DRUGS FOR THE TREATMENT OF PEPTIC ULCERS

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LECTURE OUTLINE

- Regulation of gastric acid secretion.
- Peptic ulcer & drugs used in the treatment of peptic ulcer.
- Pharmacodynamic, pharmacokinetic profiles and adverse effects of drugs used in the treatment of peptic ulcer.
- Drugs used for eradication of H.pylori.
- Gastroesophageal reflux disease (GERD).

ACID-PEPTIC DISEASES

- Peptic ulcer (gastric and duodenal).
- Gastroesophageal reflux.
- Stress-related mucosal injury.

PEPTIC ULCER

Common causes	Uncommon causes
- Helicobacter pylori infection. - Nonsteroidal antiinflammatory drugs (NSAIDs). - Critical illness (stress-related mucosal damage).	- Hypersecretion of gastric acid (e.g., Zollinger-Ellison's syndrome). - Viral infections (e.g., cytomegalo virus). - Vascular insufficiency (crack cocaine associated). - Radiation Chemotherapy (e.g., hepatic artery infusions). - Rare genetic subtypes - Idiopathic.

Peptic ulcer disease

protective and agressive factors

stomach or duodenum

Non-specific symptoms ⟷ functional dyspepsia

- ❖ H pylori infection
- 90% of duodenal ulcers
- 70% of gastric ulcers
- ❖ 10 % non-steroidal anti-inflammatory drugs (NSAIDs).(gastric >bduodenal ulcers)
- ❖ gastric bypass surgery

Epigastric pain
Retrosternal pain
Early satiety
Nausea
Bloating
Bleching
Postprandial distress

Sverdén et al., 2019

❖ Idiopathic

no evidence based treatment for marginal ulcers seen ~5% patients having gastric bypass surge

