

# H<sub>2</sub> blockers and proton pump inhibitors

A golden, stylized figure with a large head and thin limbs is holding a large, white, rounded rectangular sign with a gold border. The sign contains the text 'Peptic Ulcer'. The figure is positioned behind the sign, with its arms raised to hold it.

**Peptic Ulcer**

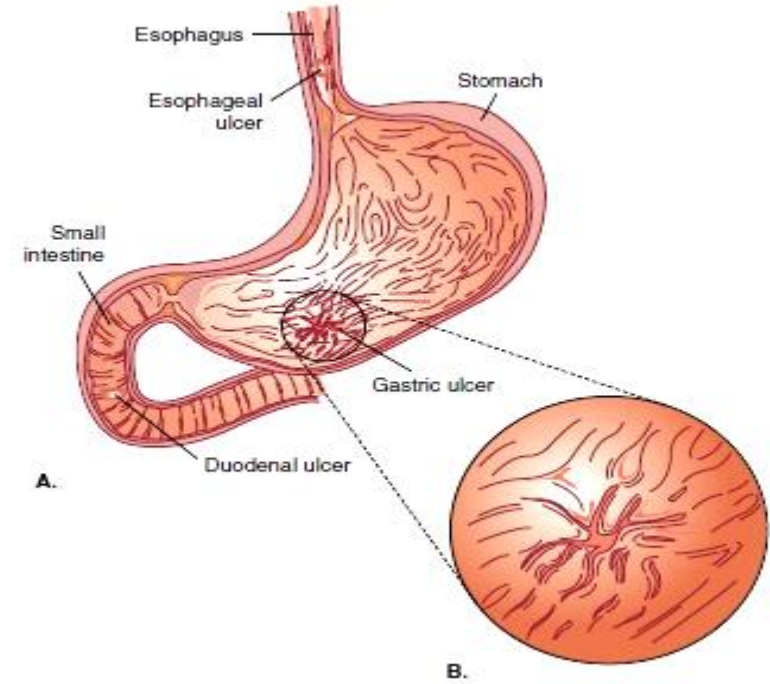
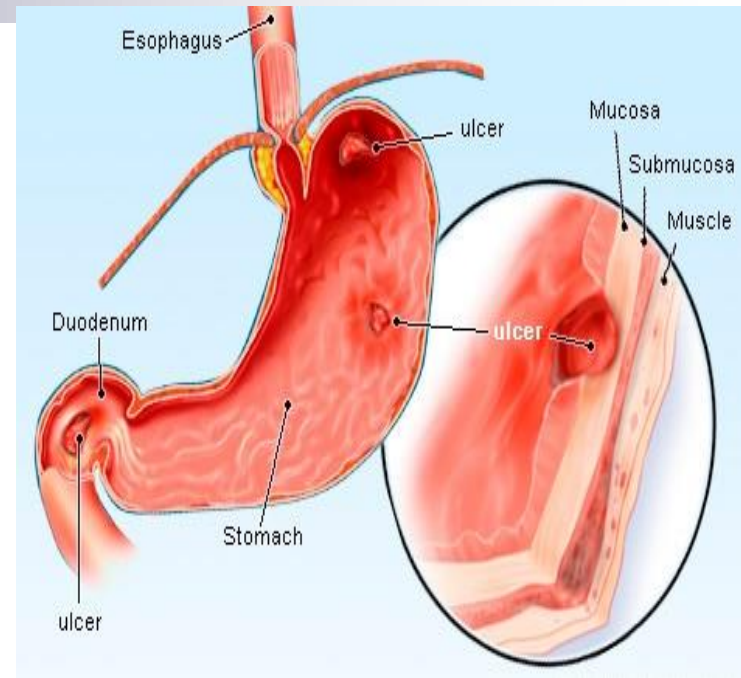
*By*  
*Prof. Hanan Hagar*

