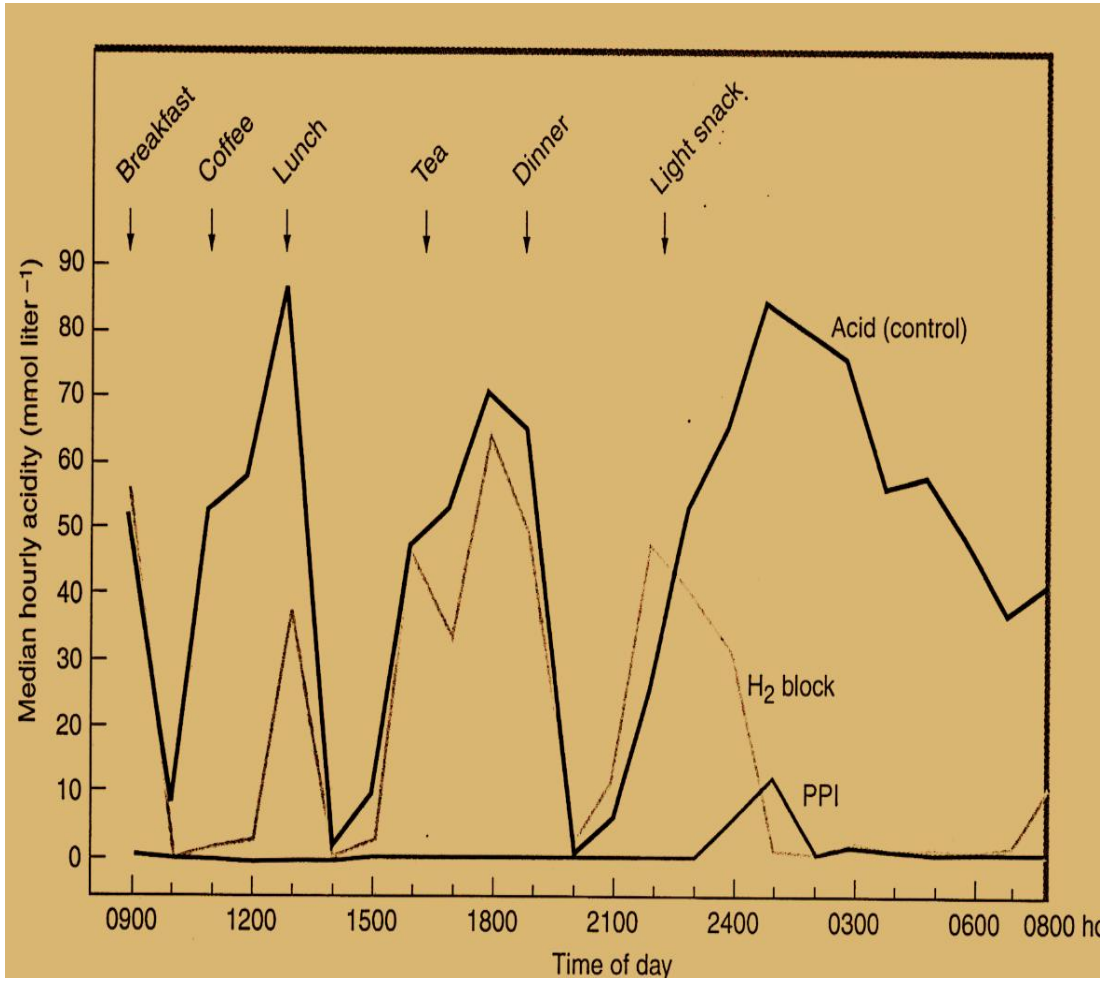
  50% first-pass metabolism bioavailability.

- **Nizatidine**

  has little first-pass metabolism.

