Lecture 2
Drugs for Gastric and Duodenal Ulcers

Prof. Omar Shaheen

Department of pharmacology

School of medicine

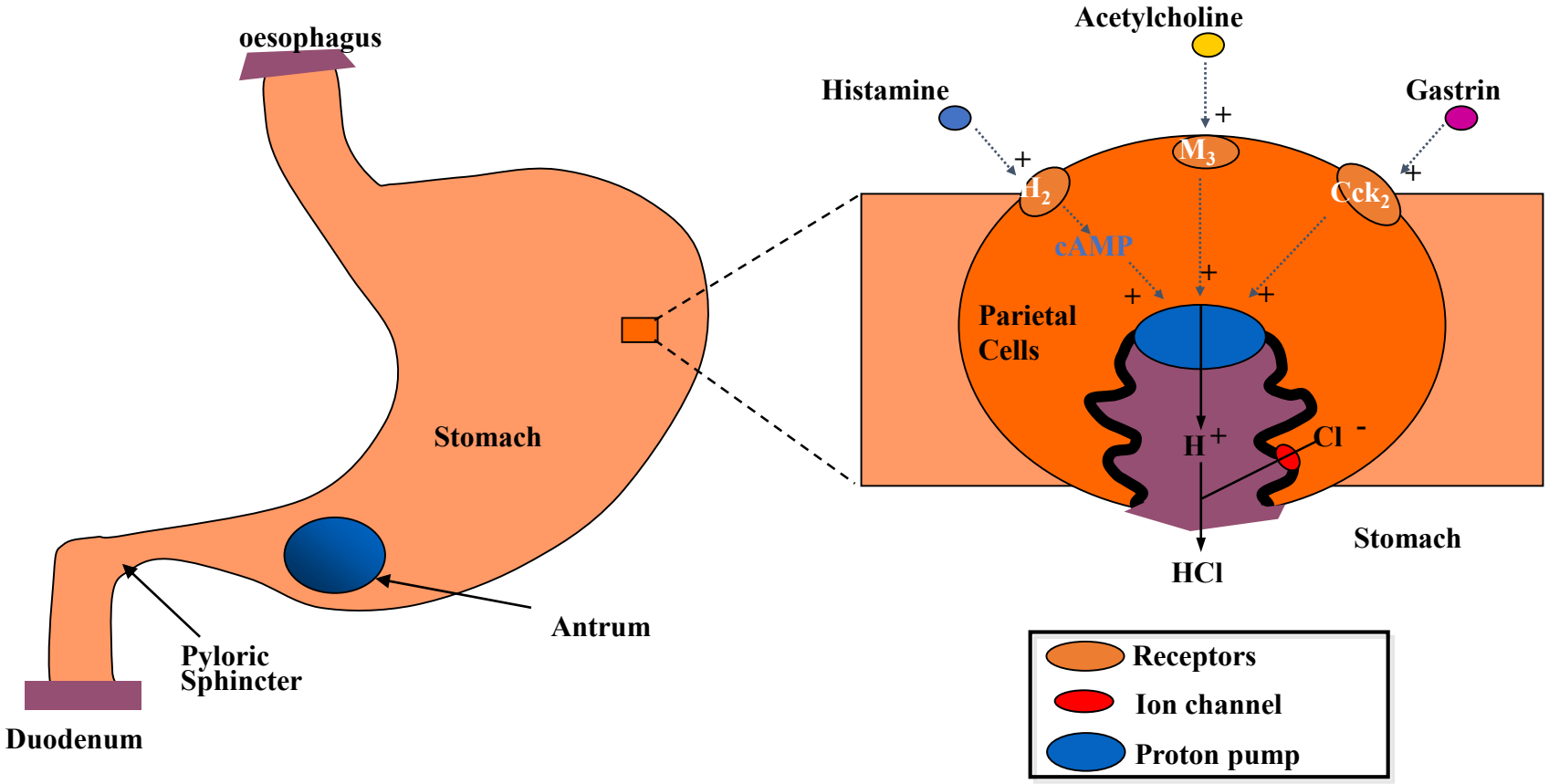
Jordan University

Amman - Jordan

b. Inhibitors of acid production

- **Drugs inhibit** their respective receptors, the transmitter acetylcholine, the hormone gastrin, and histamine released intramucosally stimulate
- the parietal cells of the gastric mucosa to increase output of HCl.
- Histamine comes from enterochromaf n-like (ECL) cells; its release is stimulated by the vagus nerve (via M1 receptors) and hormonally by gastrin.
- The effects of acetylcholine and histamine can be abolished by orally applied antagonists that reach parietal cells via the blood.
- Proton pump inhibitors are drugs of first choice for promoting healing of ulcers.
- Infection with *H. pylori* should be treated resolutely to lower the risk of ulcer recurrence, chronic gastritis, gastric carcinomas, and gastric lymphomas.

Parietal cells and gastric acid release



- **Release of gastric acid is promoted by acetylcholine, gastrin and histamine**

Antimuscarinic agents = Anticholinergic agents

- The cholinoceptor antagonist **pirenzepine and dicycloamine** preferentially blocks cholinoceptors of the M1 type which stimulates the motility of the GIT and HCl secretion; its use in peptic ulcer therapy is now very limited, because of its limited effect and because of the side effects e.g. cardiac arrythmia , dry mouth, constipation, and urinary retention.
- However , cholinergic antagonists can be used as adjuvant therapy in the treatment of peptic ulcer, Zollinger-Ellison syndrome

H_2 antihistaminics

- Histamine receptors on the parietal cells belong to the H2 type and are blocked by **H2 antihistaminics**.
- H_2 blockers inhibit more than 90% of :
    a. Basal gastric acid secretion
    b. Food stimulated HCl secretion
    c. Acute stress ulcer associated, physical trauma in high risk patients in intensive care units
- Mechanism of action:
- H2 blockers competitively block the binding of histamine to H2-receptors , therefore inhibit the action of histamine on adenylate cyclase and causes the reduction of the intracellular concentration of cyclic adenosine monophosphate cAMP and virtually decreases the secretion of HCl

H2 antihistaminics

- H2 antihistaminic also diminish responsivity to other stimulants, e. g., gastrin (in gastrin-producing pancreatic tumors, Zollinger–Ellison syndrome).
- Review article , Drugs 1984, O.Shaheen et al .Comparison between Cimetidine and Ranitidine H2 blockers,USA , Vanderbelt university
- The first H2- blocker used clinically, *cimetidine*, only rarely produces adverse effects (CNS disturbances such as confusion; endocrine effects in the male such as gynecomastia, decreased libido, impotence); however, it inhibits the hepatic biotransformation of many other drugs. Cimitidine was lately withdrawn from the market because of its side effects

