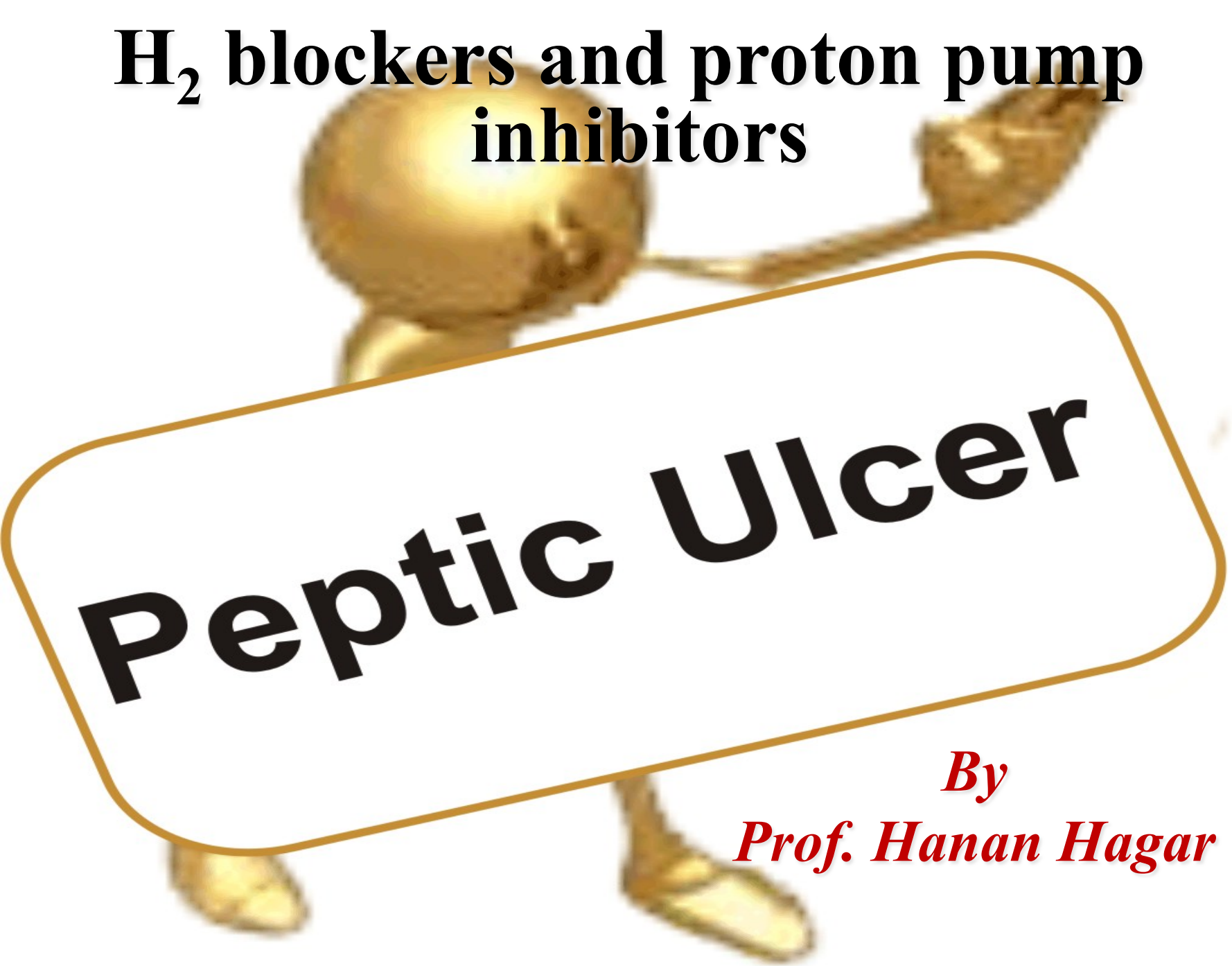
H_2 blockers and proton pump inhibitors



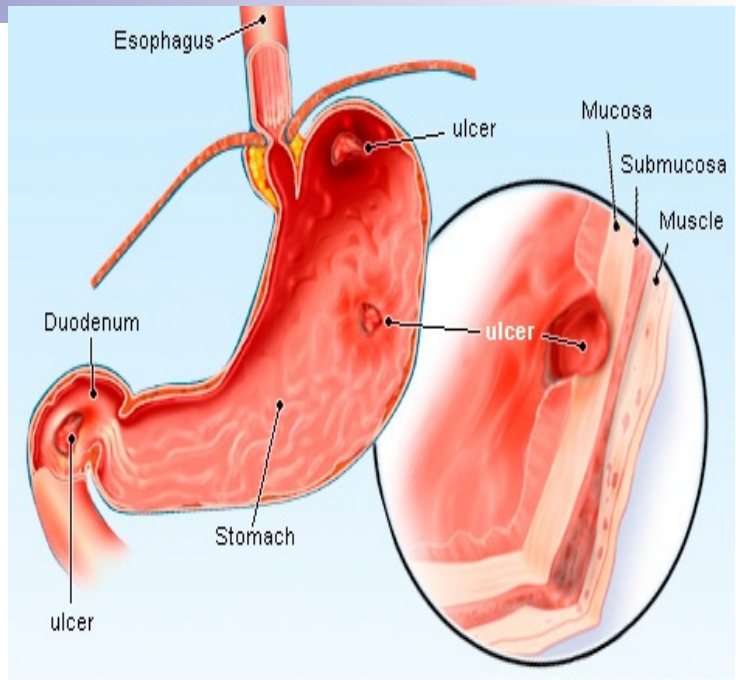
By
Prof. Hanan Hagar

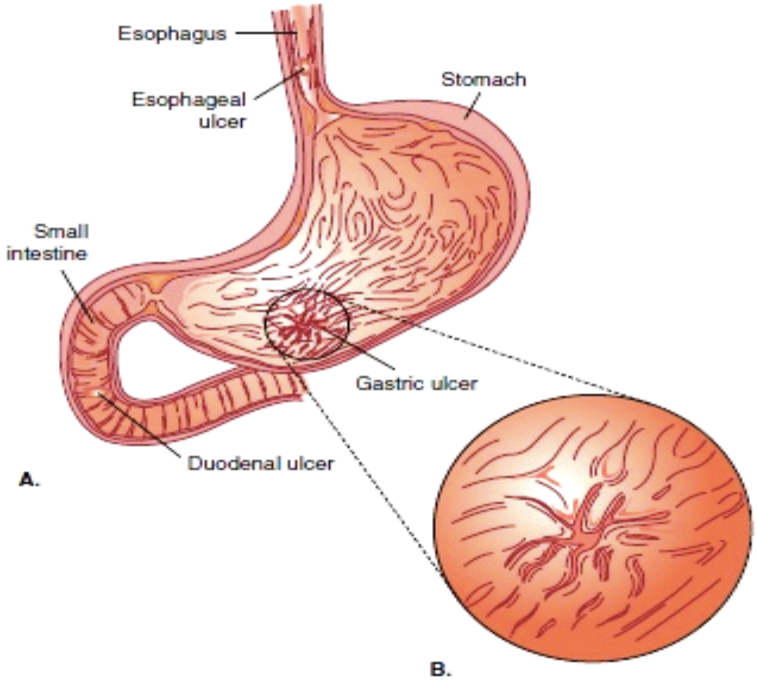
Objectives:

- Understand the key points of pathophysiology of the peptic ulcer disease