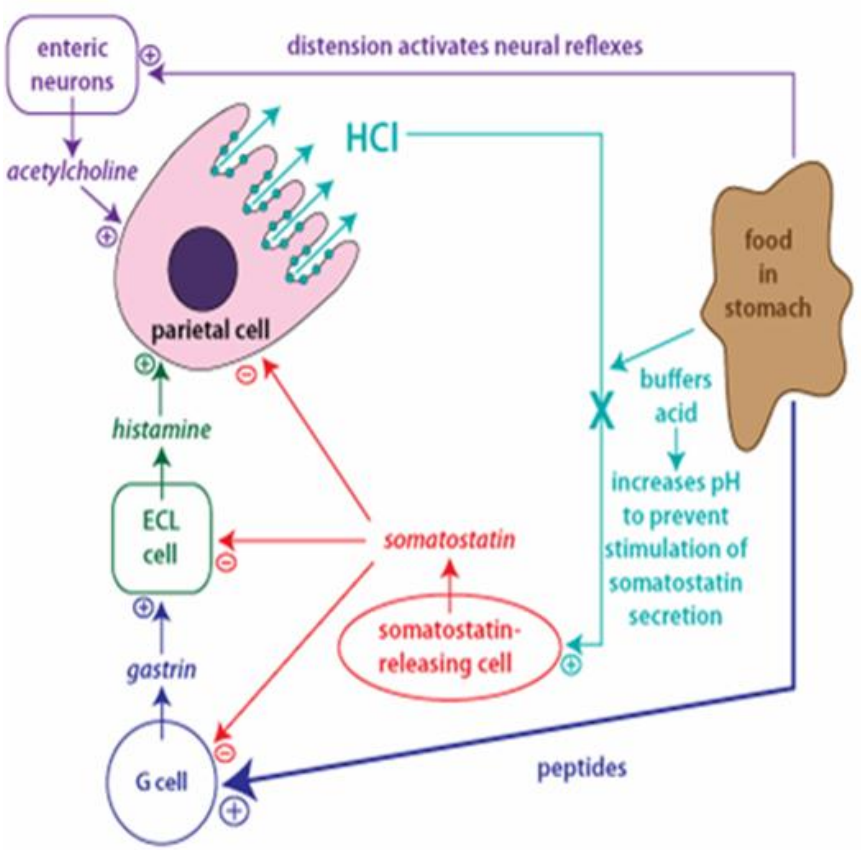
H_{2-} Receptor Antagonists

- This picture shows a comparison between H2 receptor antagonists and proton pump inhibitors.
- With H2 receptor antagonists, acid secretion **fluctuates** throughout the day due to the intake of different meals at different times.
- With proton pump inhibitors there is a **stable** level of acidity. This is why we prefer proton pump inhibitors over the H2 receptor antagonists.



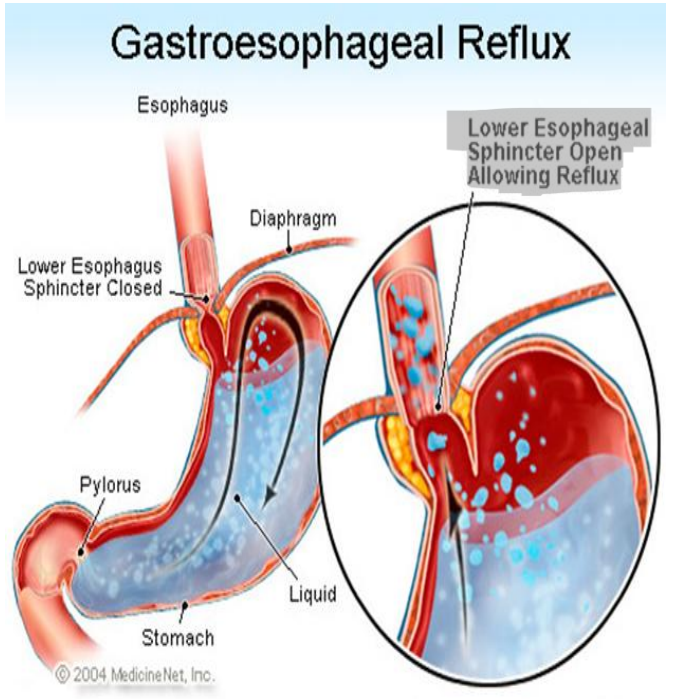
H_{2-} Receptor Antagonists

- Decrease secretion stimulated by:
  - Histamine.
  - Gastrin.
  - Acetylcholine.
- Duration of action: 12 hours.
- Inhibit 60-70% of total 24-h acid secretion.
  - 90% of nocturnal acid.
    - Nocturnal acid is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes
  - 60% of day-time, meal stimulated, acid.