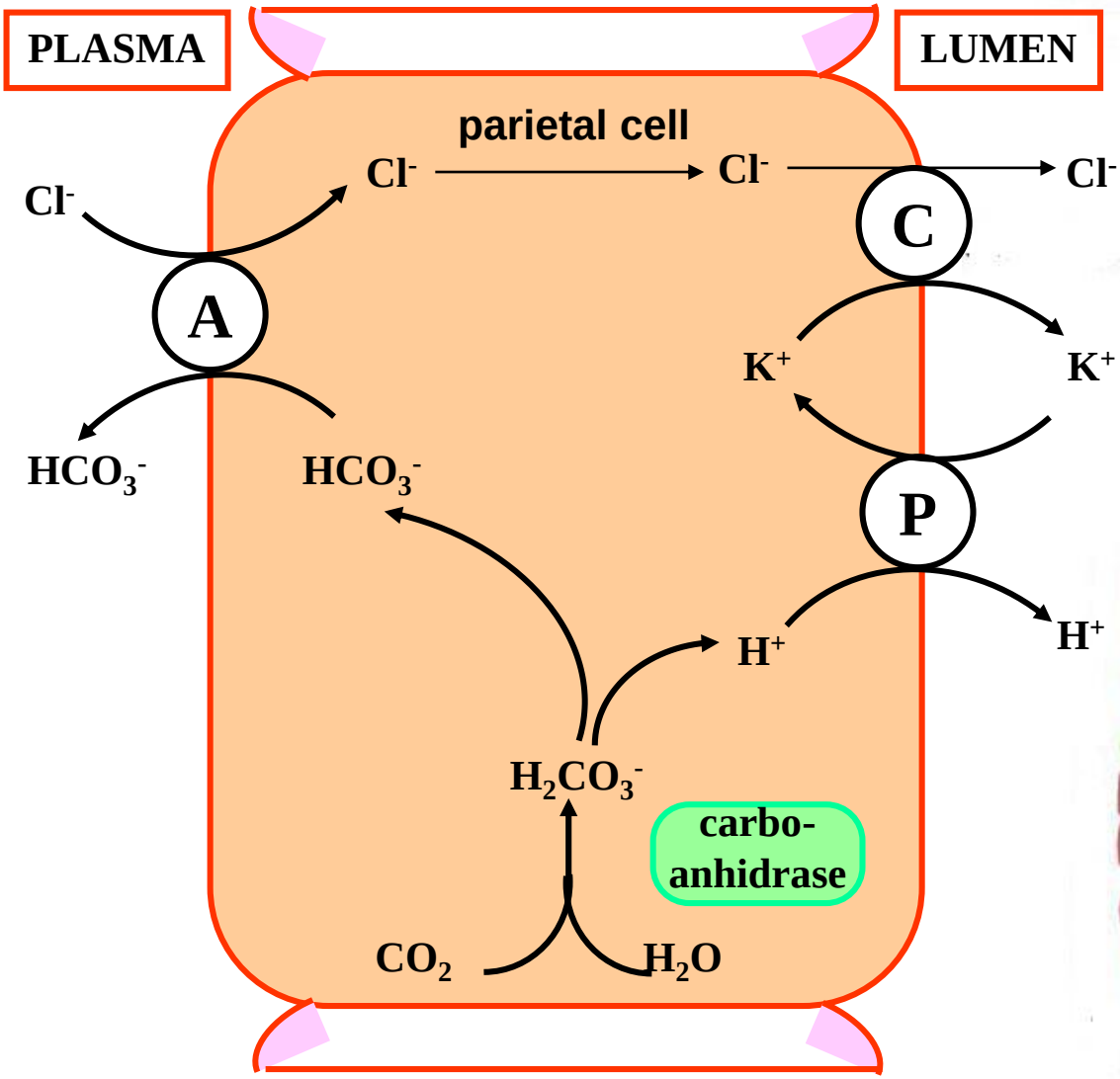
PEPTIC ULCERS

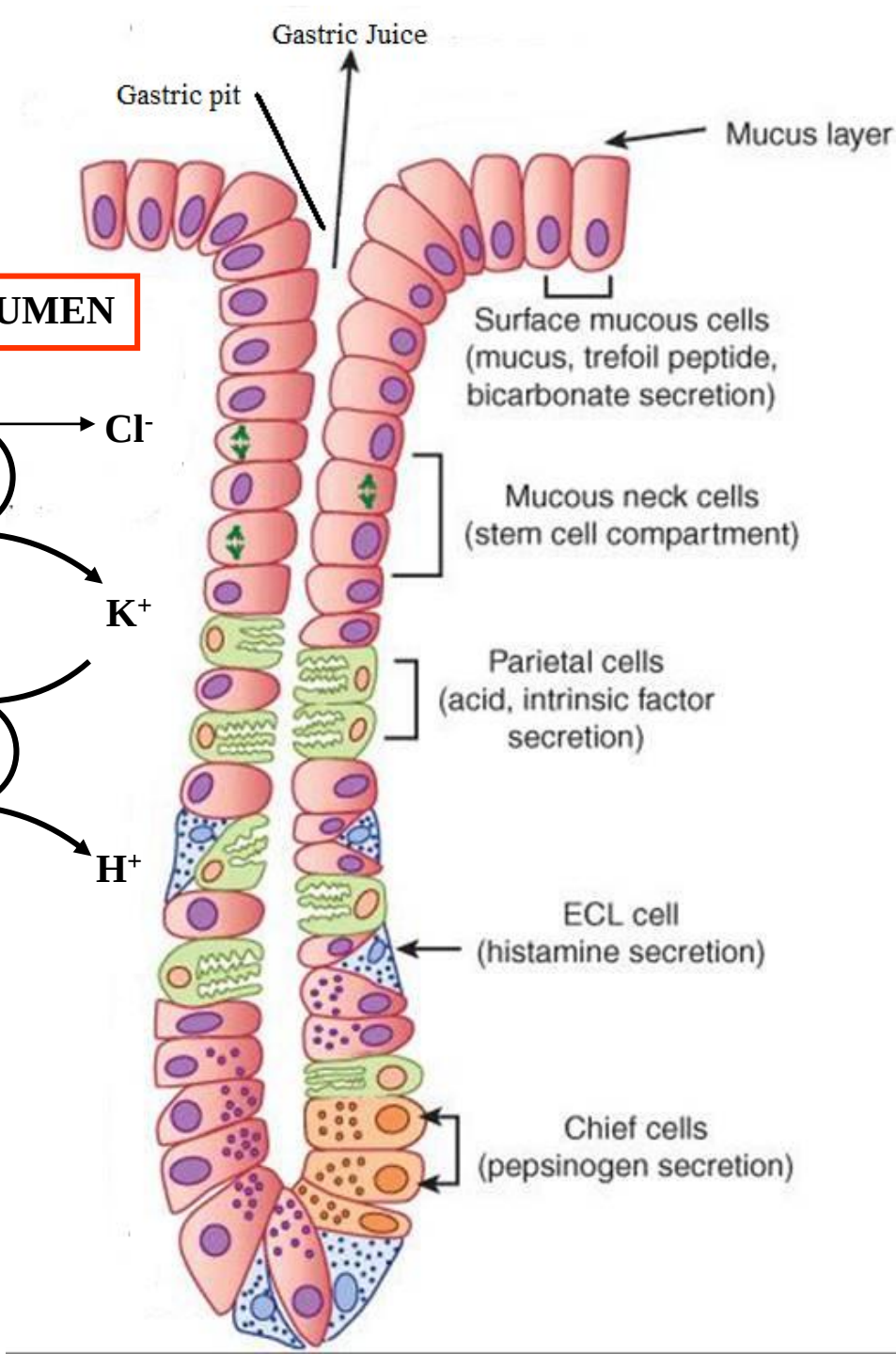
Ulcer	Characteristic
Gastric ulcer	**Acid secretion is normal or decreased.** *Helicobacter pylori infection.* *Nonsteroida anti-inflammatory* drugs (NSAIDs) use. Pain 0.5-1 h after meal. **↓ defensive factors.** Male: female (1:1), 15% of peptic ulcer. Vomiting: common Ingestion of food: no help or ↑ pain.
Duodenal ulcer	↑HCl.(in 50% of patients) *Helicobacter pylori infection*. Pain 2-3h after meal. NSAIDs. **DOMINANCY OF AGRESSIVE FACTORS** Male: female (2:1), 80% of peptic ulcer. Vomiting: Uncommon. Ingestion of food ↓ pain.

Risk factors and causes of ulcers in the stomach and duodenum

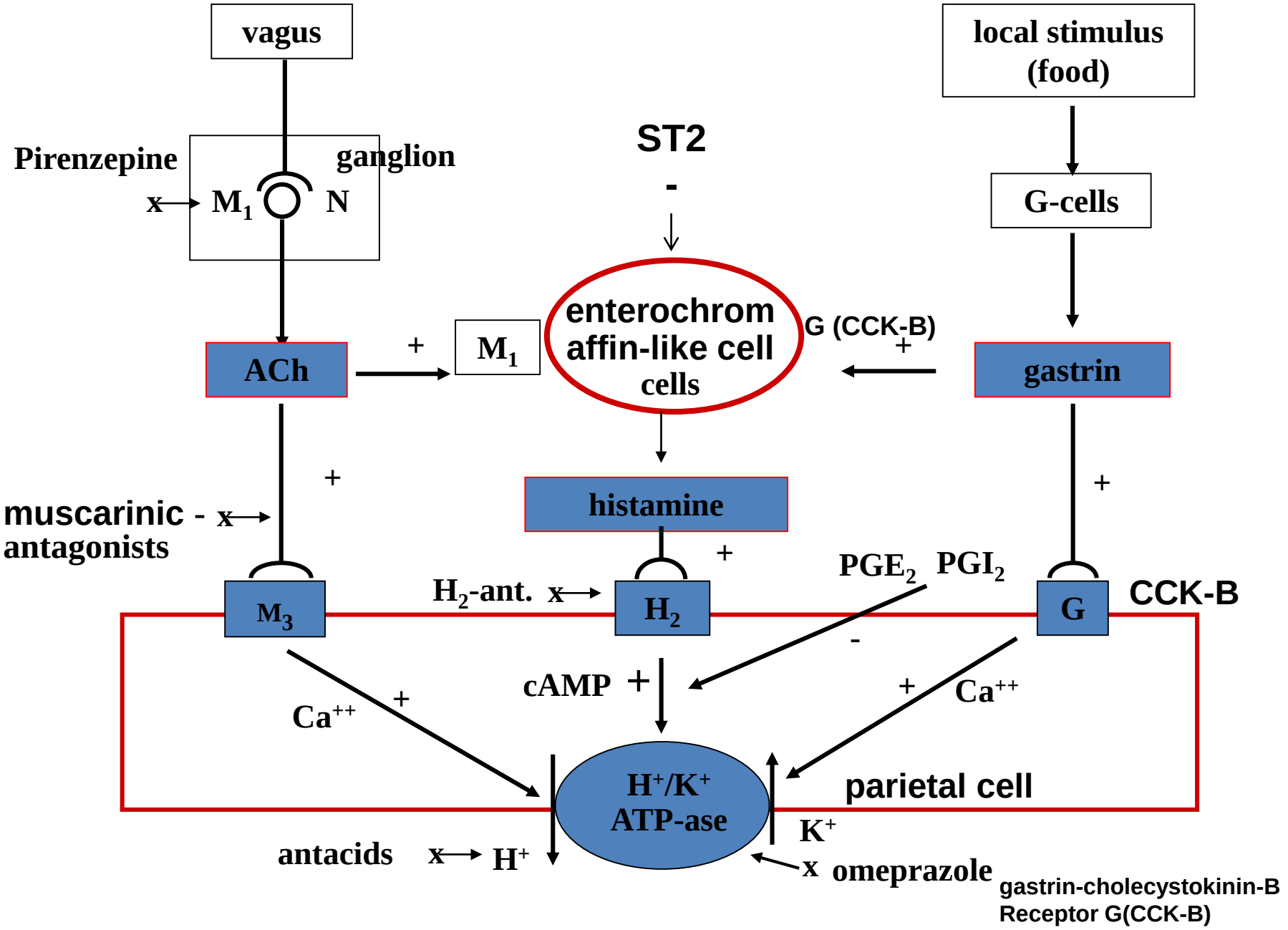
- H Pylori
- NSAIDs
- Gastric bypass surgery
- Cigarette smoking
- Selective serotonin reuptake inhibitors
- Zollinger-Ellison syndrome (uncommon, gastrin producing tumour usually located in the pancreas)
- Physiological stress associated with serious trauma and critical illness (eg, septicaemia)
- Gastric tumours mistaken for peptic ulcers
- Autoimmune diseases, eg, vasculitis, sarcoidosis, and Crohn's disease
- Infections, mainly in immunocompromised patients, eg, cytomegalovirus, tuberculosis, and syphilis
- Psychological stress is not an established risk factor for peptic ulcer disease, although some research has suggested an association.
- Consumption of alcohol or coffee does not seem to increase the risk of peptic ulcer disease

