Drugs in peptic ulcer (H_2 blockers and proton pump inhibitors)

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Learning objectives

- Classify the main different classes of hyposecretory drugs used for treating peptic ulcer.
- Know the characteristic pharmacokinetics, pharmacodynamics and side effects of proton pump inhibitors, and H2 receptor blockers.
- 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.

Peptic ulcer

- 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).

Helicobacter pylori is the major etiological factor in peptic ulcer disease (PUD).

Etiology:

- H. pylori infection
- Hypersecretory states (Zollinger Ellison syndrome)
- Drugs (e.g.) NSAIDs
- Diet factor may contribute

Gastric secretions

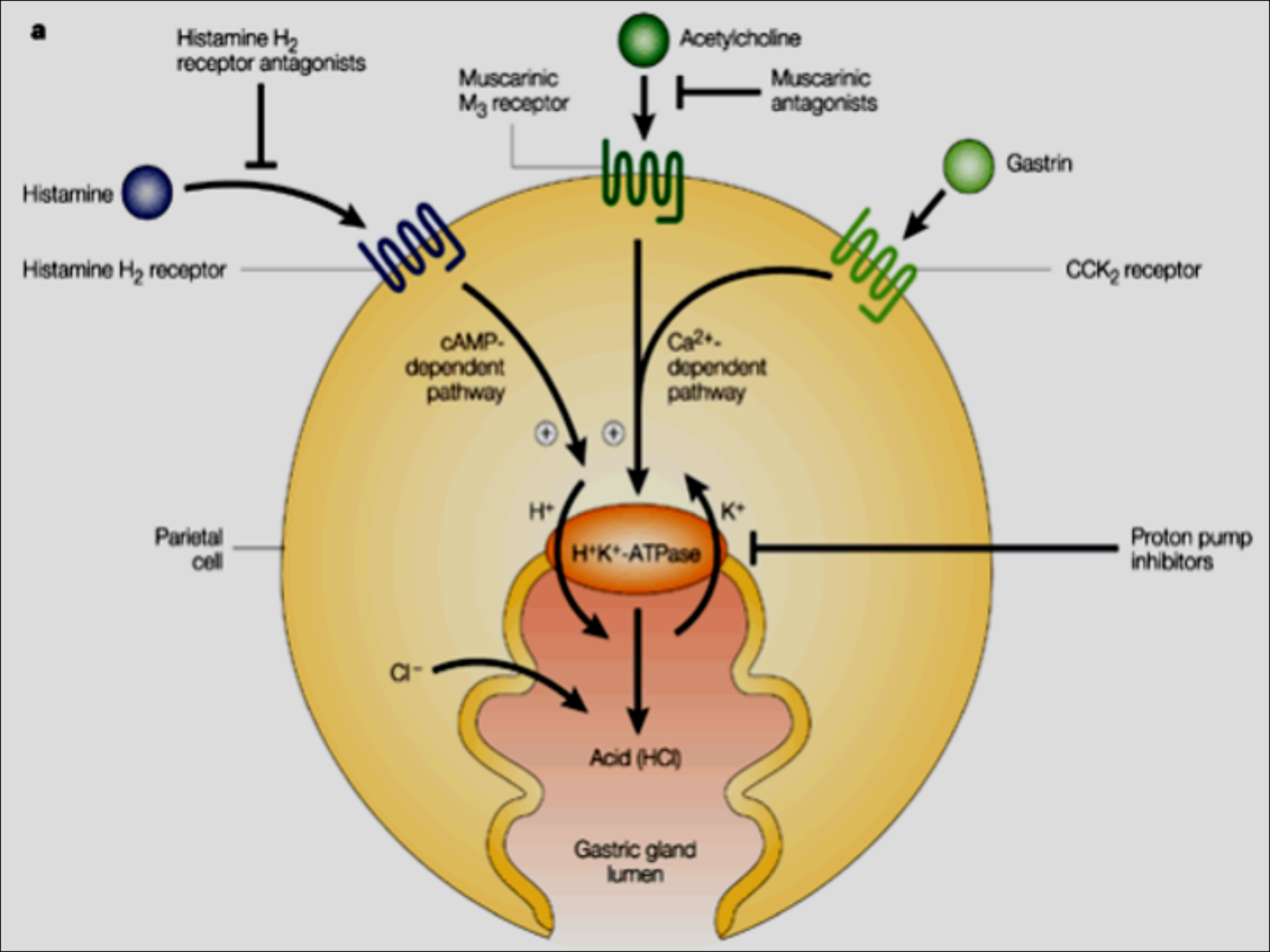
1. HCl (Parietal cells).
2. Pepsinogens (Chief cells).
3. Mucus, bicarbonate (mucus-secreting cells).