## 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.



# Peptic Ulcer Disease

**NORMAL**

**INCREASED AGGRESSION**

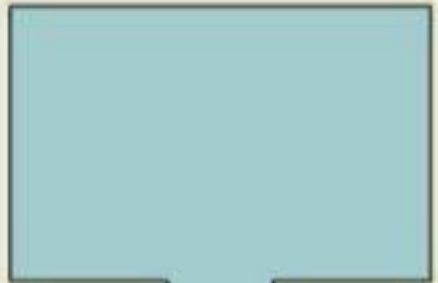
**IMPAIRED DEFENSE**

**Aggressive Forces:**

Gastric acidity  
Peptic activity

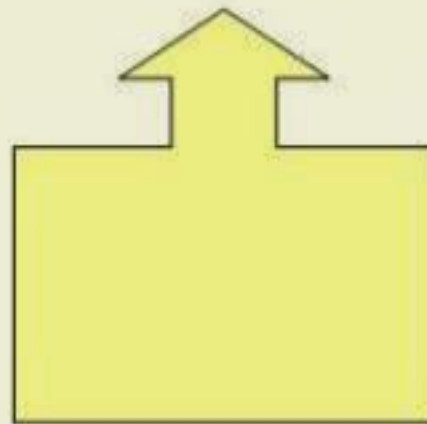
**Aggravating Causes:**

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



**Defensive Forces:**

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



**Impaired Defense:**

Ischemia, shock  
Delayed gastric emptying  
Duodenal-gastric reflux

# Pathophysiology:

## Aggressive factors

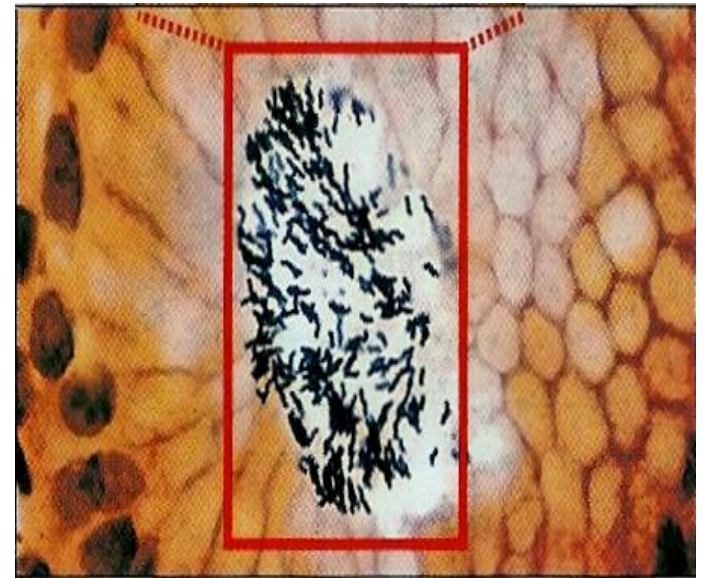
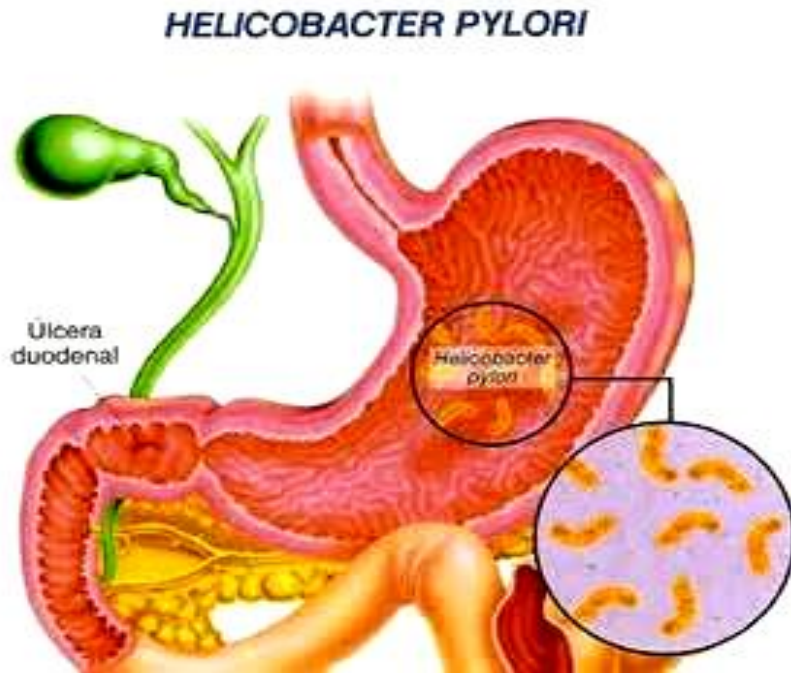
1. **Hydrochloric acid and pepsin** destroy gastric and duodenal mucosa.

## Defensive factors

1. **Mucus and bicarbonate** ion secretions protect mucosa
2. **Prostaglandins** ( $\text{PGE}_2$  &  $\text{PGI}_2$ ) protect mucosa by:
  - inhibiting acid secretion
  - increasing mucus and bicarbonate production
  - enhancing mucosal blood flow.