Sverdén et al., 2019


PLASMA
LUMEN
parietal cell
Cl-
Cl-
Cl-
Cl-
A
C
K+
K+
HCO3-
HCO3-
P
H+
H+
H2CO3-
carbo-
anhidrase
CO2
H2O


Gastric Juice
Gastric pit
Mucus layer
Surface mucous cells
(mucus, trefoil peptide,
bicarbonate secretion)
Mucous neck cells
(stem cell compartment)
Parietal cells
(acid, intrinsic factor
secretion)
ECL cell
(histamine secretion)
Chief cells
(pepsinogen secretion)

PHYSIOLOGY OF ACID SECRETION

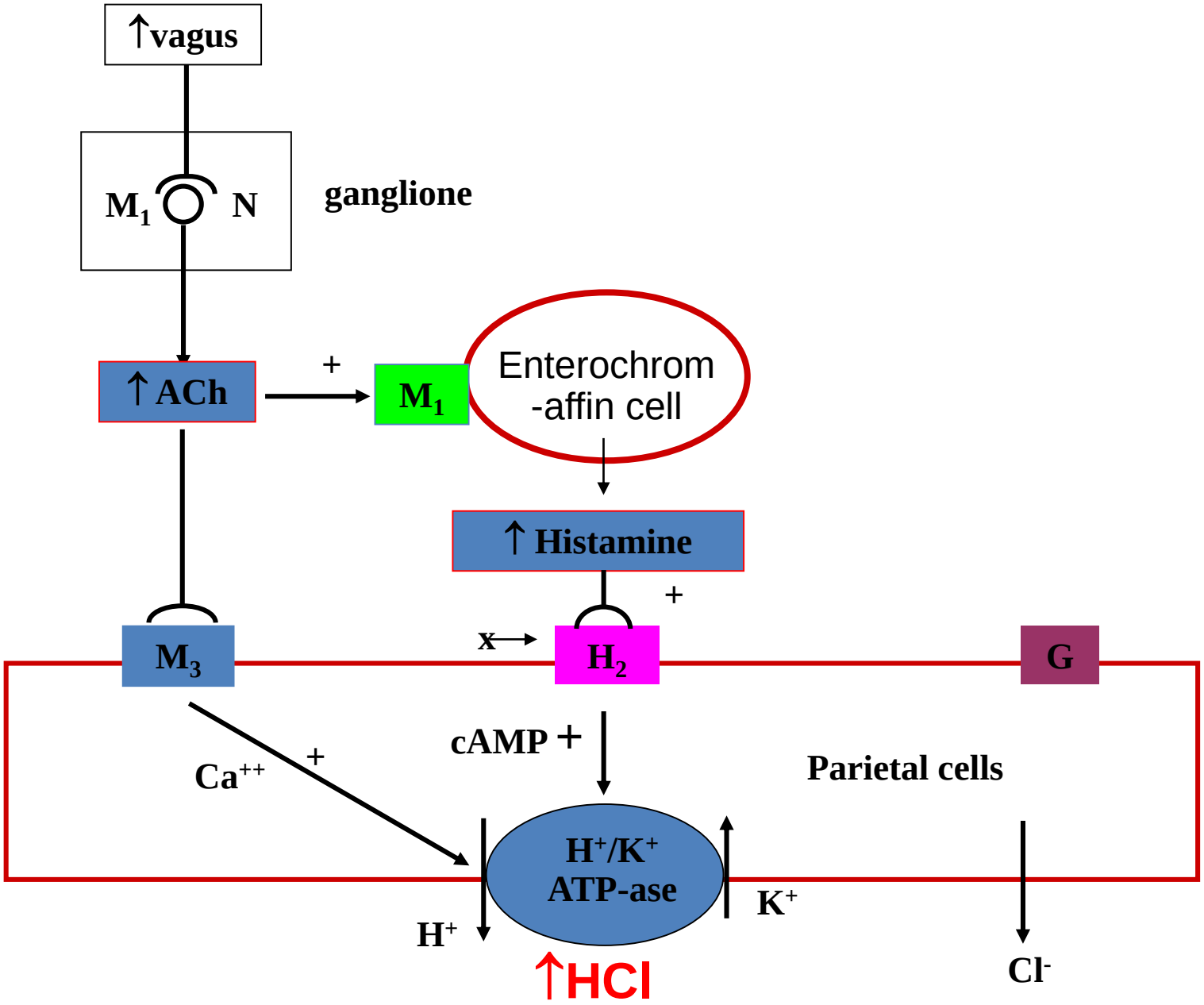


THE KEY FACTORS INVOLVED IN ACID HYPERSECRETION

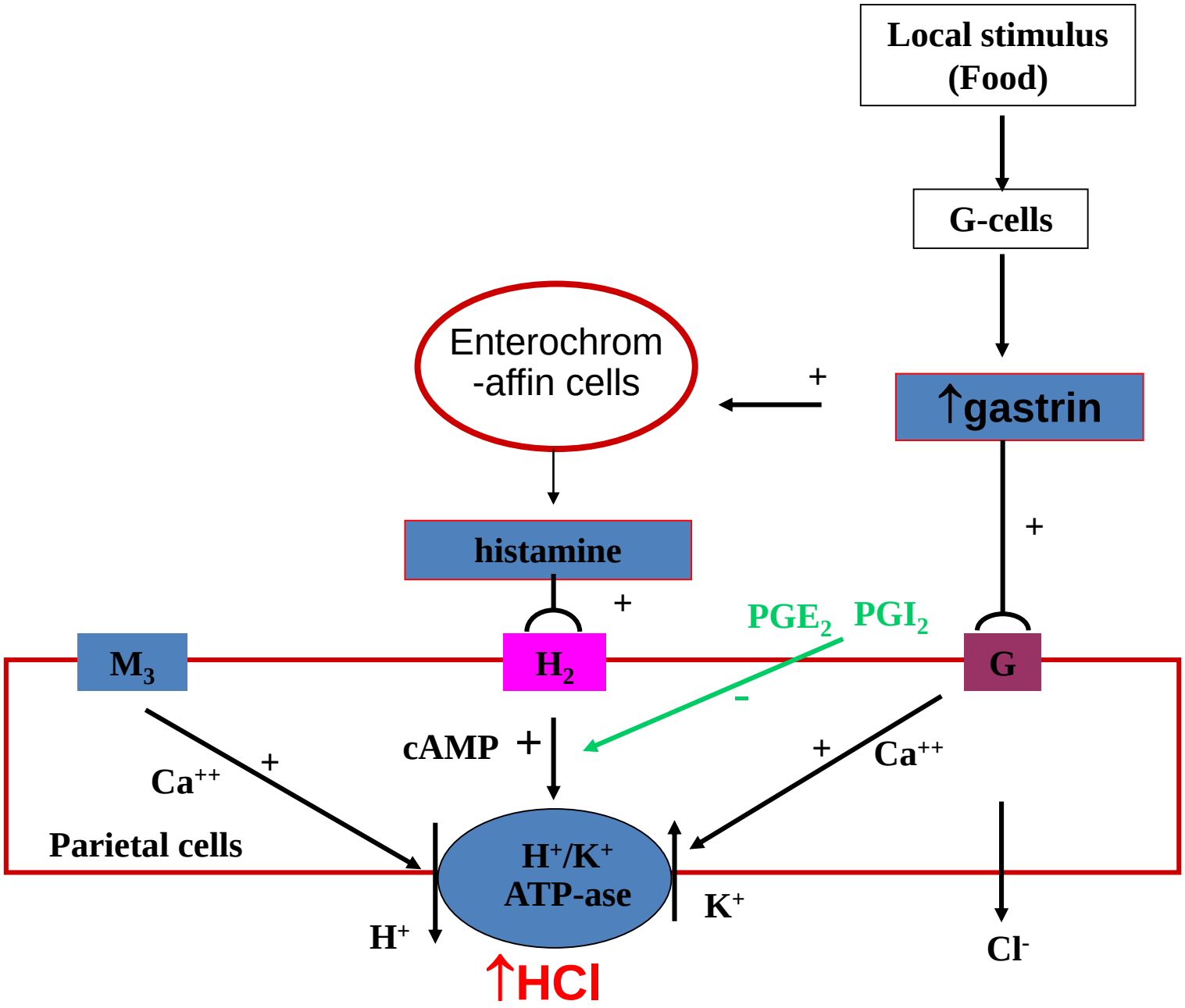
- **Neuronal mechanisms**: Increase vagus activity
- **Endocrine mechanisms**: Secretion of gastrin from antral G-cells and mast cells.
- **Paracrine mechanisms**: Release of histamine from enterochromaffin-like cells.