- Enumerate various classes of dugs 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 relief 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.



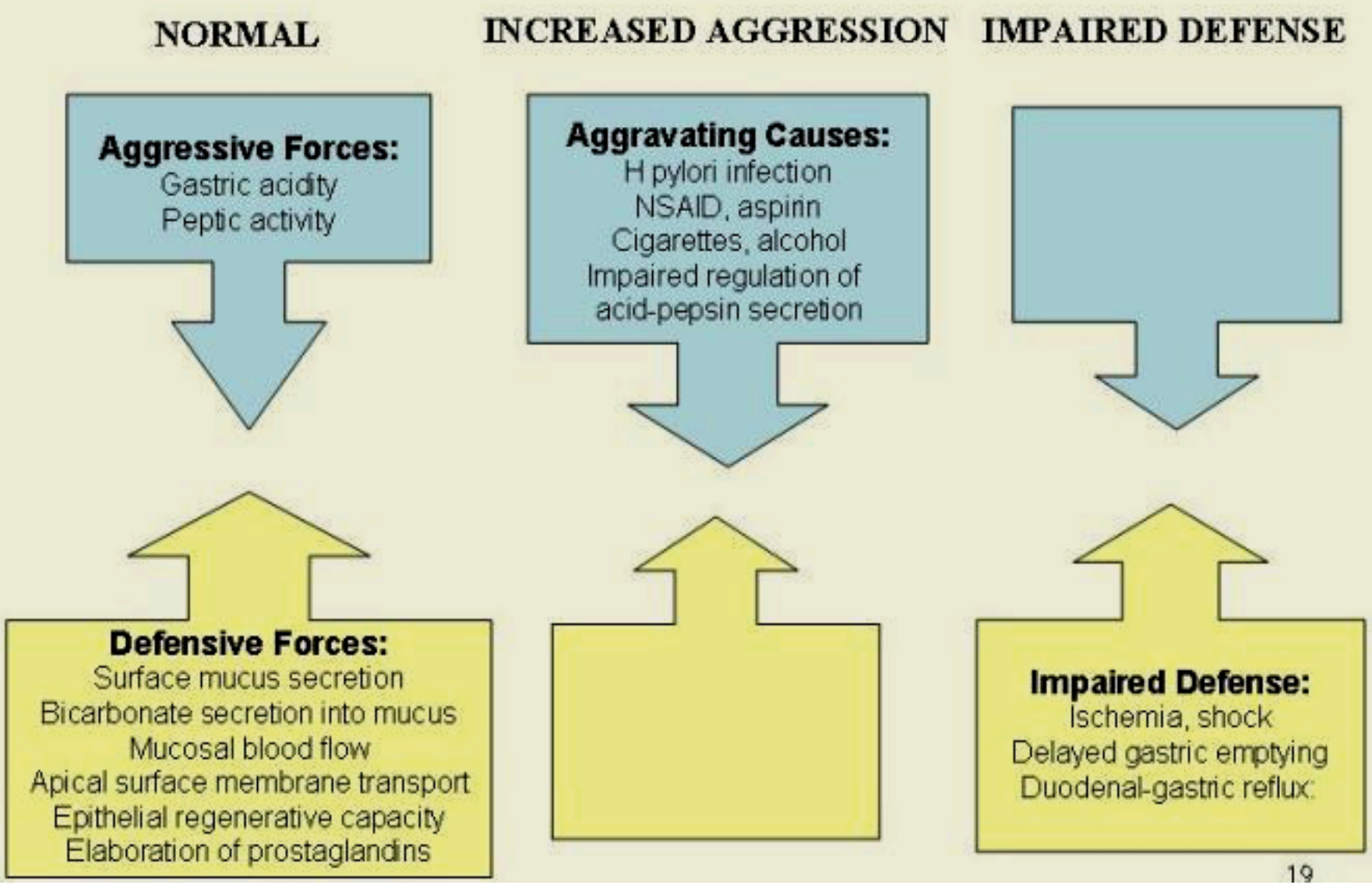


Pathophysiology:

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



Pathophysiology:

Aggressive factors

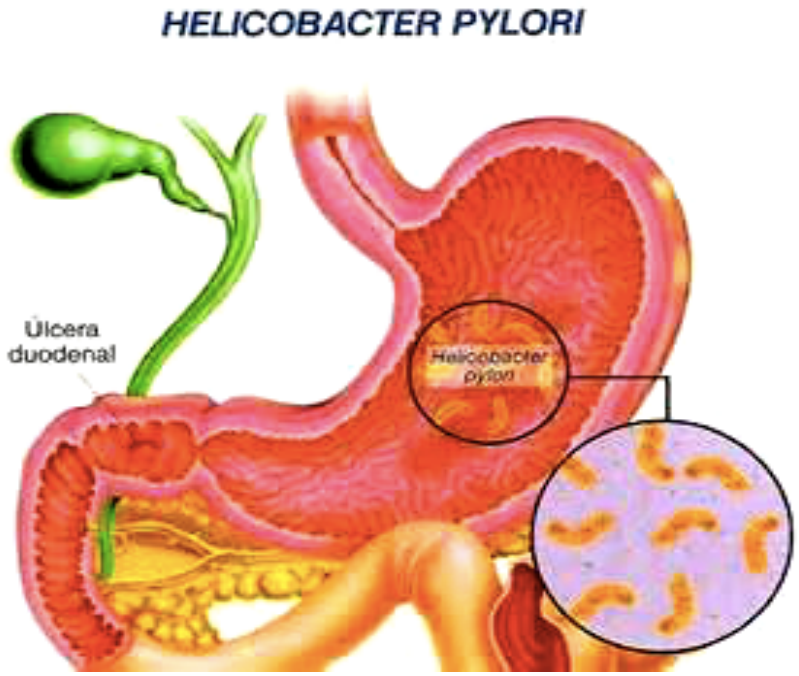
1. **Hydrochloric acid and pepsin** destroy gastric and duodenal mucosa.

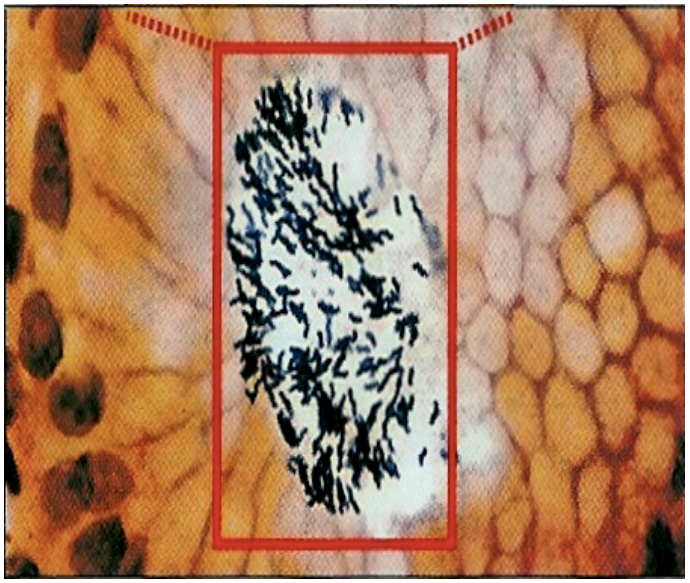
Defensive factors

1. **Mucus and bicarbonate** ion secretions protect mucosa
2. **Prostaglandins** (PGE_2 & 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.**

