

H₂ blockers and proton pump inhibitors

A 3D rendered golden figure, possibly a character or mascot, is holding a large, white, rounded rectangular sign with a golden border. The sign contains the text 'Peptic Ulcer'. The figure is positioned behind the sign, with its arms and legs visible. The background is white.

Peptic Ulcer

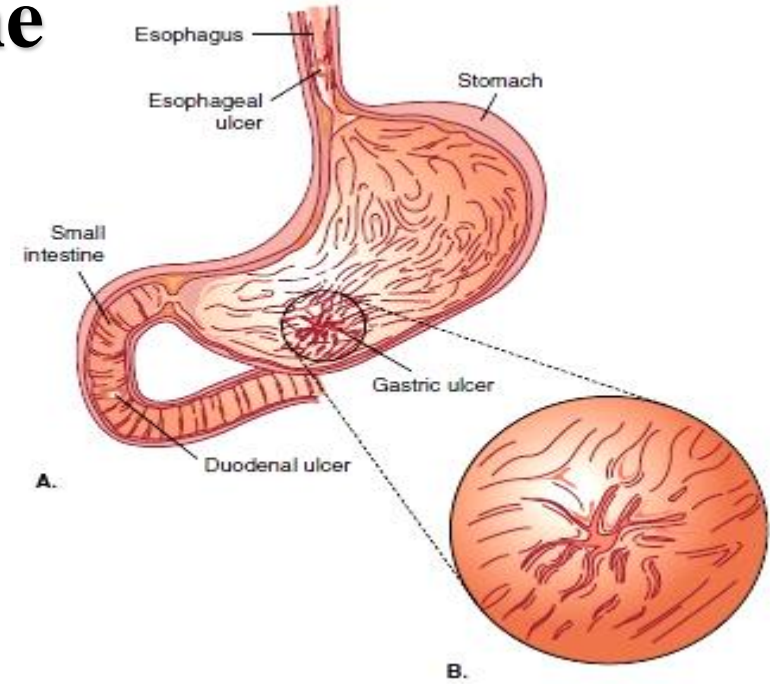
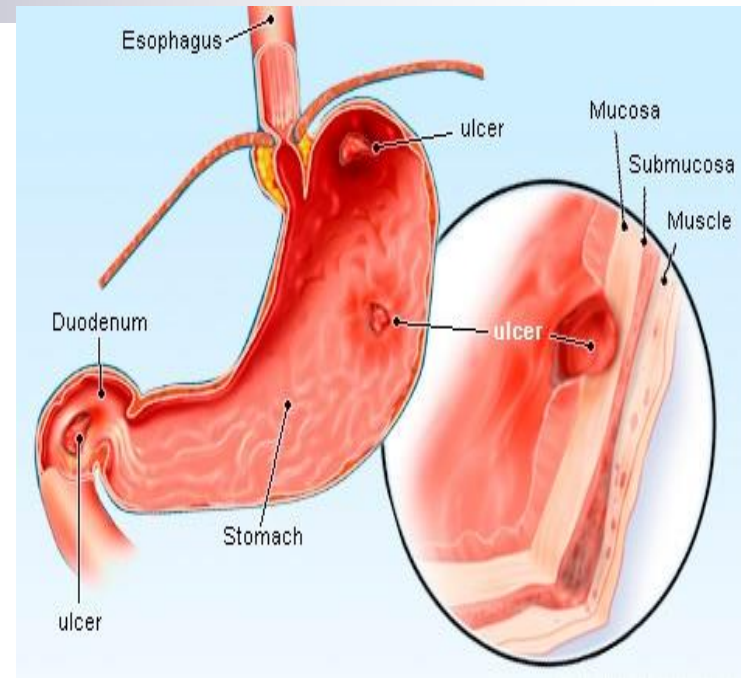
By
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Objectives:

- Understand the key points of pathophysiology of the peptic ulcer disease
- Enumerate various classes of drugs used in peptic ulcer disease
- Know the characteristic pharmacokinetics, pharmacodynamics and side effects of drugs used in peptic ulcer disease.
- Know the cytoprotective drugs mainly misoprostol and its use in NSAIDs-induced peptic ulcer.
- Identify different antacids that are used to relieve pain of peptic ulcer.
- Identify potential adverse drug interactions of anti-ulcer drugs.