A MECHANISM OF ACIDIC ACID SECRETION

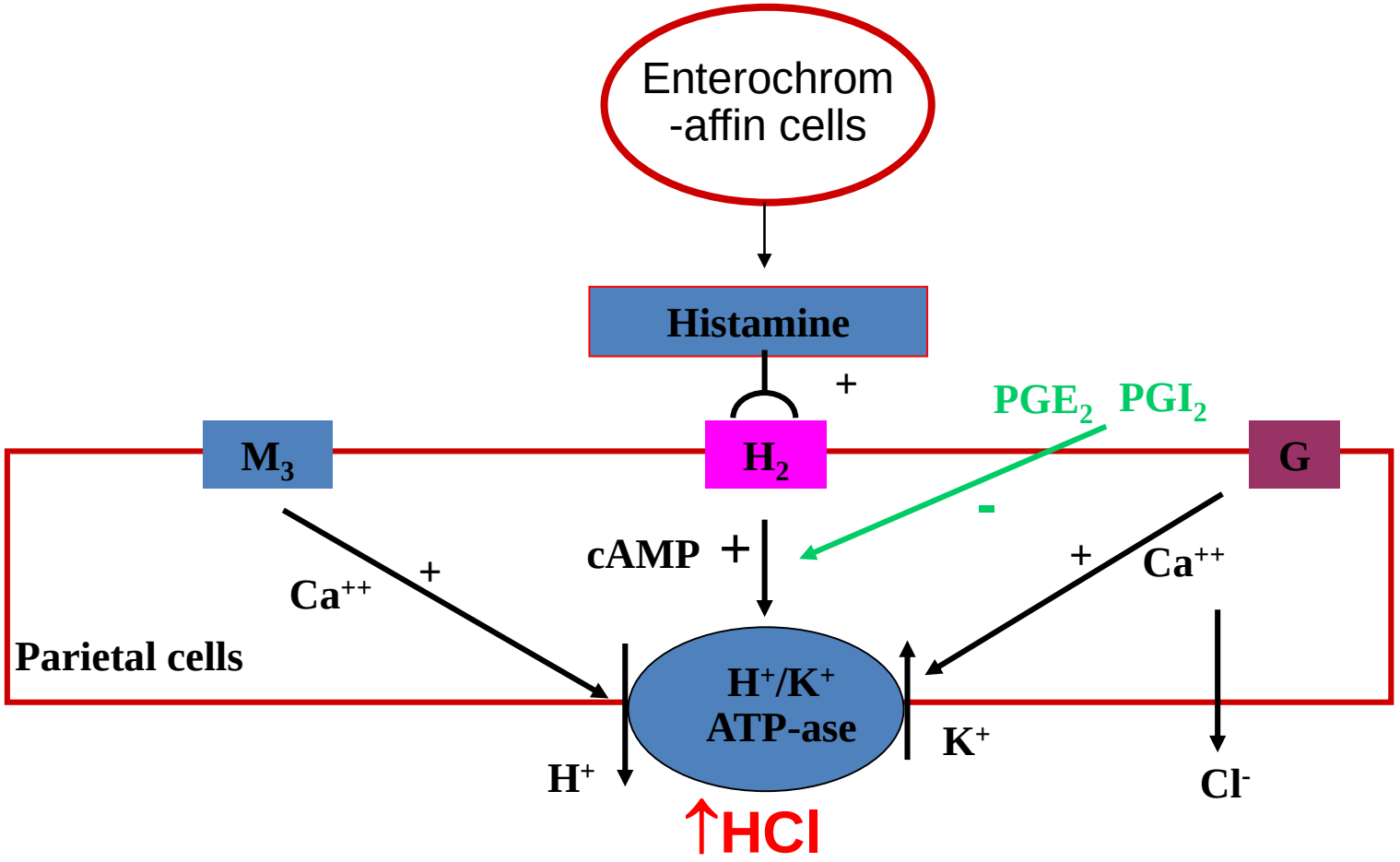
1. NEURONAL MECHANISM



2. ENDOCRINE MECHANIZM



3. PARACRINE MECHANIZM



THE ENDOGENOUS HCL SECRETION INHIBITORS

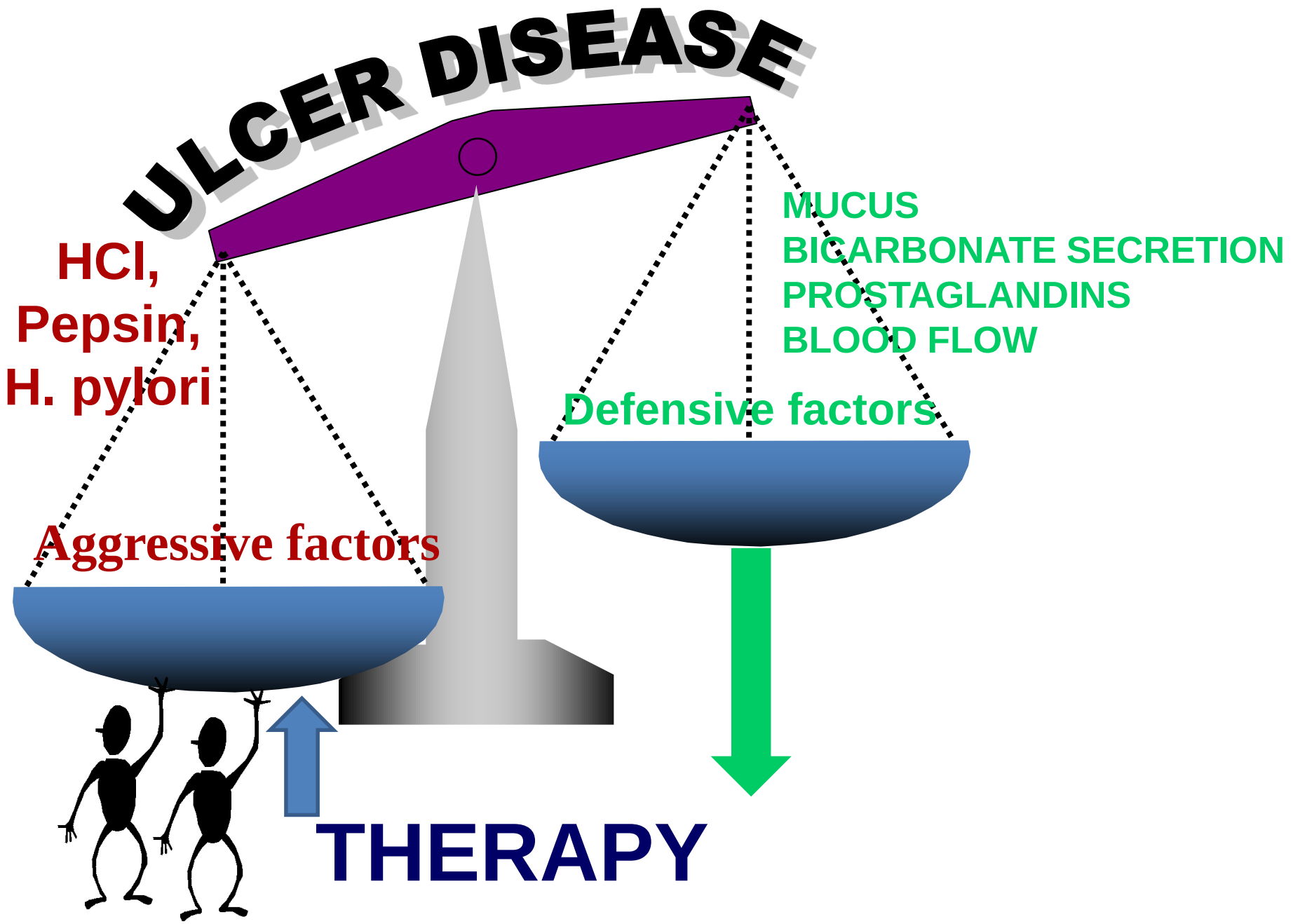
- Somatostatine (ST2,somatostatin2 receptor).
- Calcitonin.
- Glucagon.
- Vaso active intestinal peptid (VIP).
- Prostaglandins (PG-s).

INTEGRITY OF GASTRIC MUCOSA

AGGRESSIVE FACTORS	DEFENSIVE FACTORS
GASTRIC ACID PEPSIN H. PYLORI	PROSTAGLANDINS MUCUS BICARBONATE SECRETION BLOOD FLOW

Peptic ulcer occurs when the equilibrium between the aggressive factors and protective factors, is shifted in favor of aggressive factors.

Note: The integrity of the gastric mucoa depends on the amount of back-diffused H^+ ions, but not the luminal H^+ ion concentration.


ULCER DISEASE
HCl,
Pepsin,
H. pylori
Aggressive factors
MUCUS
BICARBONATE SECRETION
PROSTAGLANDINS
BLOOD FLOW
Defensive factors
THERAPY

THERAPEUTICAL AIMS

To relieve the pain.

To accelerate healing.

To prevent ulcer recurrence.