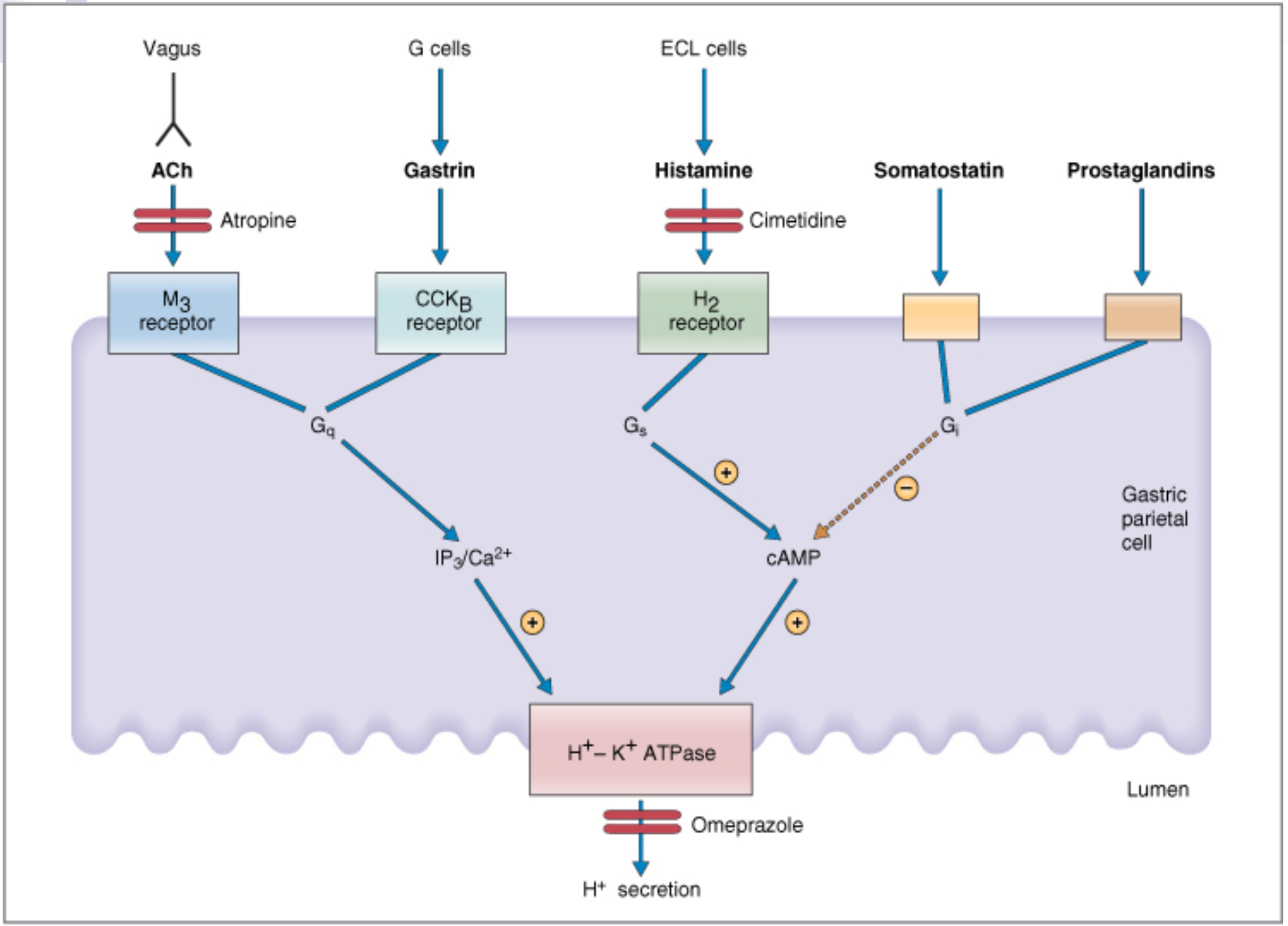
Gastric secretions

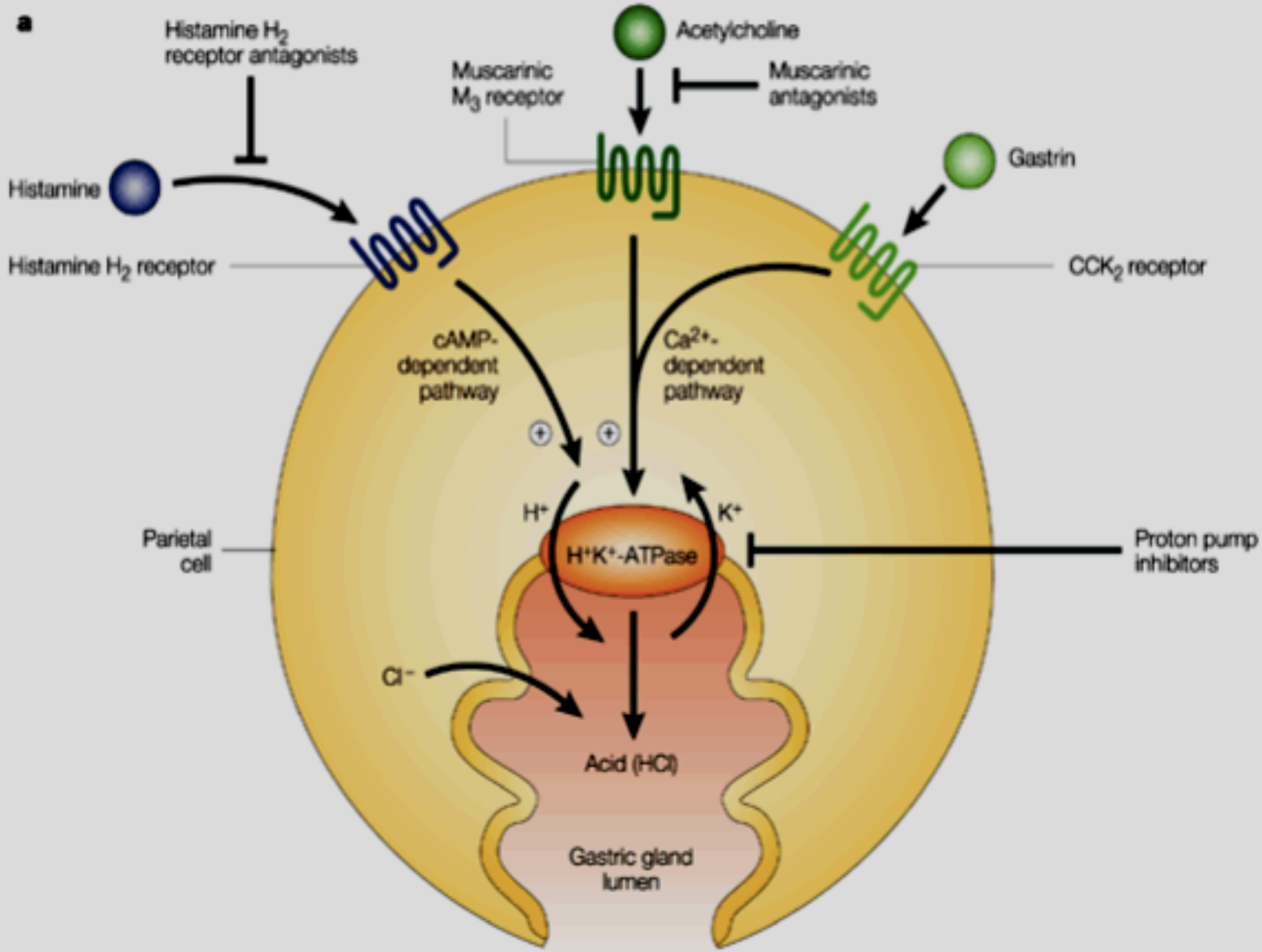
1. **HCl and intrinsic factor (Parietal cells).**
2. **Pepsinogens (Chief cells).**
3. **Mucus, bicarbonate (mucus-secreting cells).**