Peptic ulcer disease (PUD)

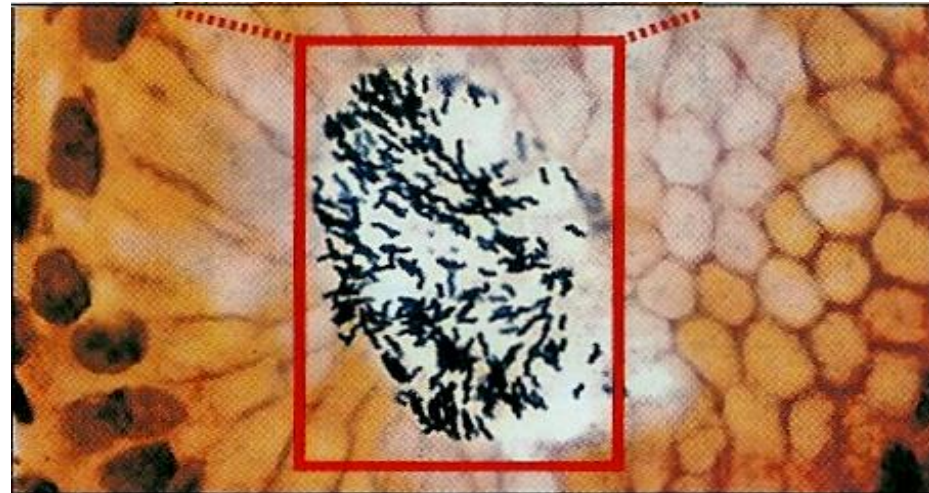
▪ a localized lesion of the mucous membrane of the stomach (**gastric ulcer**) or duodenum (**duodenal ulcer**), typically extending through the muscularis mucosa.



Pathophysiology:

is imbalance between aggressive factors (**acid & pepsin**) and defensive factors (**e.g. prostaglandins, mucus & bicarbonate layer**). However, nowadays, it seems that *H. pylori* theory is very important.

Helicobacter pylori is the major etiological factor in peptic ulcer disease (95% in duodenal and 80% in gastric ulcer).



Pathophysiology:

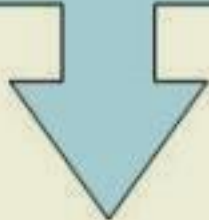
1. **Hydrochloric acid and pepsin** destroy gastric and duodenal mucosa.
2. **Mucus and bicarbonate** ion secretions protect mucosa
3. **Prostaglandins (PGE₂ & PGI₂)** protect mucosa by:
 - inhibiting acid secretion
 - increasing mucus and bicarbonate production
 - enhancing mucosal blood flow.

Peptic Ulcer Disease

NORMAL

Aggressive Forces:

Gastric acidity
Peptic activity



Defensive Forces:

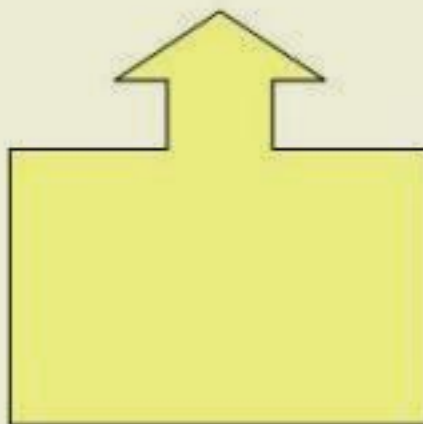
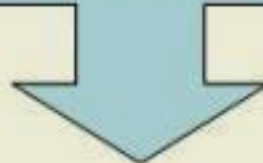
Surface mucus secretion
Bicarbonate secretion into mucus
Mucosal blood flow
Apical surface membrane transport
Epithelial regenerative capacity
Elaboration of prostaglandins



INCREASED AGGRESSION

Aggravating Causes:

H pylori infection
NSAID, aspirin
Cigarettes, alcohol
Impaired regulation of
acid-pepsin secretion



IMPAIRED DEFENSE



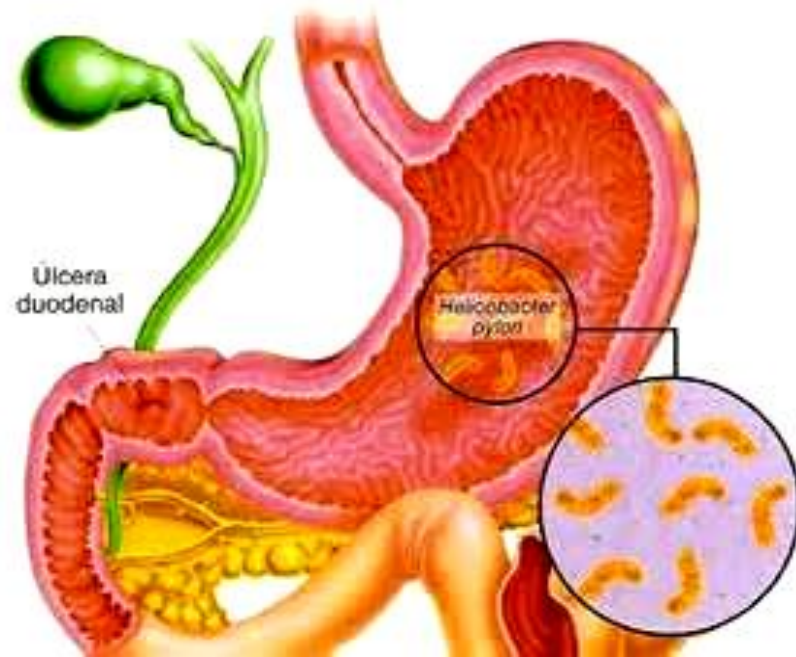
Impaired Defense:

Ischemia, shock
Delayed gastric emptying
Duodenal-gastric reflux:



Etiology:

- **H. pylori infection**
- **Alcohol**
- **Smoking**
- **Caffeine**
- **Genetic factors**
- **Diet**
- **Hypersecretory states (Zollinger Ellison syndrome)**
- **Drugs (e.g.) NSAIDs; corticosteroids**



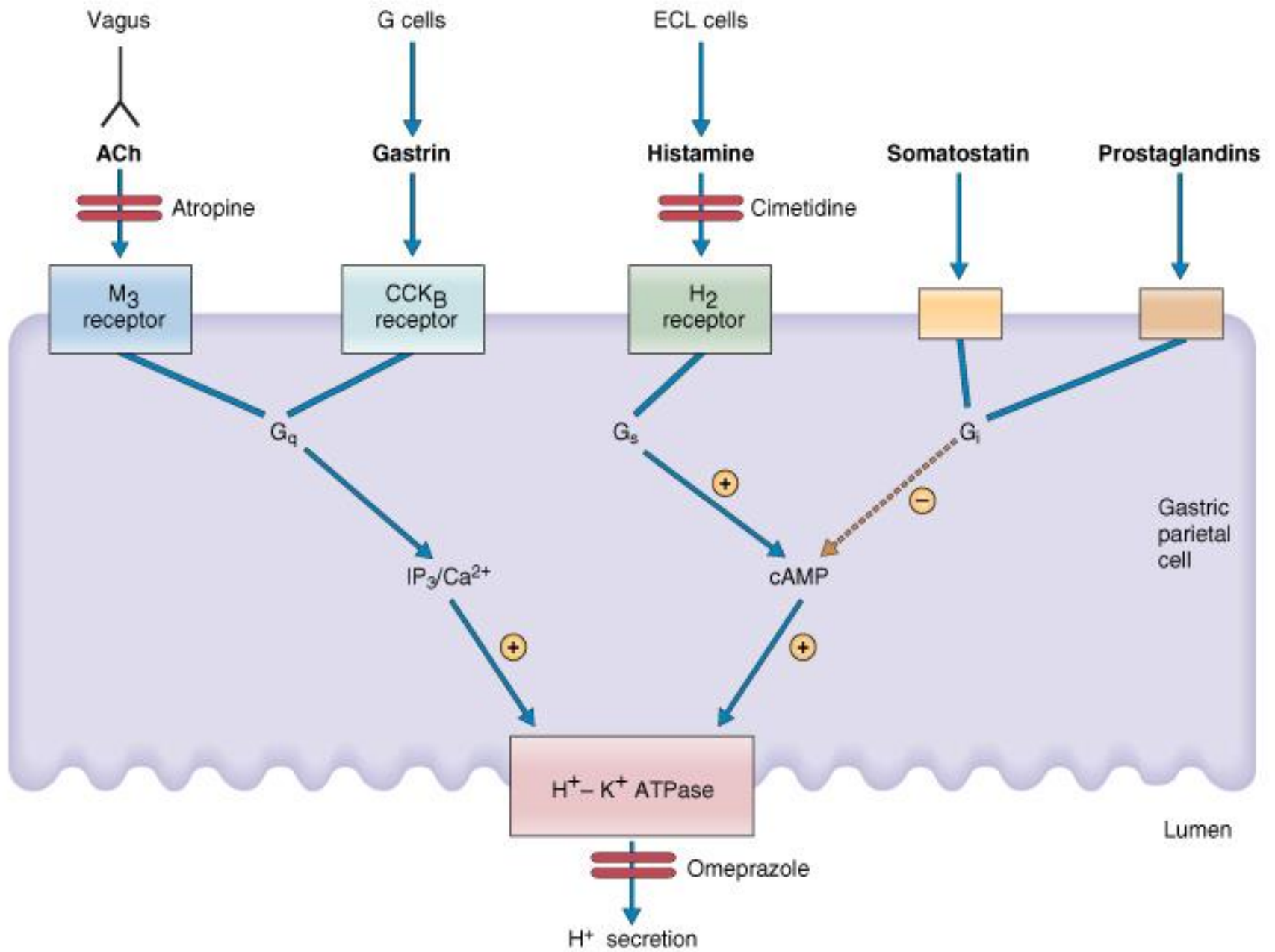
Gastric secretions

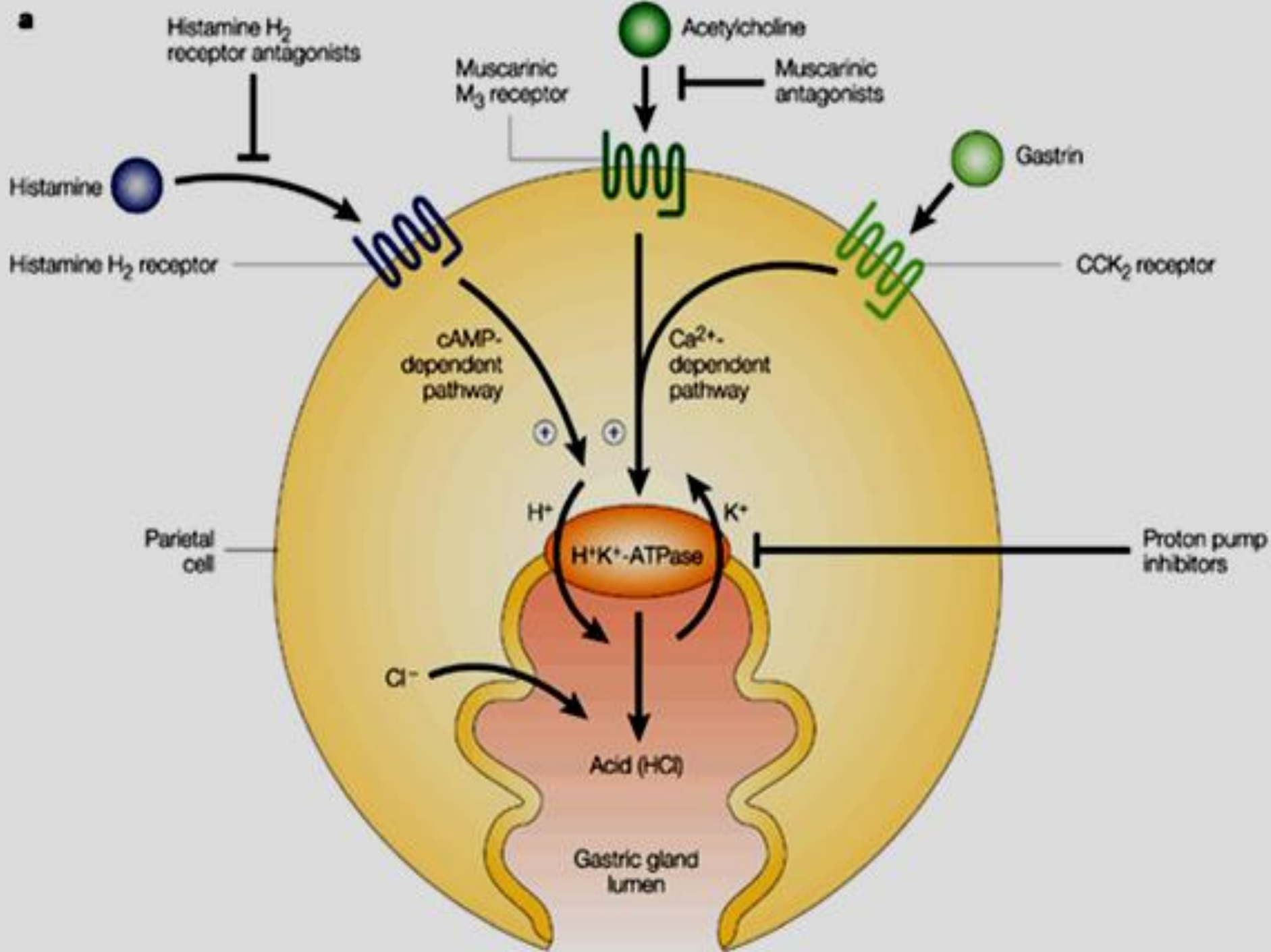
1. **HCl and intrinsic factor (Parietal cells).**
2. **Pepsinogens (Chief cells).**
3. **Mucus, bicarbonate (mucus-secreting cells).**