H2 antihistaminics…. Therapeutic uses

I. Peptic ulcer : treat pain , reduce HCl concentration, promote healing

N.B : recurrence is common

II. Acute stress ulcer e.g. intensive care units

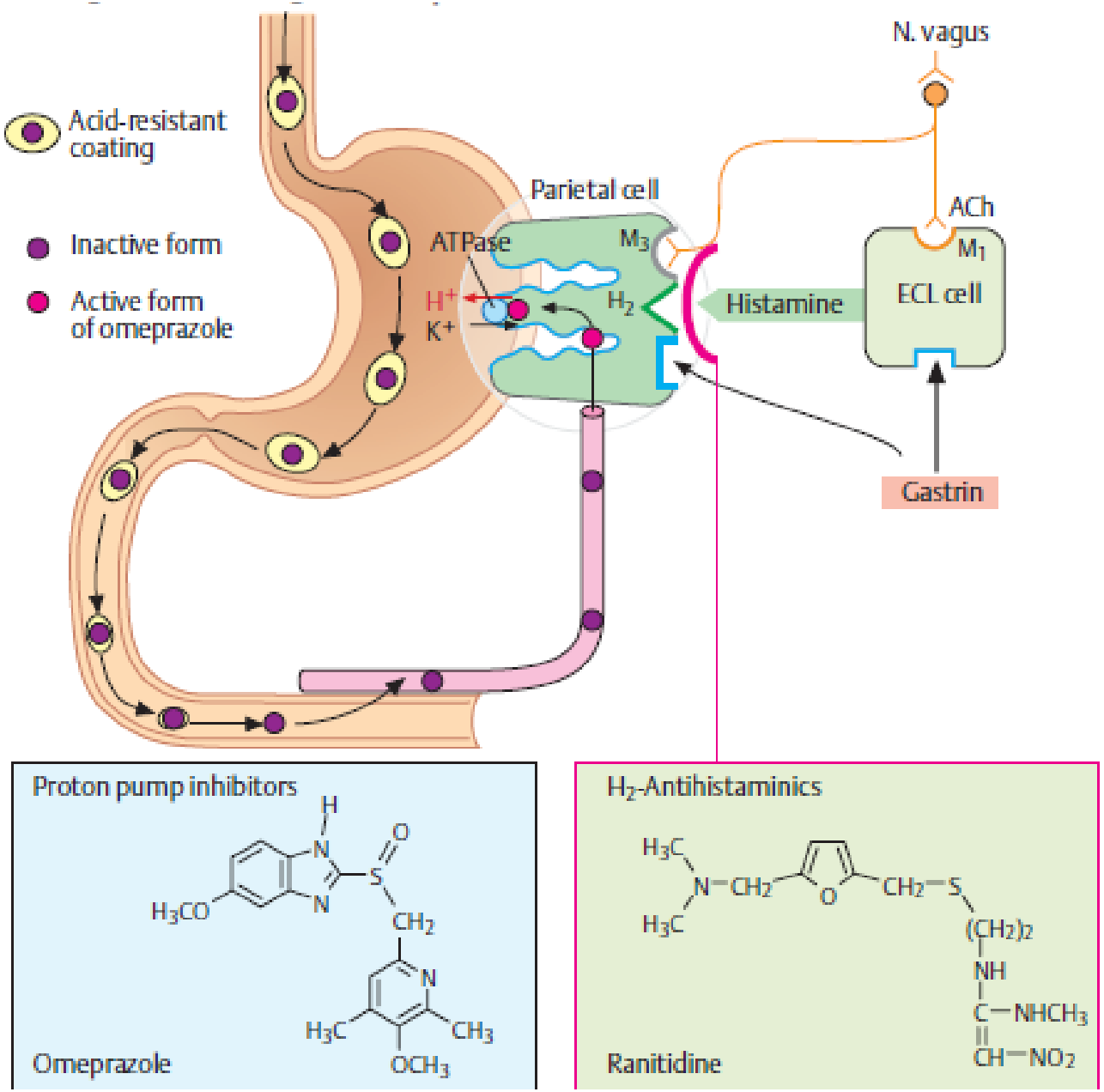
III. Gastro esophagus reflux diseases(low doses)

N.B : Tolerance to the effect of H2 blocker may occur two weeks of therapy

H2 antihistaminics

- The more recently introduced substances *ranitidine*, *nizatidine*, and *famotidine* are effective at lower dosages. Evidently, inhibition of microsomal enzymes decreases with reduced drug load; thus, these substances are less likely to interfere with the therapeutic use of other pharmaceuticals
- Adverse effects: headache, dizziness , diaharea, and muscular pain
- These side effects do not require discontinuation of the drug

Drugs used to lower gastric acid production



Proton pump inhibitors (inhibitors of H+/K+-ATPase proton pump)

- *Omeprazole* is the first drug in this class, Proton pump inhibitors bind to a group of enzyme system known as (proton pump)
- *Omeprazole* can cause maximal inhibition of HCl secretion. Given orally in gastric juice-resistant capsules, it reaches parietal cells via the blood. Where it inhibit proton pump
- These agents are prodrugs with and are formulated to be acid-resistant enteric coated (the coating is removed in the alkaline media in the duodenum)
- an active metabolite is formed and binds covalently to the ATP-driven proton pump (H+/K+-ATPase) that transports H+ in exchange for K+ into the gastric juice.
- *Lansoprazole, pantoprazole*, and *rabeprazole* produce analogous effects. With respect to dosage, the now available (*S*)-omeprazole (*esomeprazole*) represents the more potent enantiomer, but this offers no therapeutic advantage.