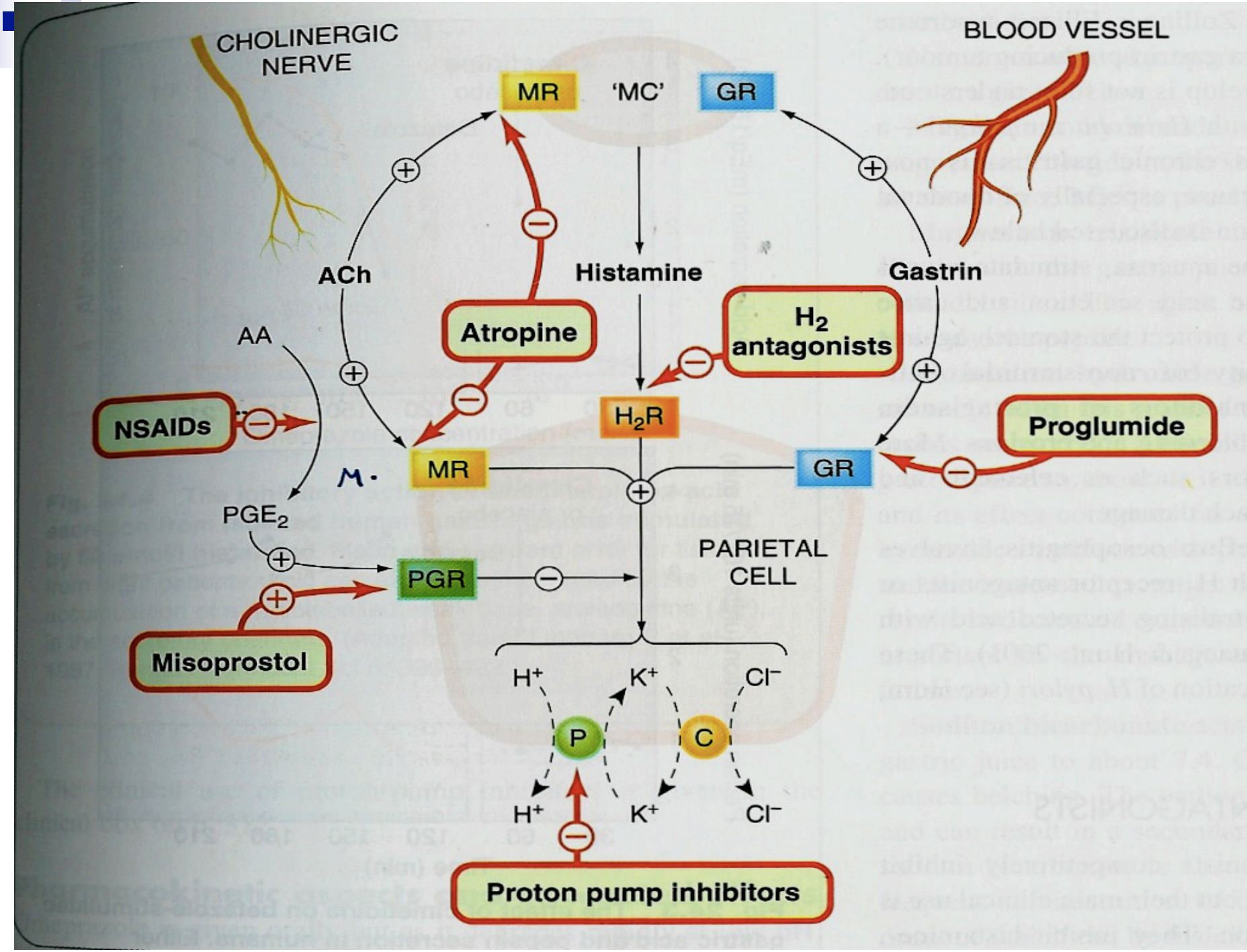
Regulation of gastric secretions

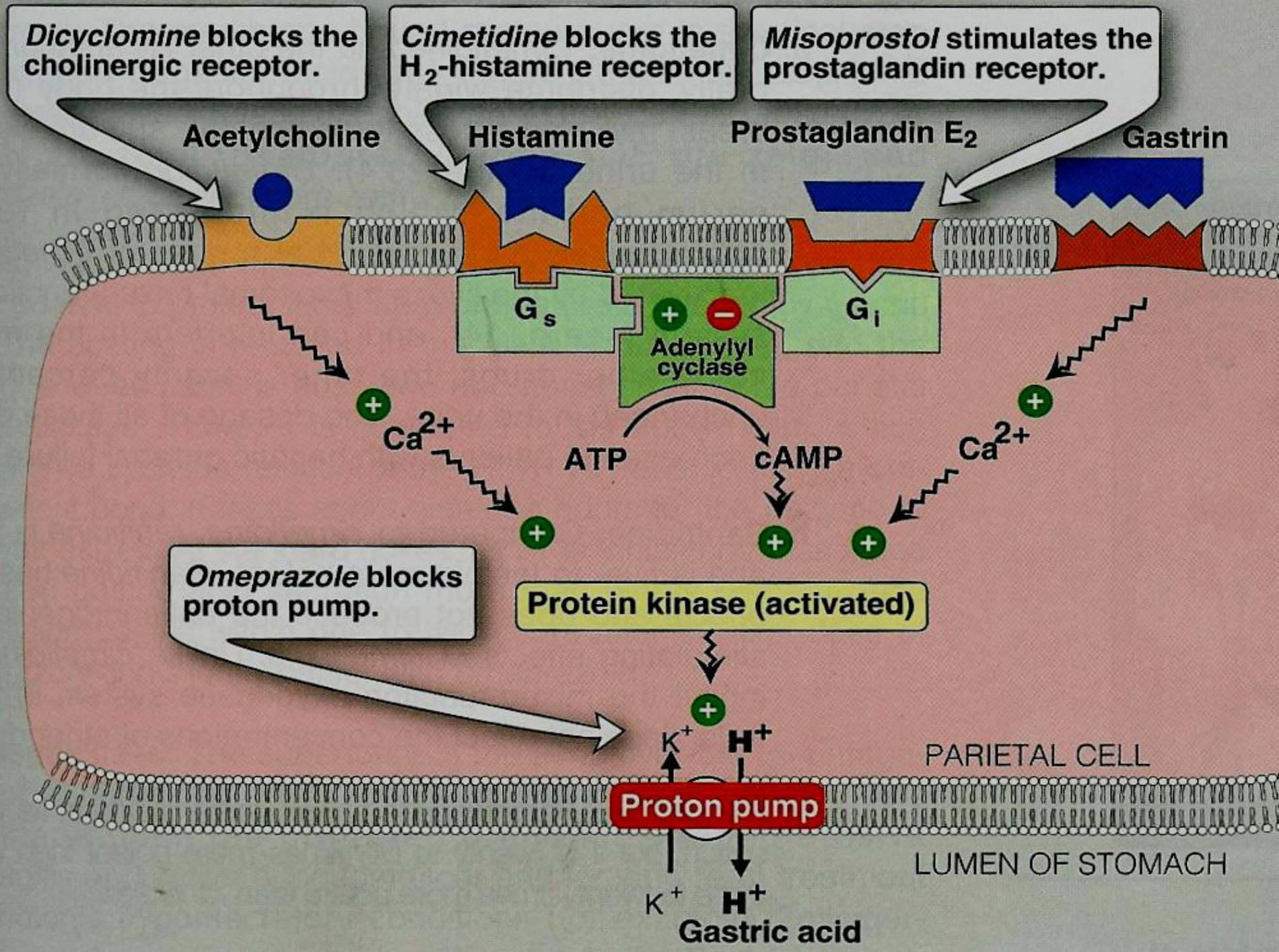
Parietal cells secrete acid in response to:

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




a
Histamine H_2 receptor antagonists
Acetylcholine
Muscarinic M_3 receptor
Muscarinic antagonists
Gastrin
Histamine
Histamine H_2 receptor
CCK_2 receptor
cAMP-dependent pathway
Ca^{2+}-dependent pathway
H^+
K^+
H^+K^+-ATPase
Parietal cell
Proton pump inhibitors
Cl^-
Acid (HCl)
Gastric gland lumen


CHOLINERGIC NERVE
BLOOD VESSEL
MR
'MC'
GR
ACh
Histamine
Gastrin
Atropine
H2 antagonists
AA
NSAIDs
H2R
Proglumide
MR
GR
PGE2
PARIETAL CELL
PGR
Misoprostol
H+
K+
Cl−
P
C
H+
K+
Cl−
Proton pump inhibitors


Dicyclomine blocks the cholinergic receptor.
Cimetidine blocks the H_2-histamine receptor.
Misoprostol stimulates the prostaglandin receptor.
Acetylcholine
Histamine
Prostaglandin E_2
Gastrin
G_s
G_i
Adenylyl cyclase
Ca^{2+}
ATP
cAMP
Ca^{2+}
Omeprazole blocks proton pump.
Protein kinase (activated)
K^+
H^+
PARIETAL CELL
Proton pump
LUMEN OF STOMACH
K^+
H^+
Gastric acid

Treatment of peptic ulcer

- Eradication of H. pylori infections
- Hyposecretory drugs.
  - Proton pump inhibitors
  - H_2 receptor blockers
  - Antimuscarinic drugs
- Mucosal cytoprotective agents.
  - Prostaglandin analogues
- Neutralizing agents (antacids).