# Pathophysiology:

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



## **Etiology:**

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

# TREATMENT OF PEPTIC ULCER

- **Eradication of *H. pylori* infections**
- **Hyposecretory drugs.**
- **Mucosal cytoprotective agents.**





# Gastric secretions

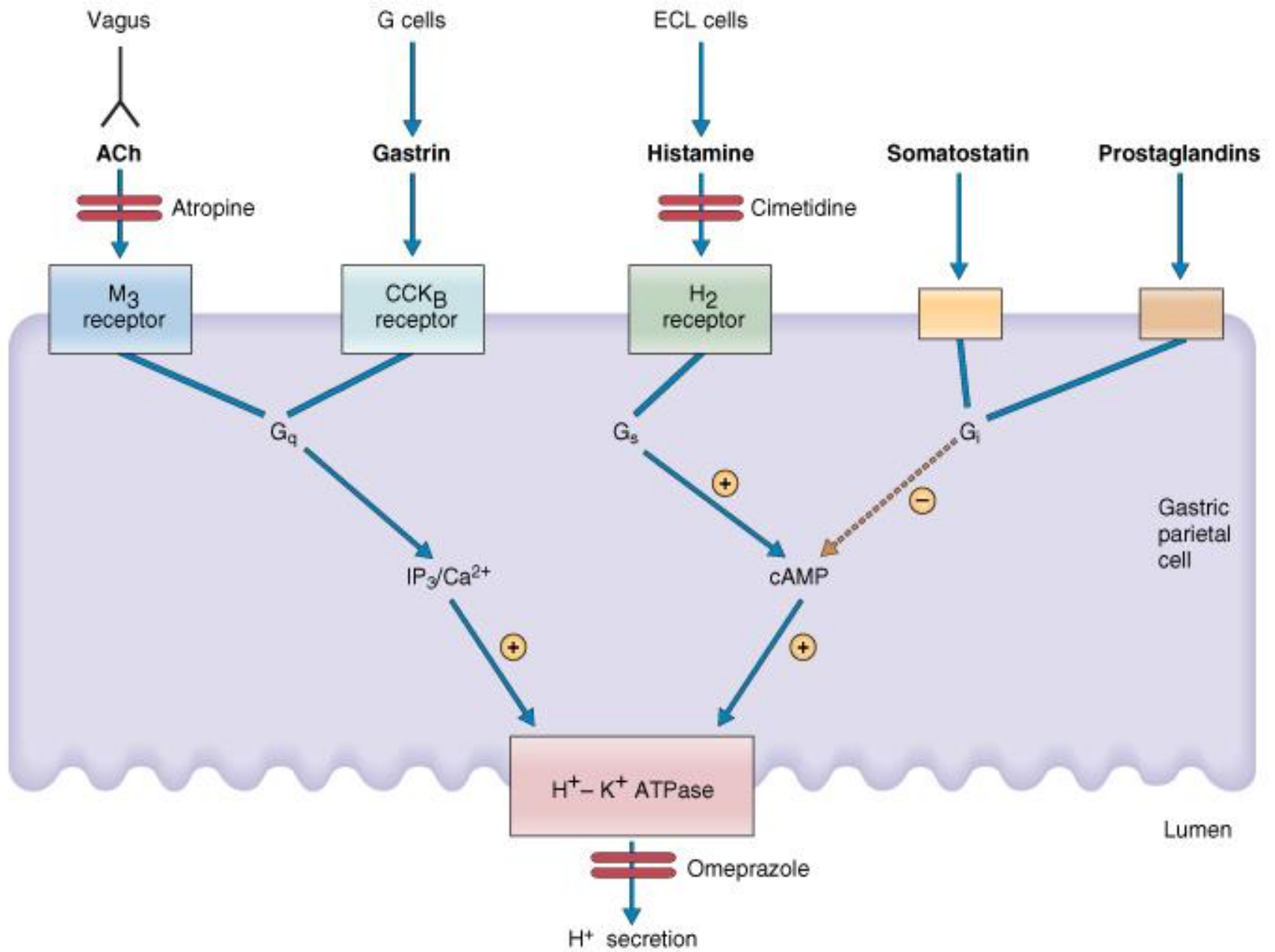
1. **HCl and intrinsic factor (Parietal cells).**
2. **Pepsinogens (Chief cells).**
3. **Mucus, bicarbonate (mucus-secreting cells).**