Regulation of gastric secretions

Parietal cells secrete acid in response to:

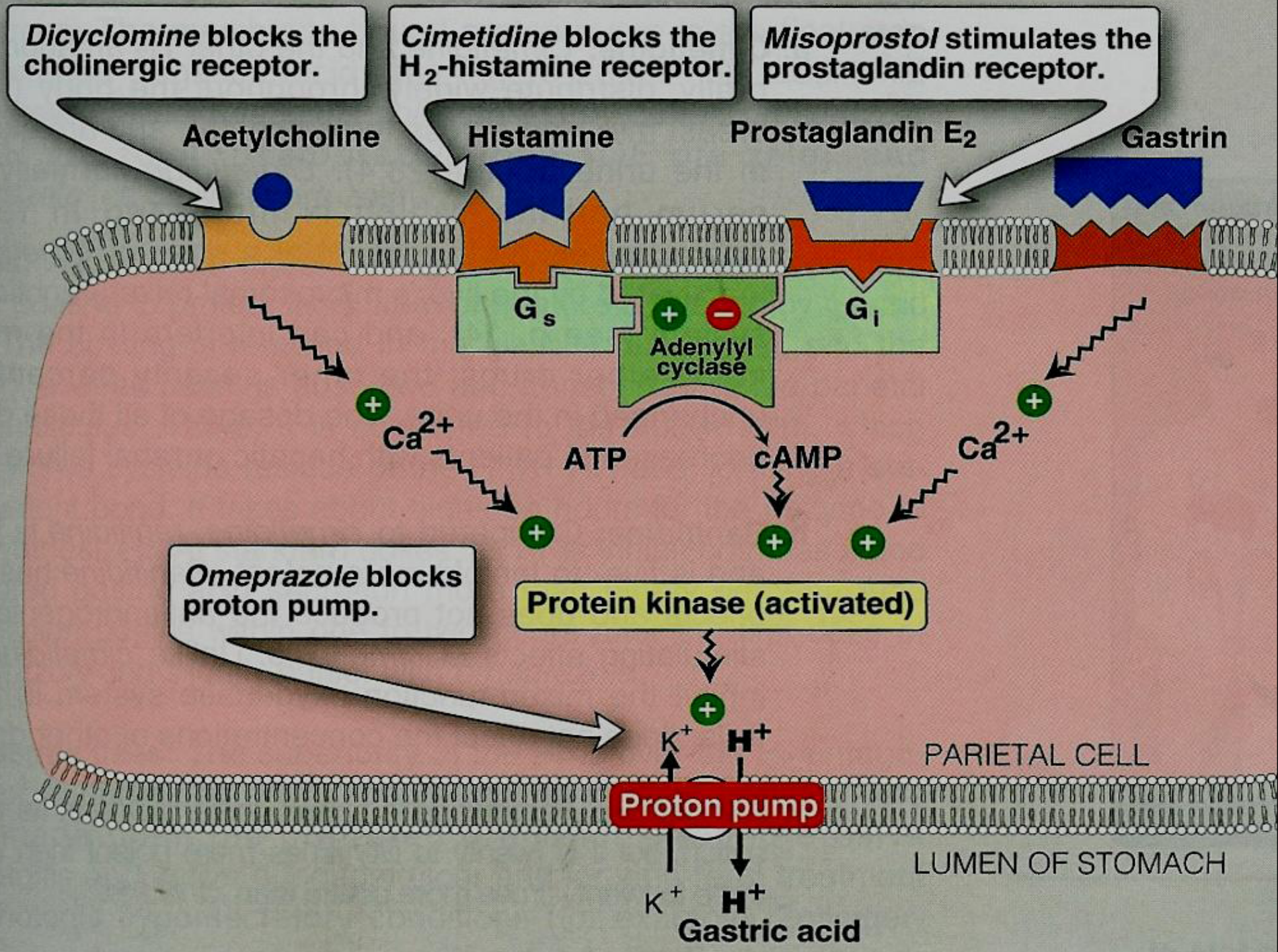
1. **Histamine (local hormone): H_2 receptors**
2. **Gastrin (hormone): CCK_2 receptors**
   (CCK cholecystokinin)