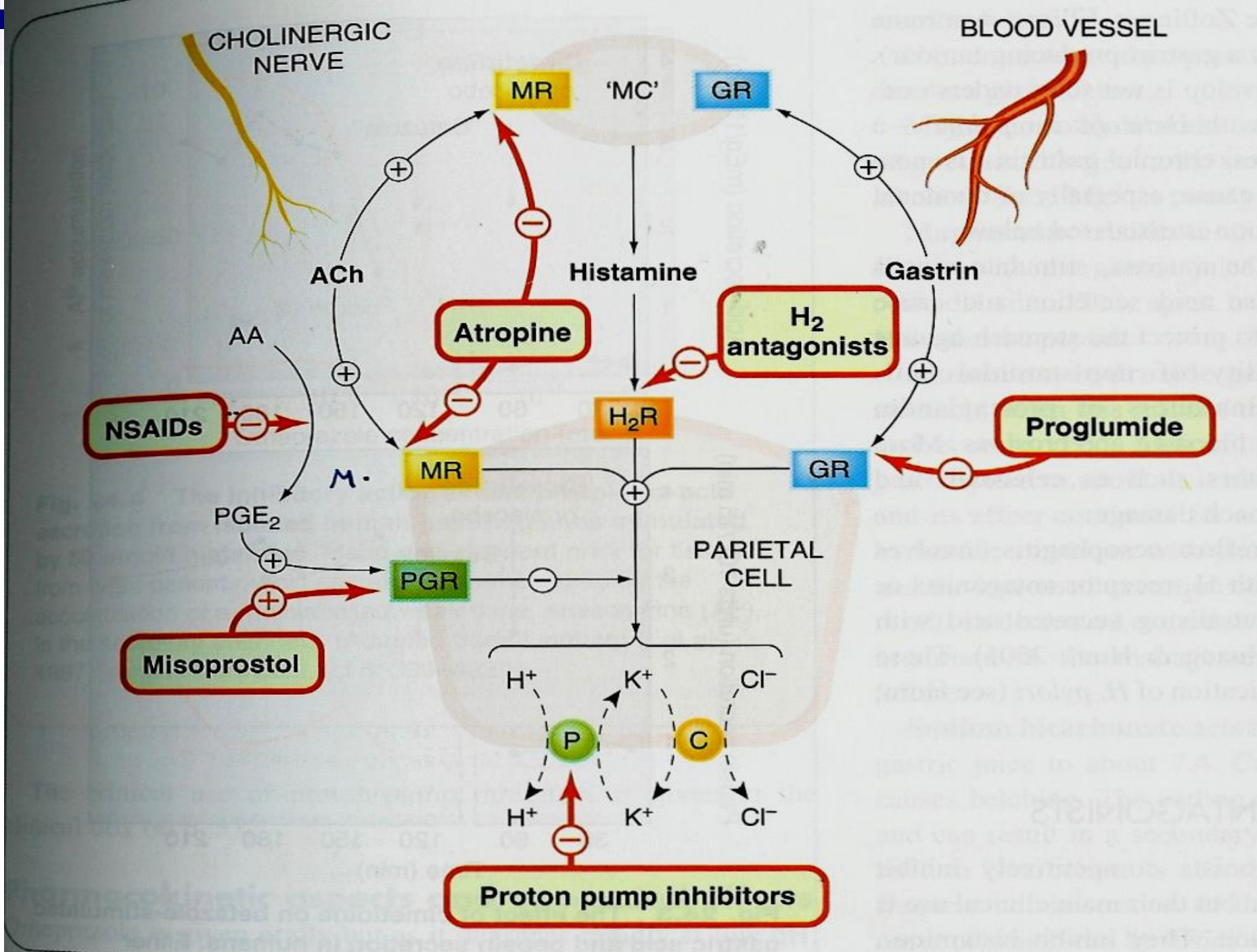
Regulation of gastric secretions

Parietal cells secrete acid in response to:

- 1. Histamine (local hormone): H_2 receptors**
- 2. Gastrin (hormone): CCK_2 receptors**
- 3. Ach (neurotransmitter): M_3 receptors**
- 4. Proton pump (H^+ / K^+ ATPase)**







Dicyclomine blocks the cholinergic receptor.

Cimetidine blocks the H_2 -histamine receptor.