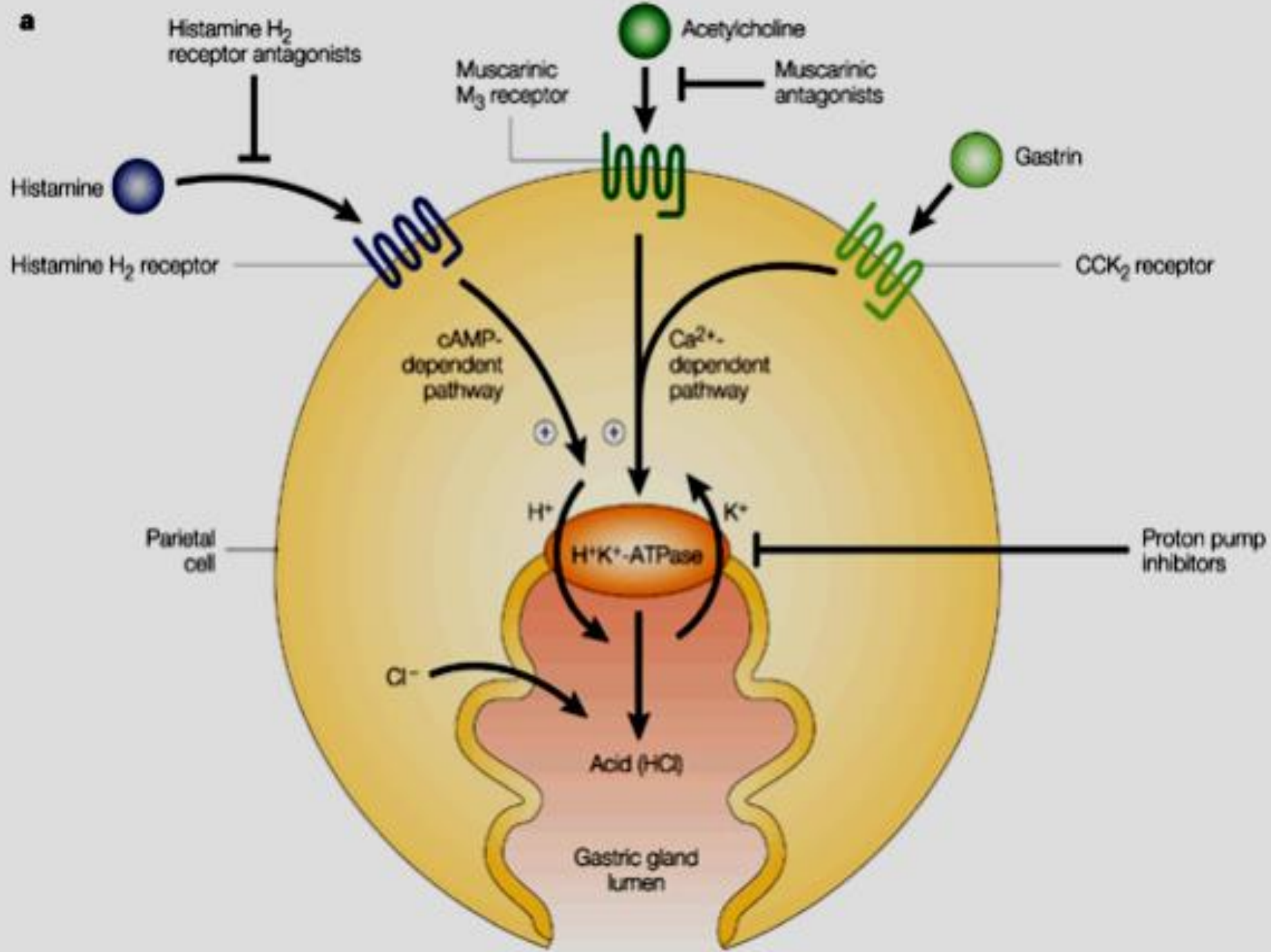


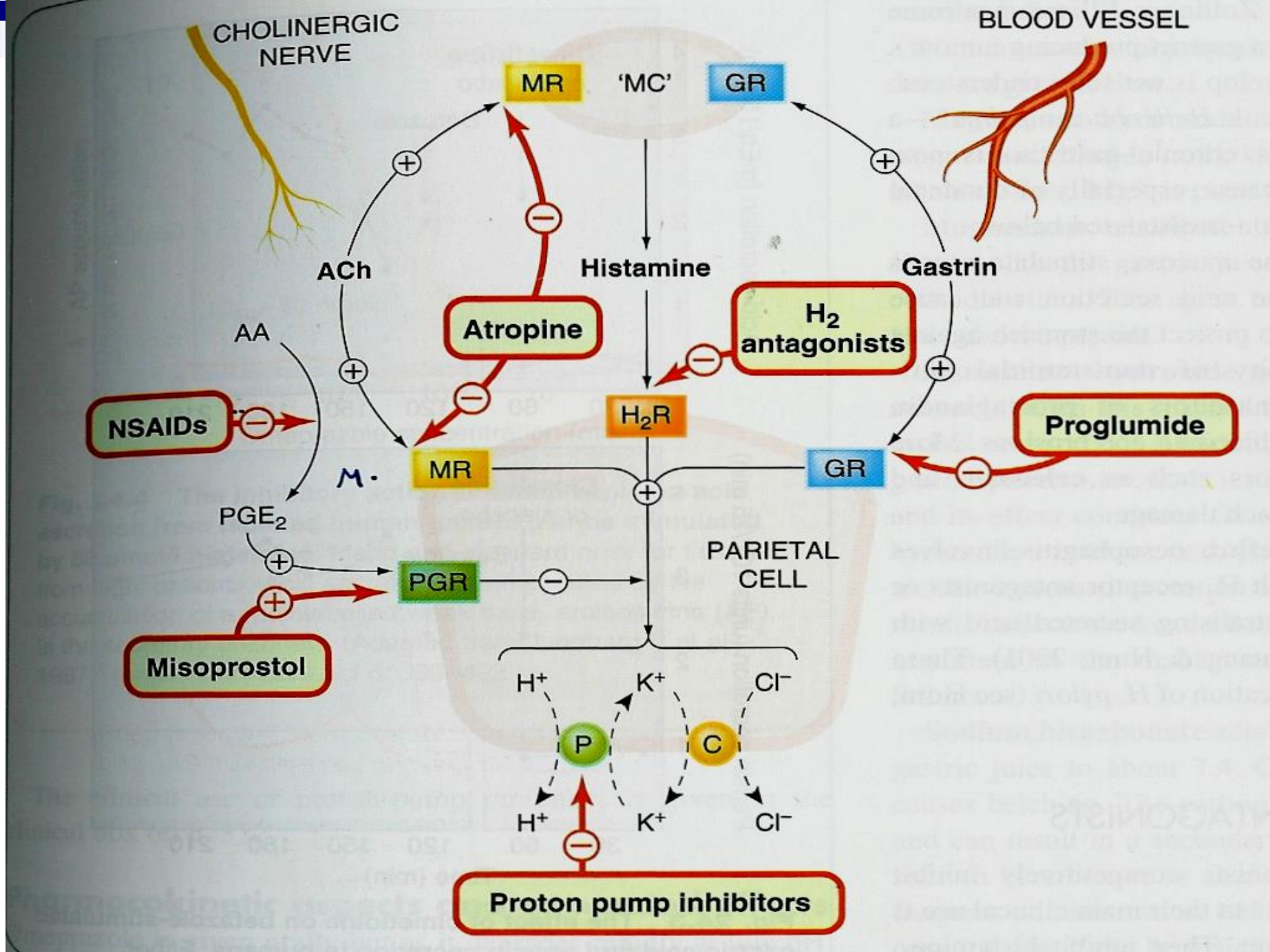
# Regulation of gastric secretions

## Parietal cells secrete acid in response to:

1. **Ach (neurotransmitter): M<sub>3</sub> receptors**
2. **Gastrin (hormone): CCK<sub>2</sub> receptors  
(cholecystokinin)**
3. **Histamine (local hormone): H<sub>2</sub> receptors**
4. **Proton pump (H<sup>+</sup>/ K<sup>+</sup> ATPase)**









*Dicyclomine* blocks the cholinergic receptor.

*Cimetidine* blocks the  $H_2$ -histamine receptor.