Proton pump inhibitors (Therapeutic uses)

- Superior over H2-antagonist for:

a. Suppression of HCl production
b. Ulcer healing
c. Long term treatment (Zollinger –Ellison syndrome)
d. Prevent ulcer recurrence
e. Reduce risk of bleeding from ulcer caused from ulcer by Aspirin and other NSAIDS
f. In combination with antibiotic regimen to eradicate H.pylori

Proton pump inhibitors (Side effects)

- These drugs are well tolerated generally

I. Long term use may cause many side effects due to increased secretion of gastrin, increased pH , and flora disturbances

e.g.

a. Gastric carcinoid tumor
b. Vit. B12 deficiency
c. Incomplete absorption of calcium carbonate
d. Superinfection with clostridium difficile

II. Drug interactions e.g. Warfarin, phenytoin, diazepam , and cyclosporine

Protective Drugs = Mucosal protective drugs

- **A. Chemical structure and protective effect of sucralfate**
- **B. Structure and protective effect of misoprostol**

Protective Drugs = cyto protective

- **Sucralfate** contains numerous aluminum hydroxide residues. However, it is not an antacid because it fails to lower the overall acidity of gastric juice.
- Mechanism of action:

a. Sulfated sucrose binds to positively charged groups of protein components of both normal and narcotic mucosa