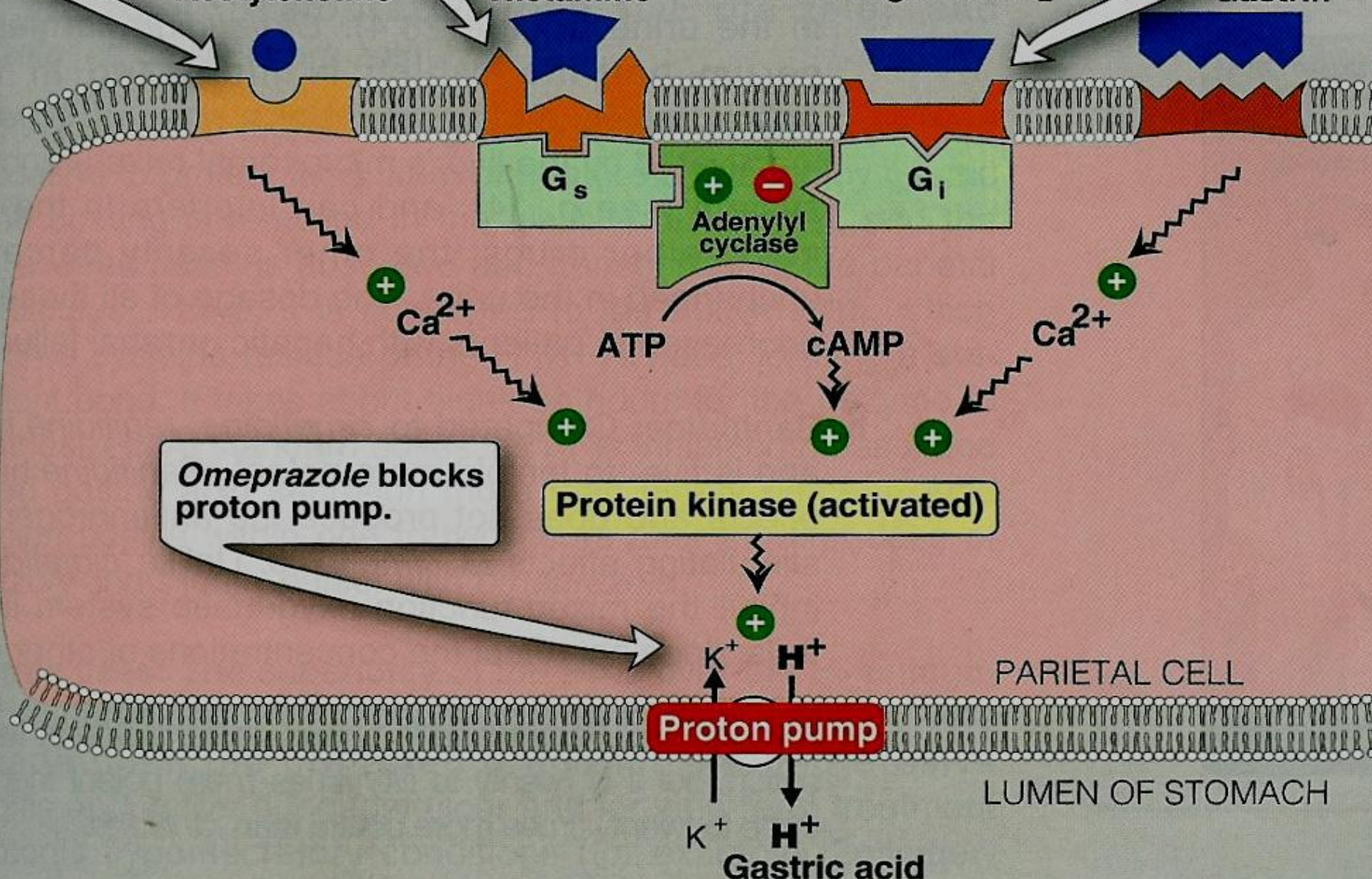
Misoprostol stimulates the prostaglandin receptor.

Acetylcholine

Histamine

Prostaglandin E_2

Gastrin



Omeprazole blocks proton pump.

Protein kinase (activated)

Proton pump

PARIETAL CELL

LUMEN OF STOMACH

K^+ H^+
 K^+ H^+
Gastric acid

Treatment of peptic ulcer

- Eradication of *H. pylori* infections
- Hyposecretory drugs.
 - Proton pump inhibitors
 - H₂ receptor blockers
 - Antimuscarinic drugs
- Mucosal cytoprotective agents.
 - Prostaglandin analogues
- Neutralizing agents (antacids).



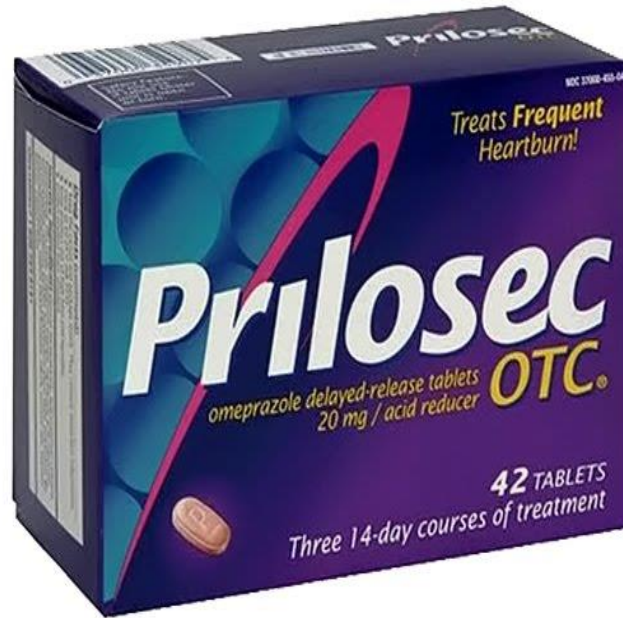
Gastric hyposecretory drugs

Hyposecretory drugs decrease gastric acid secretion → Promote healing & relieve pain.

Include:

- **Proton pump inhibitors**
- **H₂ receptor blockers**
- **Antimuscarinic drugs**