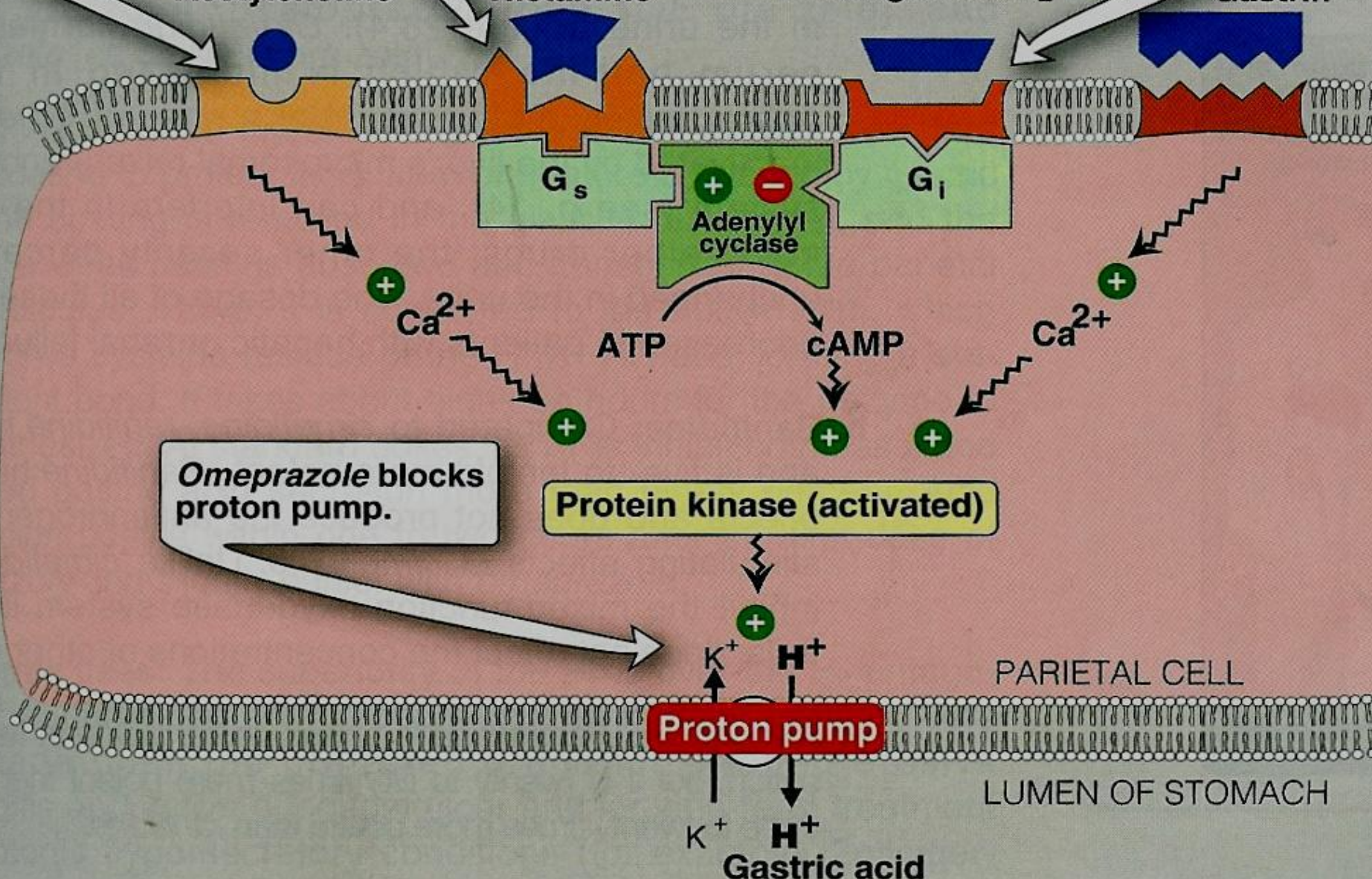
*Misoprostol* stimulates the prostaglandin receptor.

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**
  - **H<sub>2</sub> 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
- H<sub>2</sub> receptor blockers
- Antimuscarinic drugs