b. It stimulates prostaglandin release

c. Bicarbonate output

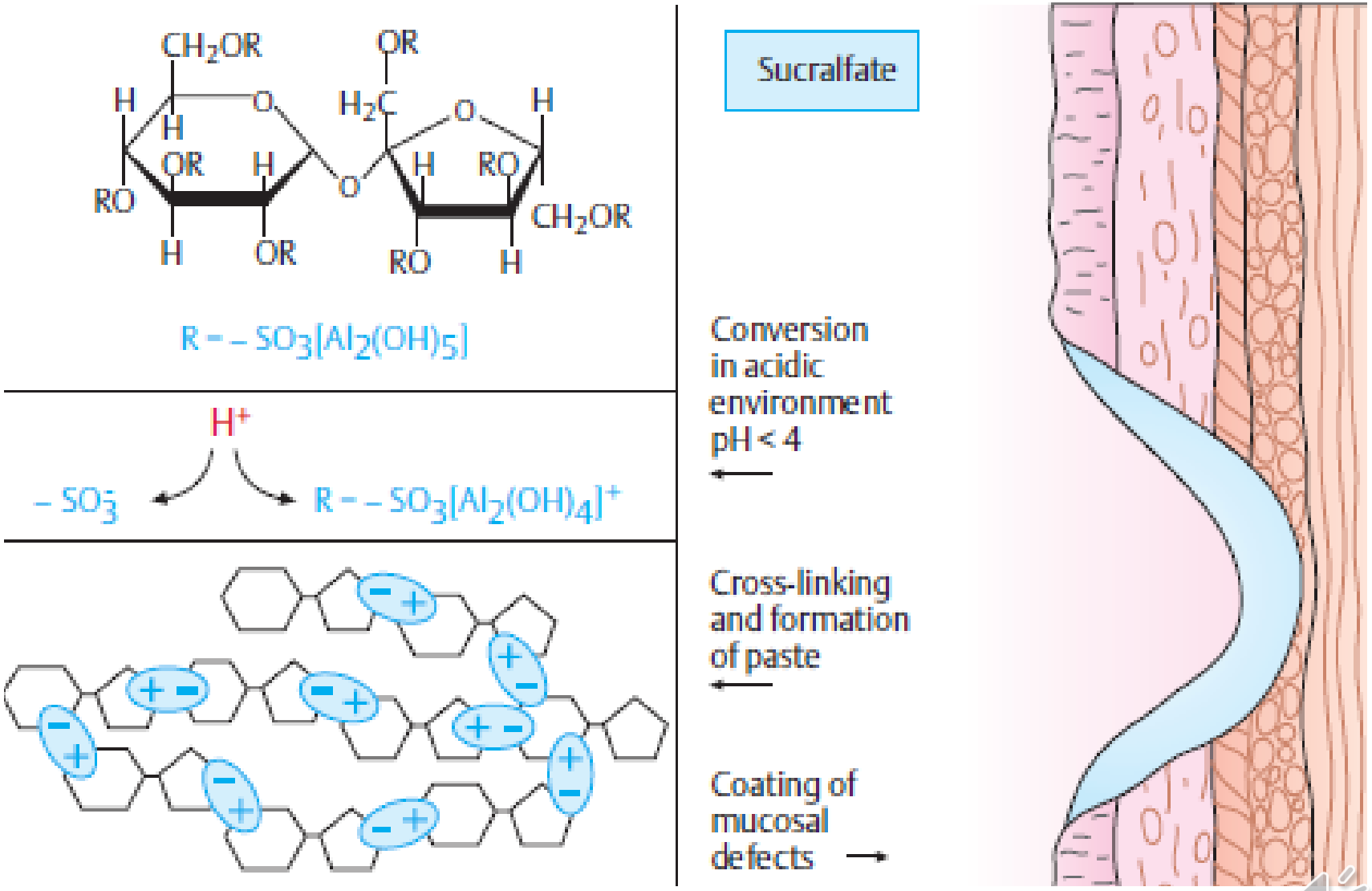
Protective Drugs = cyto-protective

- After oral intake, sucralfate molecules undergo cross-linking in gastric juice, forming a paste (complex gel with epithelial cells) that adheres to mucosal defects and exposed deeper layers. Which creates a physical barrier, which prevents the HCl and pepsin from digestion of exposed stomach tissues
- N.B: Intact gastric mucosa is the only tissue in the body that is resistant to the coastic effect of HCl
- Here sucralfate intercepts H^+. Protected from acid, and also from pepsin, trypsin, and bile acids, the mucosal defect can heal more rapidly
- rapidly.