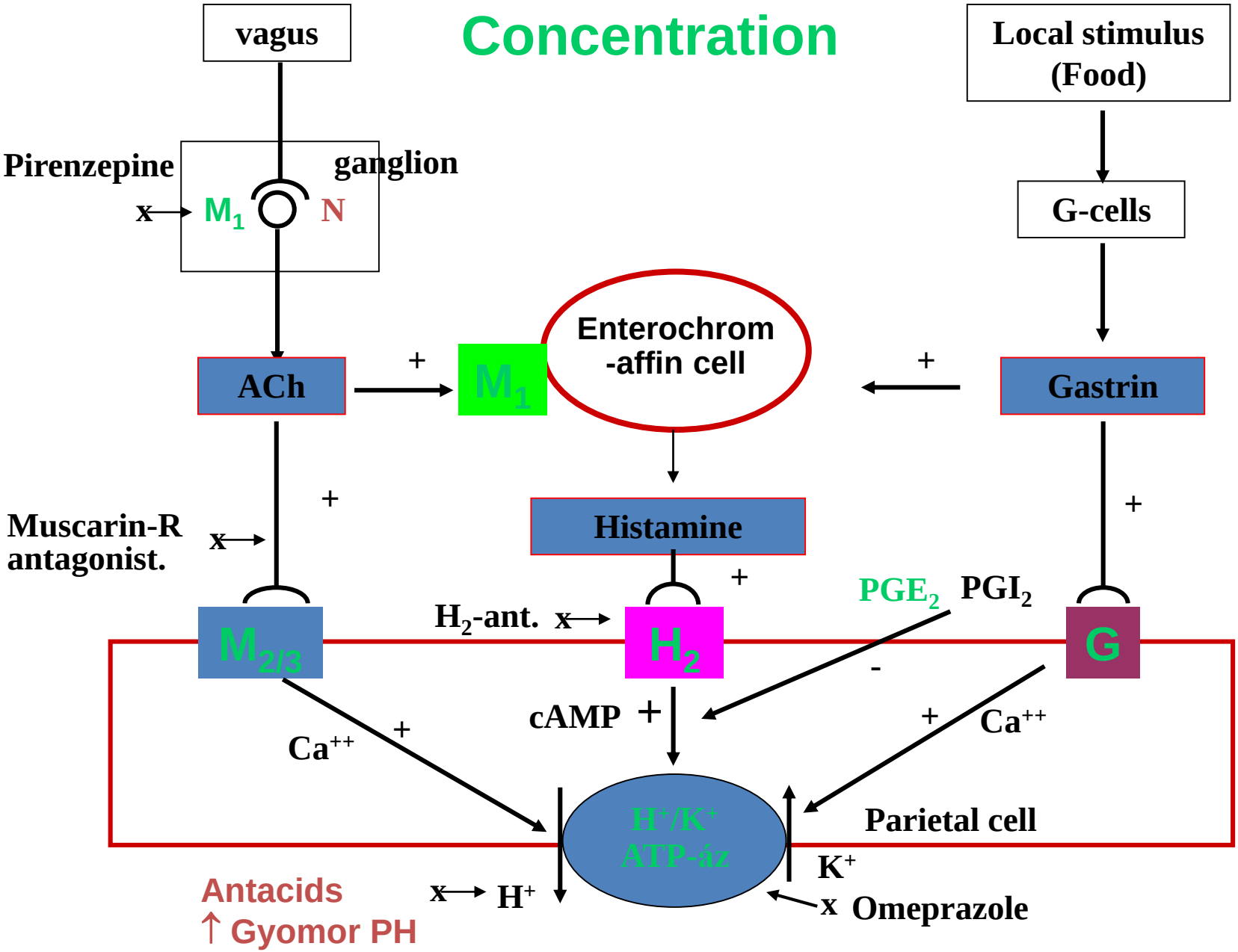
The therapeutical approaches

To reduce the aggressive factors (by lowering HCl secretion).

To enhance the protective factors.

To eradicate *Helicobacter pylori.*

Targets of Drugs for Lowering Acid Concentration



ANTIULCER DRUGS

- **Drugs inhibit acid production**
  - **H_2-Receptor Antagonists.**
  - **Proton pump inhibitors.**
  - **Anticholinergic drugs.**
- **Acid neutralizing agents (antacid drugs).**
- **Drugs increase mucosal resistence (protective drugs)**
  - **Sucralfat.**
  - **Prostaglandins.**
  - **Bismuth salts.**
- **Drugs eradicate Helicobaecter Pylori.**

H_2-Receptor Antagonists

- **Cimetidine, famotidine, ranitidine, nizatidine**

- They suppress the basal and meal-induced acid secretion and ulcer pain. Have better impact on nocturnal acid secretion.

- Smokers may need higher doses and longer duration of therapy.

- Given parenterally and orally, good GI absorption.

- All metabolite by liver (except Nizatidine), then eliminated by kidney (↓ in dose is recommended in patients with moderate to severe renal failure).

H_2-Receptor Antagonists

- **Cimetidine, famotidine, nizatidine, ranitidine**

- Binding to **CYP450** isoenzymes:

High in case of **cimetidine** (inhibitor), less in case of ranitidin wherease famotidine and nizatidine do not interact with hepatic CYP450.

Drug interaction : Cimetidine with theophylline, lidocaine, phenytoin and warfarin

Side effects:

cimetidine: loss of libido, gynecomastia, impotentia (binds to androgen R),
↑ estradiol and prolactin level**. CNS**

H_2-Receptor Antagonists

Indication

PEPTIC ULCERATION:

1000 mg cimetidine/day: 50% reduction of secret.

300 mg. ranitidine/day: 70% -"- "-"

- DUODENAL ULCER

85-90% are healed after 8 weeks treatment

- GASTRIC ULCER

50-70% are healed after 8 weeks

- Zollinger-Ellison syndrome (gastrin-producing pancreatic tumors, Zollinger-Ellison syndrome). **high doses are needed**

- OTHER CONDITIONS: reflux oesophagitis, stress ulcers

preanesthetic use in emergency

H2-Receptor Antagonists

- **Cimetidine, famotidine, nizatidine, ranitidine**

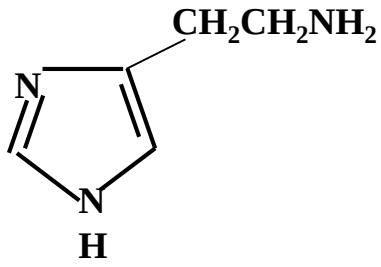
Hypochlorohydria

a) favors the survival of bacteria; candidal peritonitis

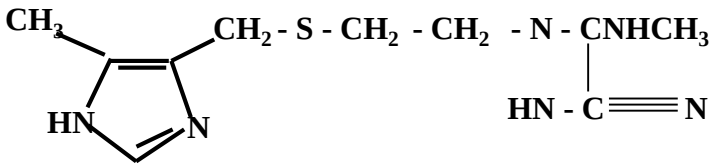
b) growth of bacteria that from ingested nitrates form carcinogen nitrosamines

Diagnosis of gastric cancer can be retarded in the presence of H_2 blockers.

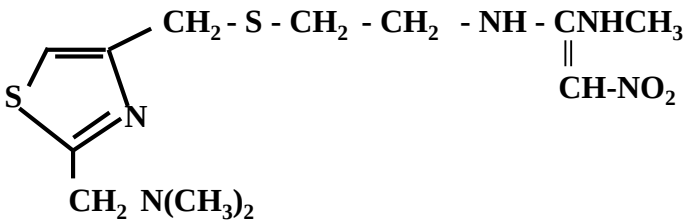
Short-term adverse effects: headache, nausea, and abdominal pain.