H_{2-} Receptor Antagonists

- <u>Clinical Uses:</u>
- Gastroesophageal Reflux:
  - Prophylactically, before meals.
  - Afford healing for erosive esophagitis, which is the inflammation of the esophagus because of the acid reflux, in less than 50% of patients.
  - Proton pump inhibitors are preferred.
- Non-Ulcer Dyspepsia.
- Stress- Related Gastritis:
  - Can prevent bleeding, usually given IV.
- Peptic Ulcer Disease:
  - Replaced by PPI.
  - H2 receptor antagonists are no longer used, if used Healing rate greater than 80-90% after 6-8 weeks, which is considered a long time.
  - Not effective in the presence of *H. pylori* infection.
  - Not effective if NSAID is continued, if NSAIDs are the cause of the peptic ulcer.



Normally, the LES is closed and prevents acid reflux into the esophagus, in pathologies that make it loose allowing acid reflux can lead to GERD, etc.

H_{2-} Receptor Antagonists

Adverse Effects:

- Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation.
- CNS:
  - Confusion, hallucinations occur only with IV **cimetidine** to elderly patients in ICU.
- Endocrine Effects:
  - Again, only with **cimetidine**, can inhibit estradiole metabolism, and can increase prolactin serum levels, which can be associated with infertility cases among women.
- Pregnancy and Nursing Mothers:
  - Can cross placental barrier and appear in breast milk; **contraindicated**.
- Other Effects:
  - Rarely can cause bradycardia and hypotension.

H_{2-} Receptor Antagonists

Drug Interactions:

- Cimetidine can inhibit cytochrome P450 enzymes(CYP1A2, CYP2C9, CYP2D6, and CYP3A4), so can increase half life of many drugs.
- Ranitidine binds 4-10 times less.
- Nizatidine and famotidine binding is negligible.

Test yourself by clicking on the antacid

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

عَن مُعَاذ بن جَبَلٍ رضي الله عنه قَالَ: قُلتُ يَا رَسُولَ الله أَخبِرنِي بِعَمَلٍ يُدخِلُني الجَنَّةَ وَيُبَاعدني من النار قَالَ: (لَقَدْ سَأَلْتَ عَنْ عَظِيْمٍ وَإِنَّهُ لَيَسِيْرٌ عَلَى مَنْ يَسَّرَهُ اللهُ تَعَالَى عَلَيْهِ: تَعْبُدُ اللهَ لاَتُشْرِكُ بِهِ شَيْئًا، وَتُقِيْمُ الصَّلاة، وَتُؤتِي الزَّكَاة، وَتَصُومُ رَمَضَانَ، وَتَحُجُّ البَيْتَ. ثُمَّ قَالَ: أَلاَ أَدُلُّكَ عَلَى أَبْوَابِ الخَيْرِ: الصَّوْمُ جُنَّةٌ، وَالصَّدَقَةُ تُطْفِئُ الخَطِيْئَةَ كَمَا يُطْفِئُ المَاءُ النَّارَ، وَصَلاةُ الرَّجُلِ فِي جَوْفِ اللَّيْلِ ثُمَّ تَلا : (تَتَجَافَى جُنُوبُهُمْ عَنِ الْمَضَاجِعِ) حَتَّى بَلَغَ: (يَعْلَمُونْ) [السجدة:16-17] ثُمَّ قَالَ: أَلا أُخْبِرُكَ بِرَأْسِ الأَمْرِ وَعَمُودِهِ وَذِرْوَةِ سَنَامِهِ ؟ قُلْتُ: بَلَى يَارَسُولَ اللهِ، قَالَ: رَأْسُ الأَمْرِ الإِسْلامُ وَعَمُودُهُ الصَّلاةُ وَذروَةُ سَنَامِهِ الجِهَادُ ثُمَّ قَالَ: أَلا أُخبِرُكَ بِملاكِ ذَلِكَ كُلِّهِ ؟ قُلْتُ:بَلَى يَارَسُولَ اللهِ. فَأَخَذَ بِلِسَانِهِ وَقَالَ: كُفَّ عَلَيْكَ هَذَا. قُلْتُ يَانَبِيَّ اللهِ وَإِنَّا لَمُؤَاخَذُونَ بِمَا نَتَكَلَّمُ بِهِ ؟ فَقَالَ: ثَكِلَتْكَ أُمُّكَ يَامُعَاذُ. وَهَلْ يَكُبُّ النَّاسَ فِي النَّارِ عَلَى وُجُوهِهِمْ أَو قَالَ: عَلَى مَنَاخِرِهِمْ إِلاَّ حَصَائِدُ أَلسِنَتِهِمْ) رواه الترمذي وقال: حديث حسن صحيح.