- Sucralfate is taken on an empty stomach (1 hour before meals and at bedtime). It is well tolerated, but released Al^{3+} ions can cause constipation.
- N.B because it requires low pH (acidic pH) to be activated it should not be administred with H2 blockers or antacids

Protective Drugs (Side effects)

- It interferes with the absorption of the drugs due to complexation
- Absorption of Al^{+3} from ulcer may cause heavy metal toxicity

Chemical structure and protective activity of Sucralfate



Misoprostol

- **Misoprostol is an analogue of prostaglandin E_2**
- **Prostaglandin E_2 is produced by gastric mucosa and it :**

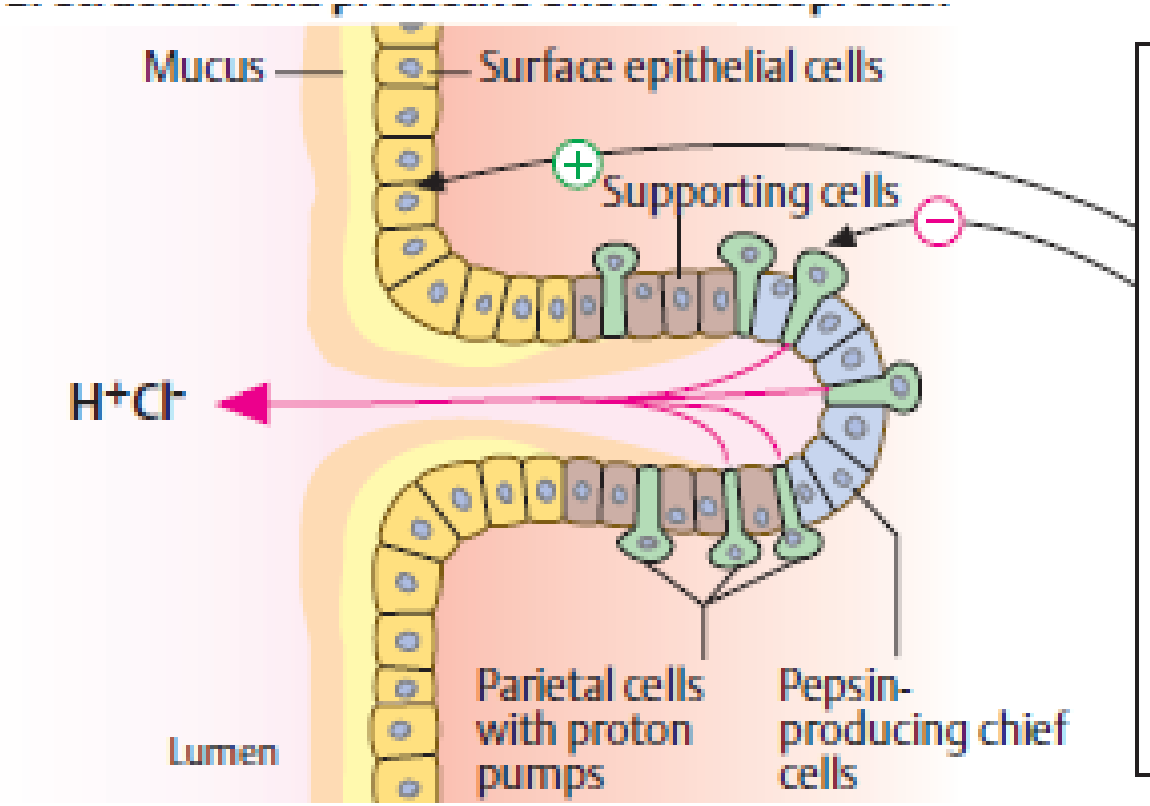
a. **Inhibits HCL secretion (High doses)**
b. **Stimulates mucus secretion**
c. **Stimulates bicarbonate secretion**