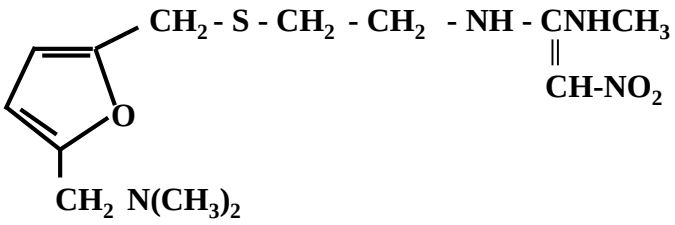
Histamine



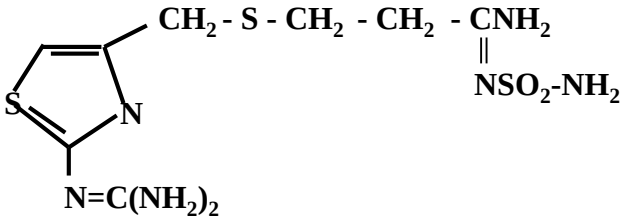
Cimetidine



Nizatidin



Ranitidine



Famotidine

H_2-Receptor Antagonists

DOSES:

cimetidine:	800 mg at bedtime 4 x 200 mg 2 x 400 mg
ranitidine:	300 mg at bedtime 2 x 150 mg
famotidine:	40 mg at bedtime 2 x 20 mg

PROTON-PUMP INHIBITORS (PPIs)

OMEPRAZOL
ESOMEPRAZOL

PANTOPRAZOL
LANSOPRAZOL
RABEPRAZOL

pro-drugs

Activation site
Stomach

Inactive at neutral pH.
At low pH transformed to sulfonamide form, which bind to SH group of enzyme.

Mechanism of action: Irreversibly Inhibit the H^+/K^+-adenosine triphosphatase (ATPase)enzyme.

- Inhibit basal and stimulated gastric acid secretion.

Omeprazole, esomeprazole, and lansoprazole: in delayed-release enteric-coated.
lansoprazole: rapidly disintegrating tablets.
Rabeprazole, pantoprazole: delayed release enteric-coated tablets

PROTON-PUMP INHIBITORS (PPIs)

Indication

- Zollinger-Ellison syndroma 60-80-120 mg/day.

- Peptic ulcer (like H_2 blocking drugs) 20-40 mg/day.

- Reflux esophagitis (better than H_2 blocking drugs) 20-40mg/day.

Drug interaction:

Omeprazole: enzym inhibitors, CYP2C19-inhbitor.

inhibits the metabolism of warfarin, phenytoin, diazepam.

Clopidogrel (prodrug)↔ omeprazole (inhibition of P450)

PROTON-PUMP INHIBITORS (PPIs)

Gastro-Resistant tablet or capsule

Pantoprazole: (Caps., IV) is not recommended for use in patients <18 years.

No dose adjustment is required in patients with renal impairment.

In severe hepatic impairment max. 20 mg daily

PROTON-PUMP INHIBITORS (PPIs)

Side effects

- Hypergastrinaemia (hyperplasia, carcinoid tumor?)

- Potential risk: bacterial overgrowth

- Rarely: gastrointestinal disturbance (diarrhea)

- CNS: headache, dizziness skin rash, leukopenia

- Short-term adverse effects: are similar to H2RAs.

- Osteoprosis (chronic use ?, bone H+/K+-ATP-ase, Ca^{2+} absorption)

M1 MUSCARIN RECEPTOR ANTAGONIST

Pirenzepine, Telenzepine

Gastric secretion is blocked in lower doses than other cholinergic functions. Decrease the basal HCL (~10%)

They ↓ GI spasm.

Absorbtion: poorly absorbed

Indication: duodenal ulcer 2x 50 mg/day
gastric ulcer 3x 50 mg/day

Side effects:

blurred vision less frequently dry mouth
constipation-diarrhoea frequently
headache frequently
CNS frequently

ANTACIDS

Neutralize gastric acid, inactivate pepsin

1- Sodium bicarbonate ($NaHCO_3$).

2- Calcium carbonate (also in milk)

3- Magnesium hydroxyde

poor solubility, prolonged neutralizing effect

cathartic effect

4- Aluminium compounds

5- Combination: $Mg(OH)_2$+ $Al(OH)_3$

ANTACIDS

local effect Neutralizing HCL (therapeutic)	local effects (Unwanted)	systemic effects (unwanted)	Note
NaHCO3	CO_2 production	↑Na (Fluid retention) + alkalosis	Sympatetic relief
CaCO3	Rebound HCl secretion (activation of Gastr. Secretion)	↑ Ca+ alkalosi (milk-alkali syndrome)	only for short treatment
$Mg(OH)_2$	osmotic diarrhea		
$Al(OH)_3$	Constipation	if absorbed: encephalopathy, Alzheimer**?**	also suppress *H. pylori* and increase mucosal defense.
$Mg(OH)_2$+ $Al(OH)_3$	↓		

Chelating action with many drugs

ENHANCEMENT OF GASTRIC MUCOSAL DEFENSE

Bismuth Preparations: Bismuth subsalicylate and bismuth subcitrate.

Prostaglandins.

Sucralfate: nonabsorbable aluminum salt of sucrose octasulfate.

1. Bismuth Salts.

Mechanism

forming coat.

Show antipeptic activity.

Indication: gastric, duodenal ulcer (= with H_2 blocking drugs, less relapse).

Dose: 4x120 mg (30’ min before meals 2^h after last meal)

Adverse effect: darkening of oral cavity, encephalopathy, osteodistrophy (only: if renal damage!!)

2. Sucralfate (sucrose octasulphate)

Should be taken on an empty stomach to prevent binding to dietary protein and phosphate.

Mechanism

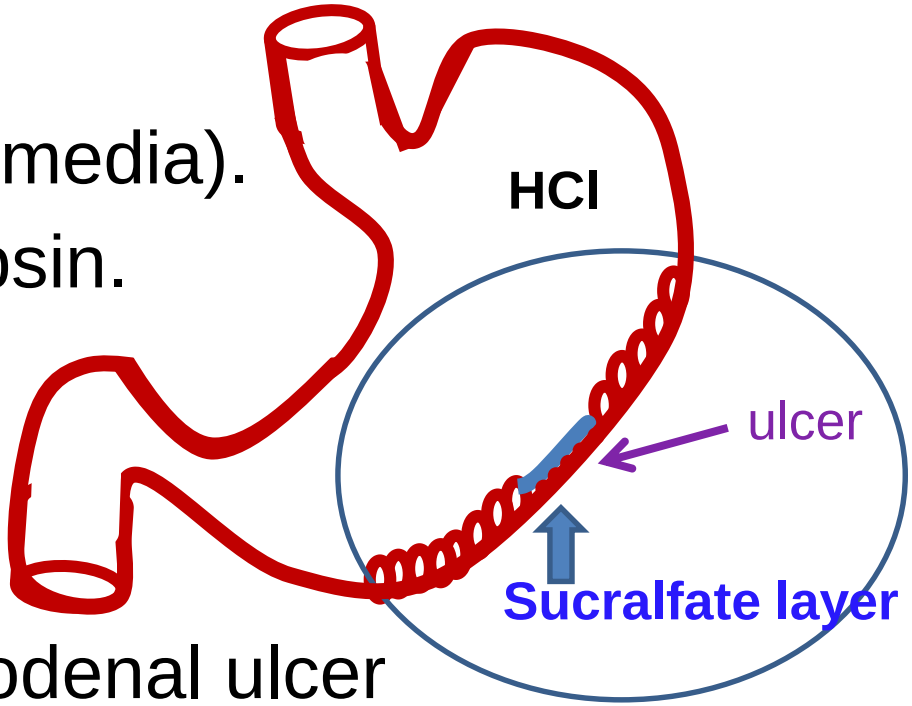
forming gel layer (in acidic media).