Proton Pump Inhibitor Drugs



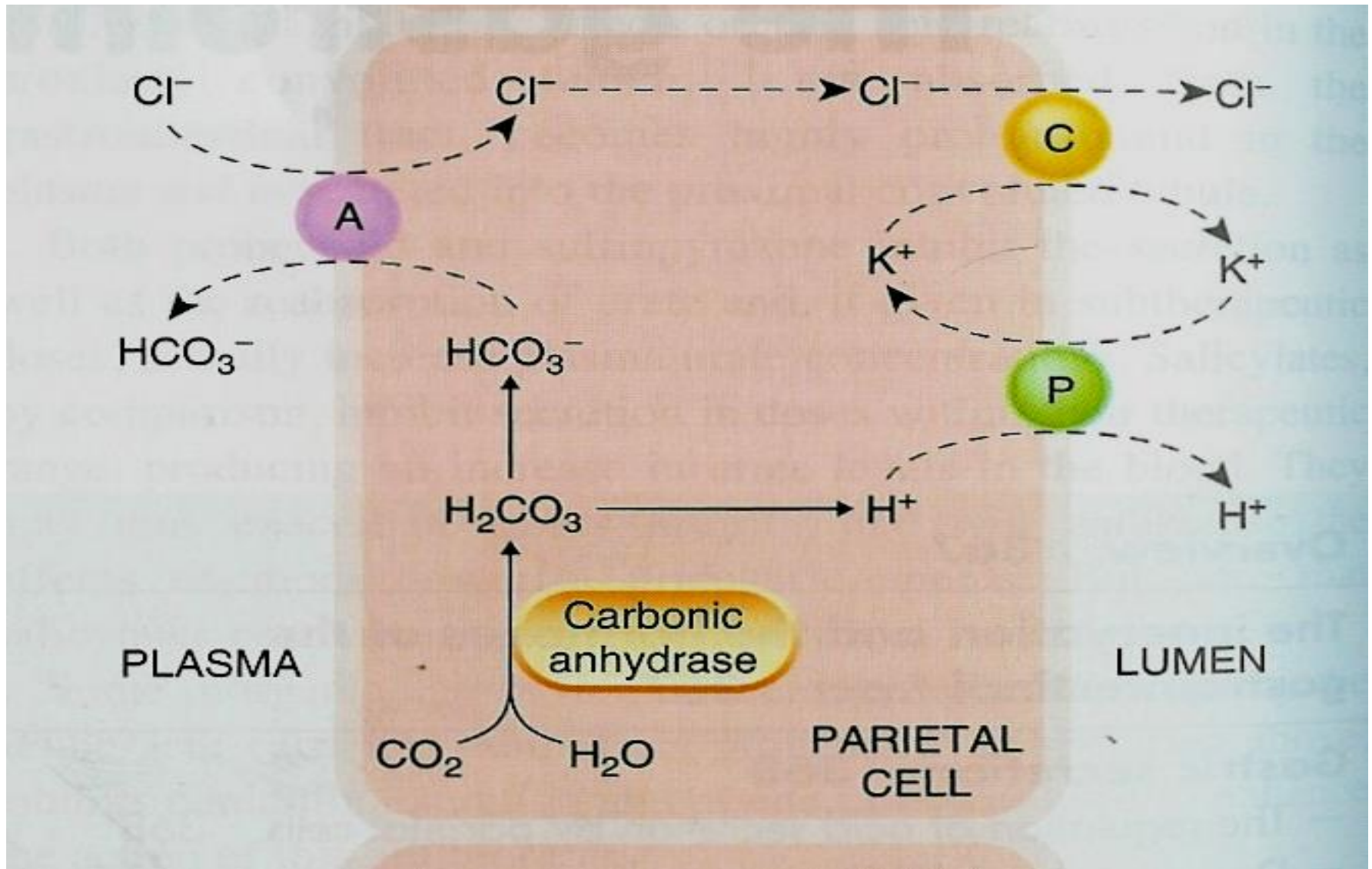
Proton Pump Inhibitors (PPIs)

Omeprazole – Lansoprazole

Pantoprazole -Raprazole

Acts by irreversible inhibition of proton pump (H⁺/ K⁺ ATPase) that is responsible for final step in gastric acid secretion from the parietal cell.

Gastric secretion by parietal cells




Pharmacodynamics

- They are **the most potent inhibitors** of acid secretion available today.
- Produce marked inhibition of basal & meal stimulated-acid secretion (90-98%).
- Reduce pepsin activity.
- Promote mucosal healing & decrease pain.
- Proton pump inhibitors heal ulcers faster than H₂ blockers, and have H. pylori inhibitory properties.

Pharmacokinetics of PPIs

- Given orally
- Are pro-drugs
- Given as enteric coated formulations
(unstable in acidic medium in stomach).
- Are rapidly absorbed from the intestine.
- Are activated within the acidic medium of parietal cell canaliculi.
- At neutral pH, PPIs are **inactivated**.
- Should not combined with H₂ blockers or antacids.

- 
- **Bioavailability is reduced by food.**
 - **Given one hour before the meal.**
 - **Have long duration of action (> 12 h-24 h).**
 - **Once daily dose is sufficient**
 - **Metabolized in the liver by Cyt-P450.**
 - **Dose reduction is required in severe liver failure.**

USES of PPIs

- **Eradication of *H. pylori* (combined with antimicrobial drugs).**
- **Resistant severe peptic ulcer (4-8 weeks).**
- **Reflux esophagitis.**
- **Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma (First choice).**

Zollinger Ellison syndrome

Gastrin -secreting tumor of the pancreas.

Gastrin produces:

- Parietal cell hyperplasia (trophic factor).
- Excessive gastric acid production.