1. **Ach (neurotransmitter): M_3 receptors**
2. **Proton pump (H^+/ K^+ ATPase)**


a
Histamine H2 receptor antagonists
Acetylcholine
Muscarinic M3 receptor
Muscarinic antagonists
Gastrin
Histamine
Histamine H2 receptor
CCK2 receptor
cAMP-dependent pathway
Ca2+-dependent pathway
H+
K+
Parietal cell
H+K+-ATPase
Proton pump inhibitors
Cl−
Acid (HCl)
Gastric gland lumen

Treatment of peptic ulcer

- **Eradication of H. pylori infections (combination of metronidazole/ clarithromycin and PPIs)**
- **Hyposecretory drugs.**
  - **Proton pump inhibitors**
  - **H_2 receptor blockers**
  - **Antimuscarinic drugs**
- **Mucosal cytoprotective agents.**
  - **Prostaglandin analogues**
- **Neutralizing agents (antacids).**


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

Gastric hyposecretory drugs

Include:

- **Proton pump inhibitors**
- **H_2 receptor blockers**
- **Antimuscarinic drugs**

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

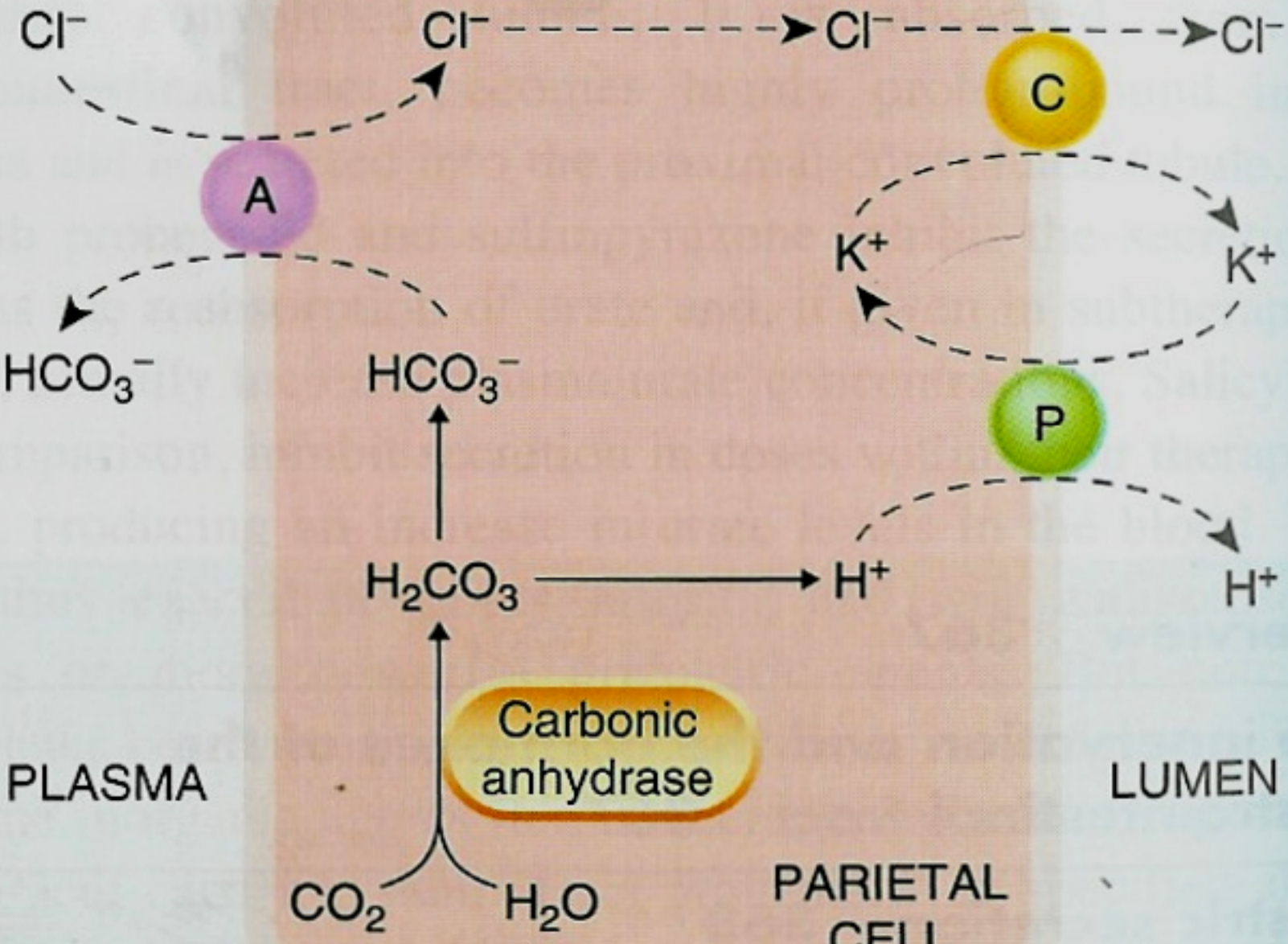
Proton Pump Inhibitors (PPIs)