# Proton Pump Inhibitor Drugs



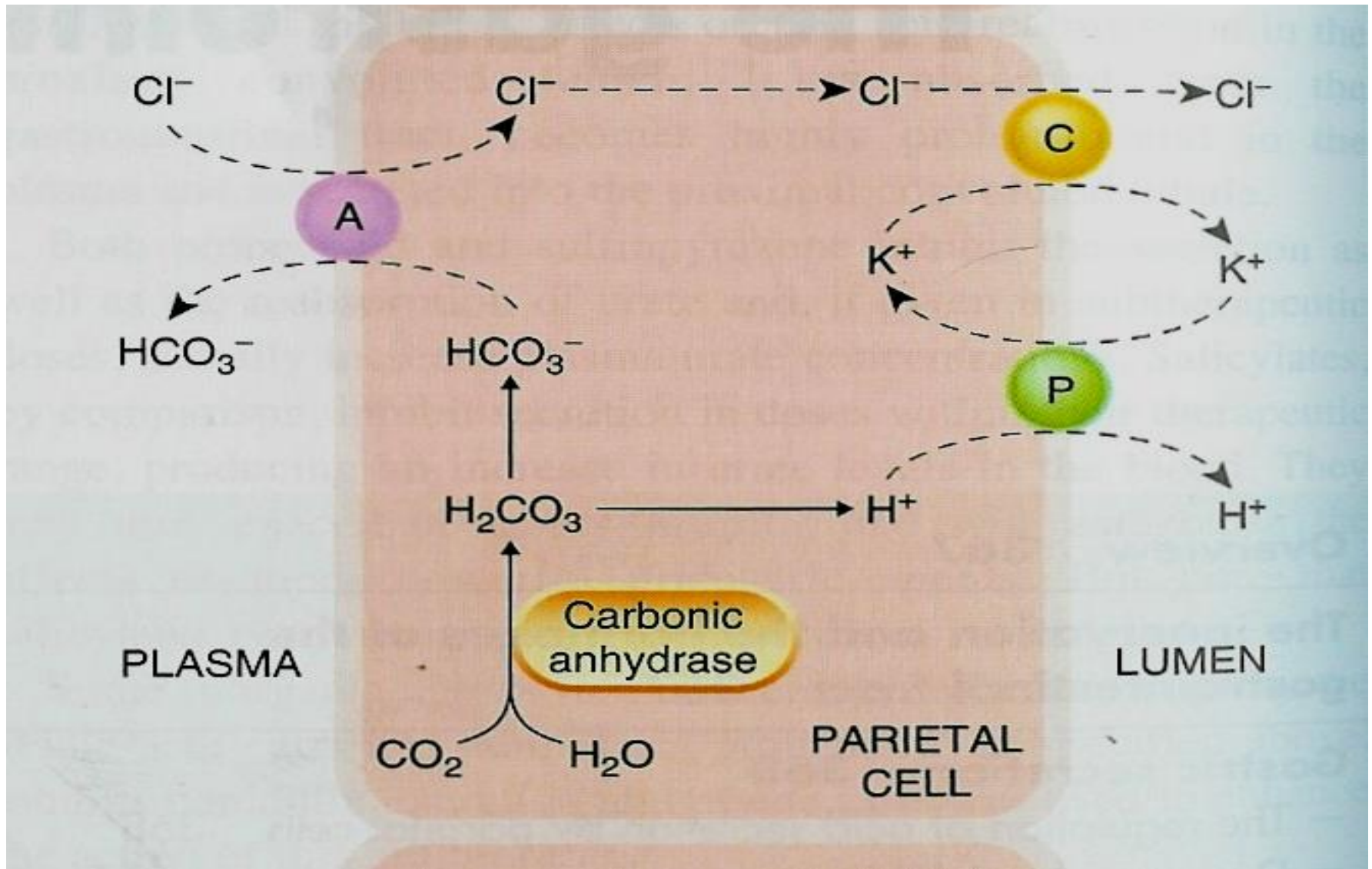
# Proton Pump Inhibitors (PPIs)

**Omeprazole – Lansoprazole**

**Pantoprazole -Raprazole**

**Acts by irreversible inhibition of proton pump (H<sup>+</sup>/ K<sup>+</sup> ATPase) that is responsible for final step in gastric acid secretion from the parietal cell (they covalently bind to the pump).**

# Gastric secretion by parietal cells





# Pharmacodynamics

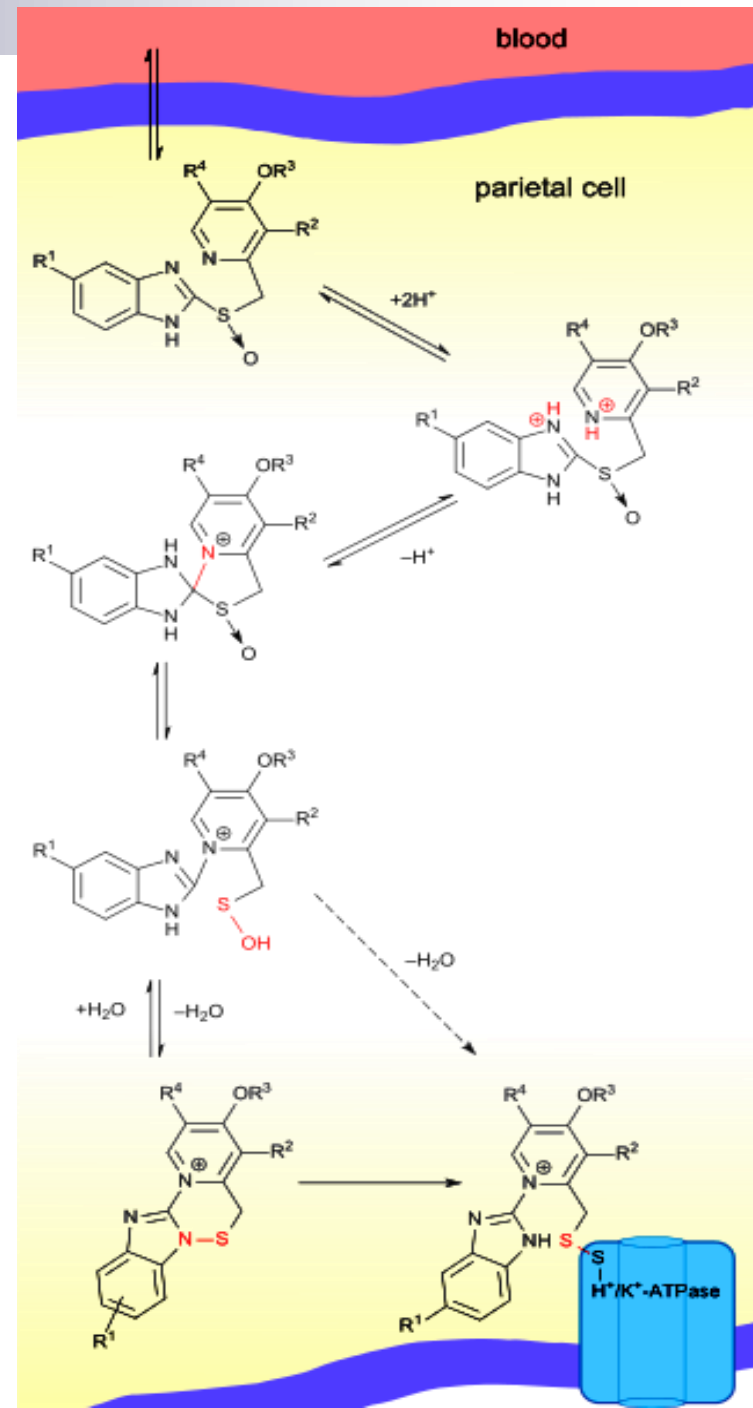
- They are **the most potent inhibitors** of acid secretion available today.
- Produce marked inhibition of basal & meal stimulated-acid secretion (90-98%).
- Reduce pepsin activity.
- Promote mucosal healing & decrease pain.
- Proton pump inhibitors heal ulcers faster than H<sub>2</sub> blockers, and 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 H<sub>2</sub> blockers or antacids.