Adverse effects to PPIs

- **CNS:** Headache
- **GIT:** Diarrhea & abdominal pain.
- Achlorhydria
- Hypergastrinaemia.
- **Gastric mucosal hyperplasia.**
 - Increased bacterial flora
 - Increased risk of community-acquired respiratory infections & nosocomial pneumonia
- **Long term use:**
 - Vitamin B₁₂ deficiency
 - Increased risk of hip fractures

H₂ receptor blockers

- **Cimetidine** - **Ranitidine**
- **Famotidine** - **Nizatidine**

Mechanism of action

They reversibly and competitively block H₂ receptors on the parietal cells.

Pharmacokinetics

- **Good oral absorption**
- **Given before meals.**
- **Famotidine is the most potent drug.**
- **Exposed to first pass metabolism (except nizatidine that has the greatest bioavailability)**
- **Duration of action (4-12 h).**
- **Metabolized by liver.**
- **Excreted mainly in urine.**

CIMETIDINE**RANITIDINE****FAMOTIDINE****NIZATIDINE**

Efficacy	+++	++ +	+++	+++
Potency	+	++	+++	++
Dose	400 mg bid	150 mg bid	20mg bid	150 mg bid
Route	orally, IV	orally, IV	orally, IV	orally
T 1/2	short (2 h)	longer (3h)	longer (3h)	shortest (1
Duration	5-6 h	10 h	12 h	11 h
CYT P 450	++	-	-	-
Antiandrogenic	++	-	-	-
Drug interactions	many	No	No	No

Pharmacological actions:

- **Reduce basal and food stimulated-acid secretion**
- **Block 90% of nocturnal acid secretion (which depend largely on histamine) & 60-70% of total 24 hr acid secretion. Therefore, it is better to be given before night sleep.**
- **Reduce pepsin activity.**
- **Promote mucosal healing & decrease pain**

Uses:

- **GERD (heartburn/ dyspepsia).**
- **Acute ulcer healing in moderate cases**
 - **Duodenal Ulcer (6-8 weeks).**
 - **Benign gastric ulcer (8-12 weeks).**
- **Pre-anesthetic medication (to prevent aspiration pneumonitis).**
- **Prevention of bleeding from stress-related gastritis.**
- **Post-ulcer healing maintenance therapy.**

Adverse effects of H₂ blockers

- **GIT disturbances: Nausea & vomiting.**
- **CNS effects: Headache - confusion**
(elderly, hepatic dysfunction, renal dysfunction).
- **Bradycardia and hypotension (rapid I.V.)**
- **CYT-P450 inhibition (Only Cimetidine)**
decrease metabolism of warfarin, phenytoin,
benzodiazepines.

Endocrine effects (**Only Cimetidine**)

- **Galactorrhea** (Hyperprolactinemia)
- **Antiandrogenic actions** (gynecomastia – impotence) due to inhibition of dihydrotestosterone binding to androgen receptors.

Precautions

Dose reduction of H₂ receptor blockers in severe renal or hepatic failure and elderly.

Prostaglandin analogues

Misoprostol

- Prostaglandin analogues (PGE1)
- ↓ HCL secretion.
- ↑ protective measures (↑ mucous/bicarbonate & gastric mucosal blood flow).
- Orally, must be taken 3-4 times/day.
- Used for NSAIDS-induced peptic ulcer.

Adverse effects:

- Abdominal cramps; diarrhea.
- Uterine contraction (dysmenorrhea or abortion).
- Vaginal bleeding.

Antacids

These drugs are mainly **inorganic salts**

e.g.: NaHCO_3 ; CaCO_3 ; $\text{Al}(\text{OH})_3$; $\text{Mg}(\text{OH})_2$

- acts by direct chemical neutralization of HCL and as a result may decrease pepsin activity.
- used to relief pain of peptic ulcer & for dyspepsia.
- All antacids ↓ absorption of some drugs as tetracycline, fluoroquinolones, iron.

NaHCO_3 (Sodium bicarbonate):

Effective, but systemic alkalosis may occur.

Contraindicated in CVS patients

Aluminum hydroxide:

- **Constipation**
- **Systemic phosphate depletion (weakness, malaise, anorexia)**

Magnesium hydroxide:

- **Diarrhea**
- **Magnesium trisilicate-- slow-acting antacid**

Calcium carbonate

- **Milk-alkali syndrome**
- **Hypercalcemia**
- **Renal failure**

Summary

- Test for *H. pylori* prior to beginning therapy.
- Acid-reducing medications are prescribed in case of PUD **without *H. pylori* infections.**
- Acid-reducing medications for PUD include:
 - H₂ receptor blockers
 - PPIs should be used for acute therapy only if H₂RAs fail or cannot be used, or as part of treatment for *H. pylori*.
- Complete *H. pylori* eradication is required to prevent relapse.
- **PUD with *H. pylori* infections can be treated with** triple therapy or quadruple therapy