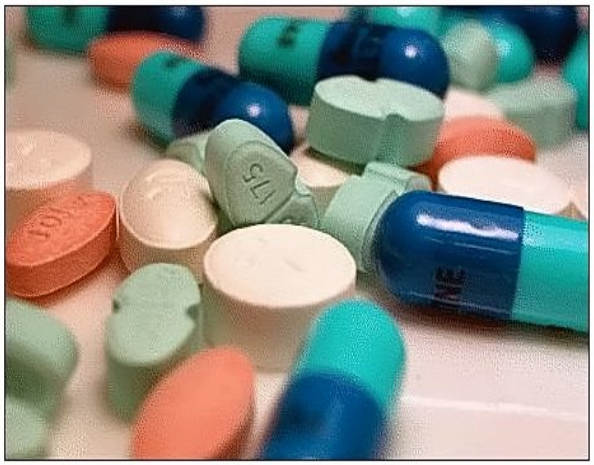
Gastric hyposecretory drugs

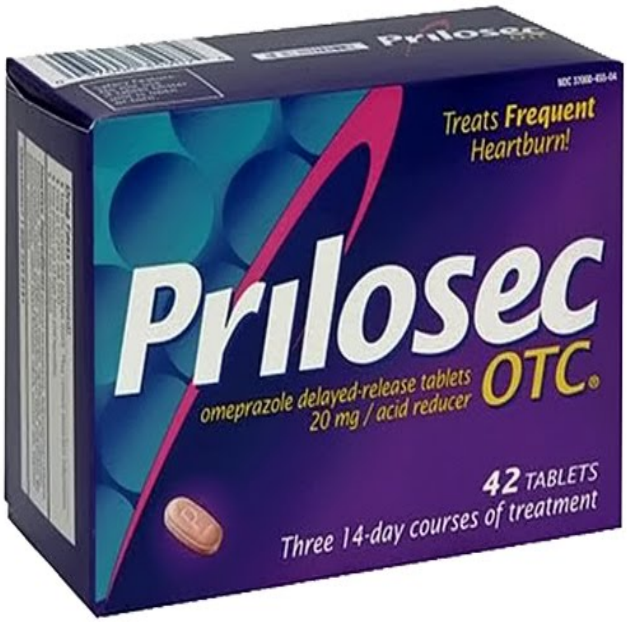
Hyposecretory drugs decrease gastric acid secretion ➔Promote healing & relieve pain.

Include:

- Proton pump inhibitors
- H_2 receptor blockers
- Antimuscarinic drugs

Proton Pump Inhibitor Drugs





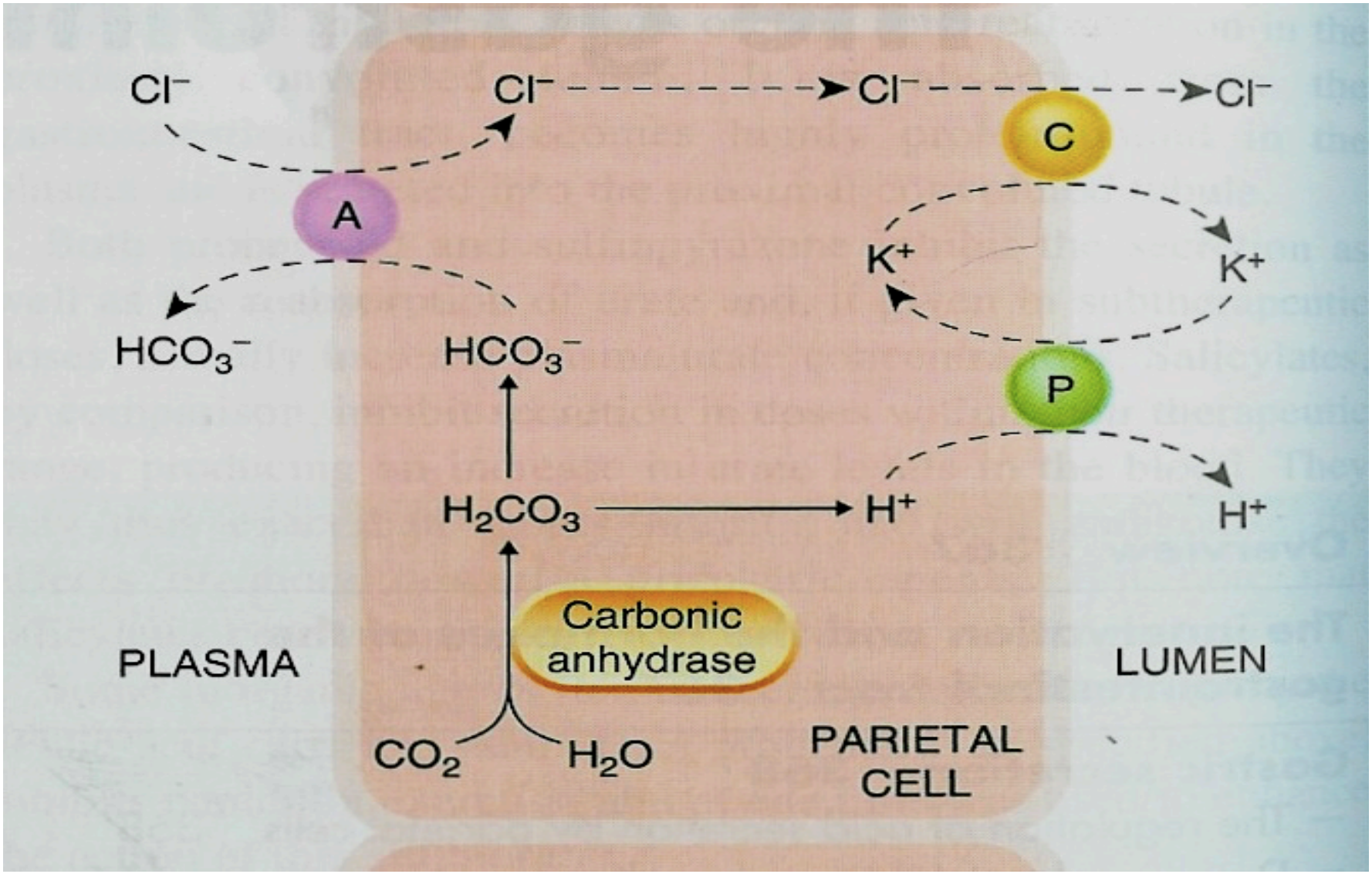
Proton Pump Inhibitors (PPIs)