Protect ulcer from HCl, pepsin.

↓H^+ back-diffusion.

Stimulate PG synthesis.

Causes rapid healing.



Indication: gastric and duodenal ulcer

Dose: 4x1 g 1 h before meal

Adverse effect: constipation (releases Al3+ ions),

Caution: patients having renal failure.

3. Prostaglandins

Misoprostol:

- synthetic prostaglandin E1 analog.
- Moderately inhibits acid secretion and enhances mucosal defense.
- Has greater stability than natural prostaglandin, oral administration.

Mechanism:

- Promotes mucus or bicarbonate production and inhibits acid secretion.

Indication: duodenal ulcers and gastric ulcers.

Has comparable action to that of standard H2RA or sucralfate .

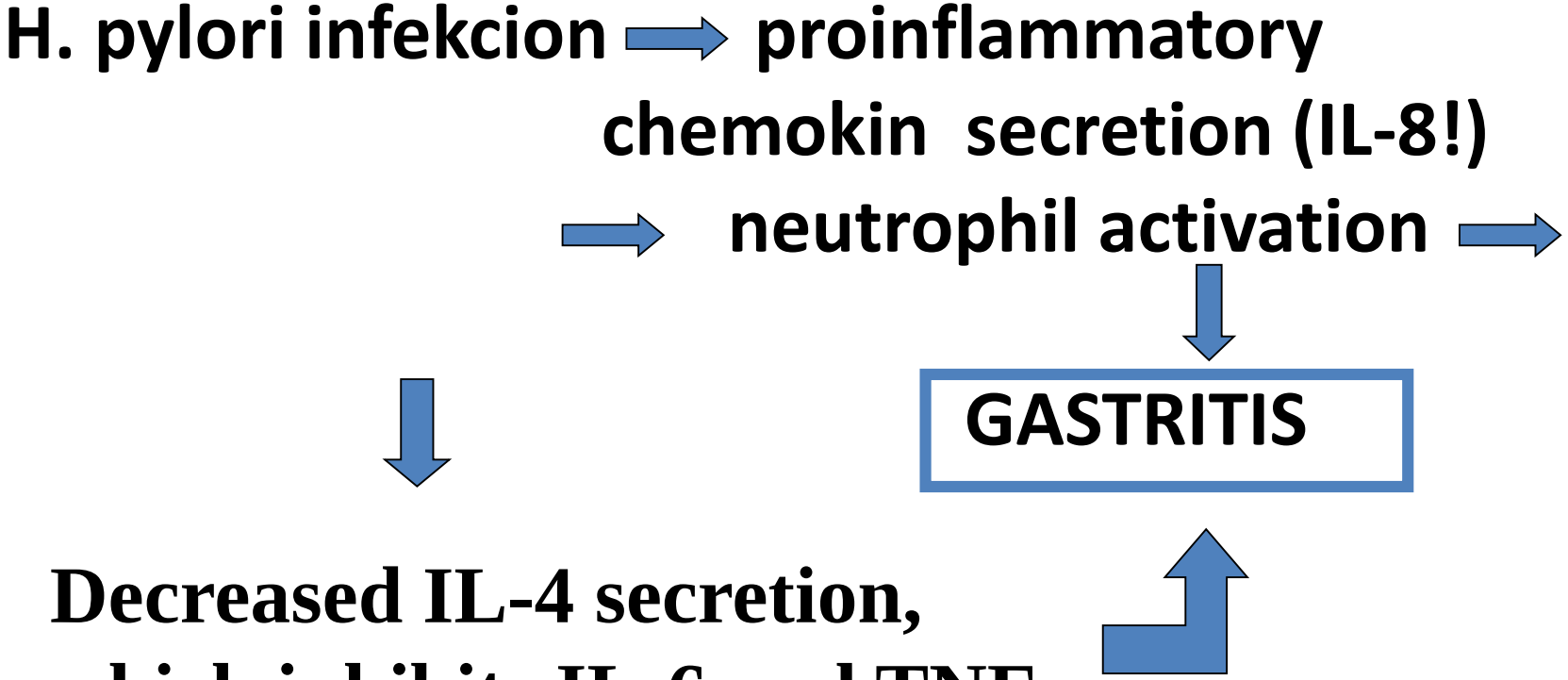
Side effects:

Diarrhea (in 30%) , Abdominal cramping, nausea, flatulence, headache, **uterine contraction.**

HELICOBACTER PYLORI INDUCED MUCOSAL DAMAGE

BARRY MARSHALL & ROBIN WARREN
2005 nobel price

HELICOBACTER PYLORI INDUCED MUCOSAL DAMAGE



ERADICATION OF HELICOBACTER PYLORI

Protocol	Drugs	Duration of treatment	Eradication rate
TRIPLE THERAPY or First-line therapy	PPI + + Claritromycin (2 x 500 mg) + Amoxicillin (2 x1000 mg)	10-14 days, Then, PPI (1/day) for 4-6 weeks	85%
TRIPLE THERAPY or First-line therapy	PPI + + Claritromycin (2 x 500 mg) + Metronidazol (2 x 500 mg)	10-14 days, Then, PPI (1/day) for 4-6 weeks	85%
QUADRUPLE THERAPY or Second-line therapy	PPI + + Bismuth subsalicylate (4 x525) + Metronidazol (4 x 250 mg) + Tetracycline (4x500mg)	10-14 days, Then, PPI (1/day) for 4-6 weeks	95%
RESCUE THERAPY or Third-line therapy	PPI + + Levfloxacin (2 x 250 mg) + Amoxicillin (2 x1000 mg)	10-14 days, Then, PPI (1/day) for 4-6 weeks	

THE MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

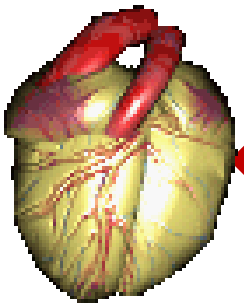
Life styl modification

Drugs

- H_2RAs
- PPIs: (standard of care for the treatment of GERD).
- Esophageal mucosal resistance (sucralfate).
- Antacids (sodium-alginate, $NaHCO_3$, $CaCO_3$).
- Prokinetic agents

(Gastric emptiny, esophageal clearance)

e.g Metoclopramide



↑ QT

Prokinetic agents

5HT4 agonists:

↑ ACh

- Mosapride
- Renzapride
- Cisapride

?

D2-antagonists:

- Metoclopramide

+ 5HT4 agonist

- Domperidone

(peripheral) QT?

Erythromycin

(tolerance)

Also in:
Gastroparesis
Nausea

Motilin R

Bethanechol

Laxatives