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 of PPIs

- 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

Pharmacokinetics of PPIs

- Given orally as enteric coated capsules (unstable in acidic medium in stomach).
- Are pro-drugs
- rapidly absorbed from the intestine.
- In the acidic medium of parietal cell, they are activated.
- Should not combined with H_2 blockers or antacids.

- **Have long duration of action (> 12 h-24 h).**
- **Once daily dose is sufficient**
- **Given 1 h before meal.**
- **Bioavailability is reduced by food.**
- **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
- Excessive gastric acid production.

Adverse effects to PPIs

- short term use is safe but long may lead to
- Achlorhydria
- Hypergastrinaemia (increased serum gastrin level).
- Gastric mucosal hyperplasia.
  - Increased bacterial flora
  - increased risk of enteric infections including C. Difficile and bacterial gastroenteritis.
- Decreased Vitamin B_{12} , iron, calcium absorption
  - increased risk of hip fractures

H2 receptor blockers

- Cimetidine - Ranitidine
- Famotidine - Nizatidine

Mechanism of action

- They competitively and reversibly 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 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 (less effective compared to PPIs).
- Block 90% of nocturnal acid secretion (which depend largely on histamine). Therefore, it is better to be given before night sleep (bed time).
- Reduce pepsin activity.
- Promote mucosal healing & decrease pain

Uses:

- GERD ((heartburn/ dyspepsia).
- Acute ulcer healing in moderate cases
  - Duodenal and gastric Ulcer
  - Benign ulcer
  - Prevention of bleeding from stress-related gastritis.
- Post–ulcer healing maintenance therapy.

Adverse effects of H_2 blockers

- **Serious adverse effects are RARE, Minor, GIT disturbances (Nausea & Vomiting).**

(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 (gynecomasteia – impotence) *due to inhibition of dihydrotestosterone binding to androgen receptors.*

Precautions

Dose reduction of H_2 RAs in severe renal or hepatic failure and elderly.

Antacids (no frequent use)

These drugs are mainly inorganic salts

e.g.: $NaHCO_3$; $Ca\ CO_3$; $Al\ (OH)_3$; $Mg\ (OH)_2$

- 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: Systemic alkalosis

Ca CO3 : milk alkali syndrome (hypercalcemia, renal failure)

Al (OH)3 : constipation; **Mg (OH)2 :** Diarrhea

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.

Summary

- Test for *H. pylori* prior to beginning therapy.
- Acid-reducing medications for PUD include:
  - H_2RAs
  - PPI's 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.
- Maintenance therapy can be given until successful H. pylori eradication.