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 (they covalently bind to the pump)**.**

Gastric secretion by parietal cells



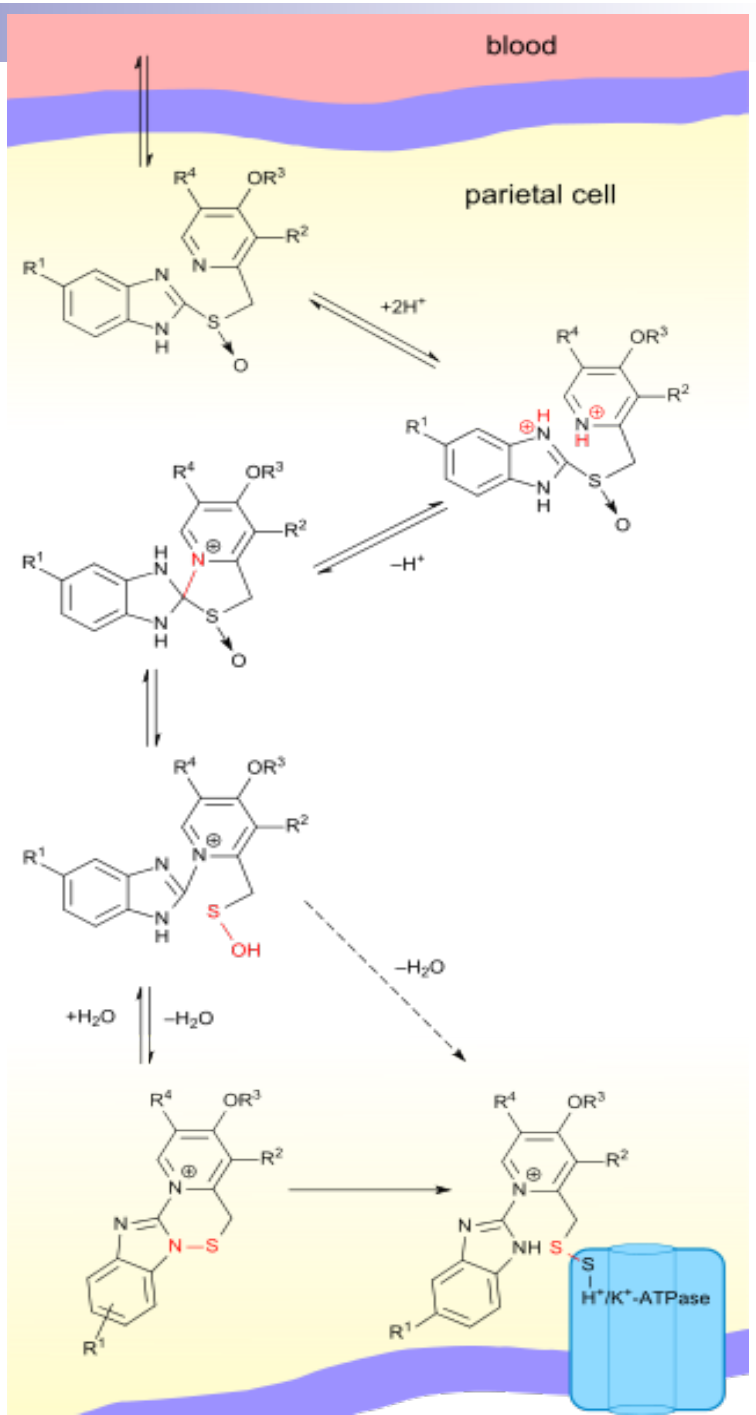
Pharmacodynamics

- 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_2 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_2 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 or GORD).**
- **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.

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 may lead to

- Vitamin B_{12} deficiency, iron, calcium absorption
  - Increased risk of hip fractures

Adverse effects to PPIs

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

H2 receptor blockers

- Cimetidine - Ranitidine
- Famotidine - Nizatidine

Mechanism of action

They reversibly and competitively block H_2 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).**
  - **Prevention of bleeding from stress-related gastritis.**
- **Pre-anesthetic medication (to prevent aspiration pneumonitis).**
- **Post–ulcer healing maintenance therapy.**

Adverse effects of H_2 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_2 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.: $NaHCO_3$; $CaCO_3$; $Al(OH)_3$; $Mg(OH)_2$

- **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.**

NaHCO3 (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**
- **Hyercalcemia**
- **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:
  - H_2 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 quadrable therapy