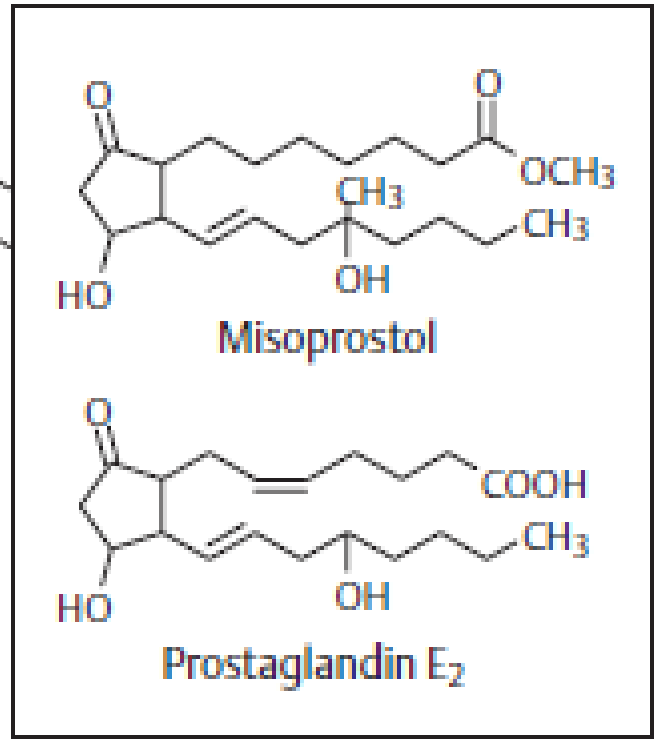
- **Prostaglandin E_2 production is decreased by NSAIDs**

Misoprostol

- **Misoprostol** is a semisynthetic prostaglandin derivative with greater stability than natural prostaglandin, permitting absorption after oral administration. Locally released prostaglandins (PGF2α, PGE2) promote mucus production in superficial cells and inhibit acid secretion of parietal cells
- Inhibition of physiological PG synthesis by drugs (e. g., NSAIDS) explains the mucosal injury from these pharmaceuticals: (so Misoprostol is used as a protective drug)
- protection by the mucus layer is diminished and acid production is enhanced. Misoprostol mimics the action of the prostaglandins on the mucosal tunic and thus can attenuate
- the adverse effects produced by inhibitors of PG synthesis, at least as regards the gastric mucosa. Additional systemic effects (frequent diarrhea; risk of precipitating contractions of the gravid uterus) significantly restrict its therapeutic utility.
- Misoprostol is contraindicated in pregnant woman

Structure and protective effect of misoprostol





Eradication of Helicobacter pylori

- Colloidal bismuth compounds are also effective; however, as they entail the problem of heavy metal exposure, this treatment can no longer be recommended.

Eradication of Helicobacter pylori

- This organism plays an important role in the pathogenesis of chronic gastritis and peptic ulcer disease.
- The combination of antibacterial drugs and omeprazole has proved effective.
- If amoxicillin or clarithromycin cannot be tolerated, metronidazole
- may serve as a substitute.

Drugs used in eradication of H.Pylori