# Activation of Proton Pump Inhibitors In Parietal cell



- 
- **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).**
- **Gastroesophageal reflux disease (GERD).**
- **Hypersecretory conditions as Zollinger Ellison syndrome and gastrinoma (First choice).**

# Zollinger Ellison syndrome

is a disease in which tumors cause the stomach to produce too much acid, resulting in peptic ulcers. Symptoms include abdominal pain and diarrhea.

## Gastrin produces:

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

# Adverse effects to PPIs

- **CNS:** Headache
- **GIT:** Diarrhea & abdominal pain.
- Achlorhydria & hypergastrinaemia.
- **Gastric mucosal hyperplasia.**
- **Infection**
  - Increased bacterial flora
  - Increased risk of community-acquired respiratory infections & nosocomial pneumonia

## Long term use may lead to

- Vitamin B<sub>12</sub> deficiency
- Hypomagnesaemia
- Osteoporosis

# Adverse effects to PPIs

- Precaution should be given not to combine omeprazole (**CYP2C19 inhibitor**) and clopidogrel (CYP2C19 is required for activation of clopidogrel).



# H<sub>2</sub> receptor blockers

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

## Mechanism of action

They reversibly and competitively block H<sub>2</sub> 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**

<b>Efficacy</b>	+++	++ +	+++	+++
<b>Potency</b>	+	++	+++	++
<b>Dose</b>	400 mg bid	150 mg bid	20mg bid	150 mg bid
<b>Route</b>	orally, IV	orally, IV	orally, IV	orally
<b>T 1/2</b>	short (2 h)	longer (3h)	longer (3h)	shortest (1
<b>Duration</b>	5-6 h	10 h	12 h	11 h
<b>CYT P 450</b>	++	-	-	-
<b>Antiandrogenic</b>	++	-	-	-
<b>Drug interactions</b>	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).
- **Prevention of bleeding from stress-related gastritis.**
- **Pre-anesthetic medication (to prevent aspiration pneumonitis).**
- **Post-ulcer healing maintenance therapy.**

# Adverse effects of H<sub>2</sub> 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 H<sub>2</sub> 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.:  $\text{NaHCO}_3$ ;  $\text{CaCO}_3$ ;  $\text{Al}(\text{OH})_3$ ;  $\text{Mg}(\text{OH})_2$

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

**$\text{NaHCO}_3$  (Sodium bicarbonate):**

Effective, but systemic alkalosis may occur.

\* Contraindicated in CVS patients

## **Aluminum hydroxide:**

- Constipation
- Hypophosphatemia (weakness, malaise, anorexia)
- Seizure

## **Magnesium hydroxide:**

- Diarrhea
- Hypotension & Cardiac arrest

## **Calcium carbonate**

- Milk-alkali syndrome
- Hypercalcemia
- Renal failure
- ↓ absorption of tetracycline

# 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:
  - H<sub>2</sub> receptor blockers
  - PPIs should be used for acute therapy only if H<sub>2</sub>RAs 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