Gastric acid and GI disorders

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- 2. Phases of gastric acid secretion
- 3. Molecular control pathways
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1. Physiology of Gastric Acid Secretion

Physiology of Gastric acid secretion

- 1. Gastric Acid Composition
  - Hydrochloric acid (HCl) is secreted by parietal cells in the gastric glands
  - Maintains a luminal pH of 1.5–3.5
  - Functions
    - Protein denaturation
    - Activation of pepsinogen → pepsin
    - Defense against pathogens

Physiology of Gastric acid secretion

- 2. Parietal Cell Function
  - Located in the fundus and body of the stomach
  - Acid is secreted via H^+/K^+-ATPase (proton pump) on the apical membrane

Physiology of Gastric acid secretion

- 3. Stimulation of Acid Secretion
  - Neural
    - Vagus nerve (CN X) → Acetylcholine binds to M3 receptors → ↑ HCl
  - Hormonal
    - Gastrin from G-cells (antrum)
    - Stimulates parietal cells directly
    - Stimulates enterochromaffin-like (ECL) cells → Histamine → H_2 receptors
  - Paracrine
    - Histamine from ECL cells binds to H_2 receptors → activates adenylate cyclase → ↑ cAMP → ↑ H^+ secretion

Physiology of Gastric acid secretion

- 4. Inhibition of Acid Secretion
  - Somatostatin from D cells (antrum) inhibits
    - G cells (↓ gastrin)
    - ECL cells (↓ histamine)
    - Parietal cells directly
  - Prostaglandins (PGE2) inhibit acid by
    - Decreasing cAMP in parietal cells
    - Enhancing mucosal protection by ↑ mucus and bicarbonate

2. Phases of Gastric Acid Secretion

Phases of Gastric Acid Secretion

Phase	Stimulus	% Total Acid	Mechanism
Cephalic	Sight, smell, thought of food	~30%	Vagal stimulation
Gastric	Food in stomach (distension, peptides)	~60%	Gastrin, vagal, local reflexes
Intestinal	Chyme in duodenum	~10%	Initially stimulates, then inhibits via secretin, CCK

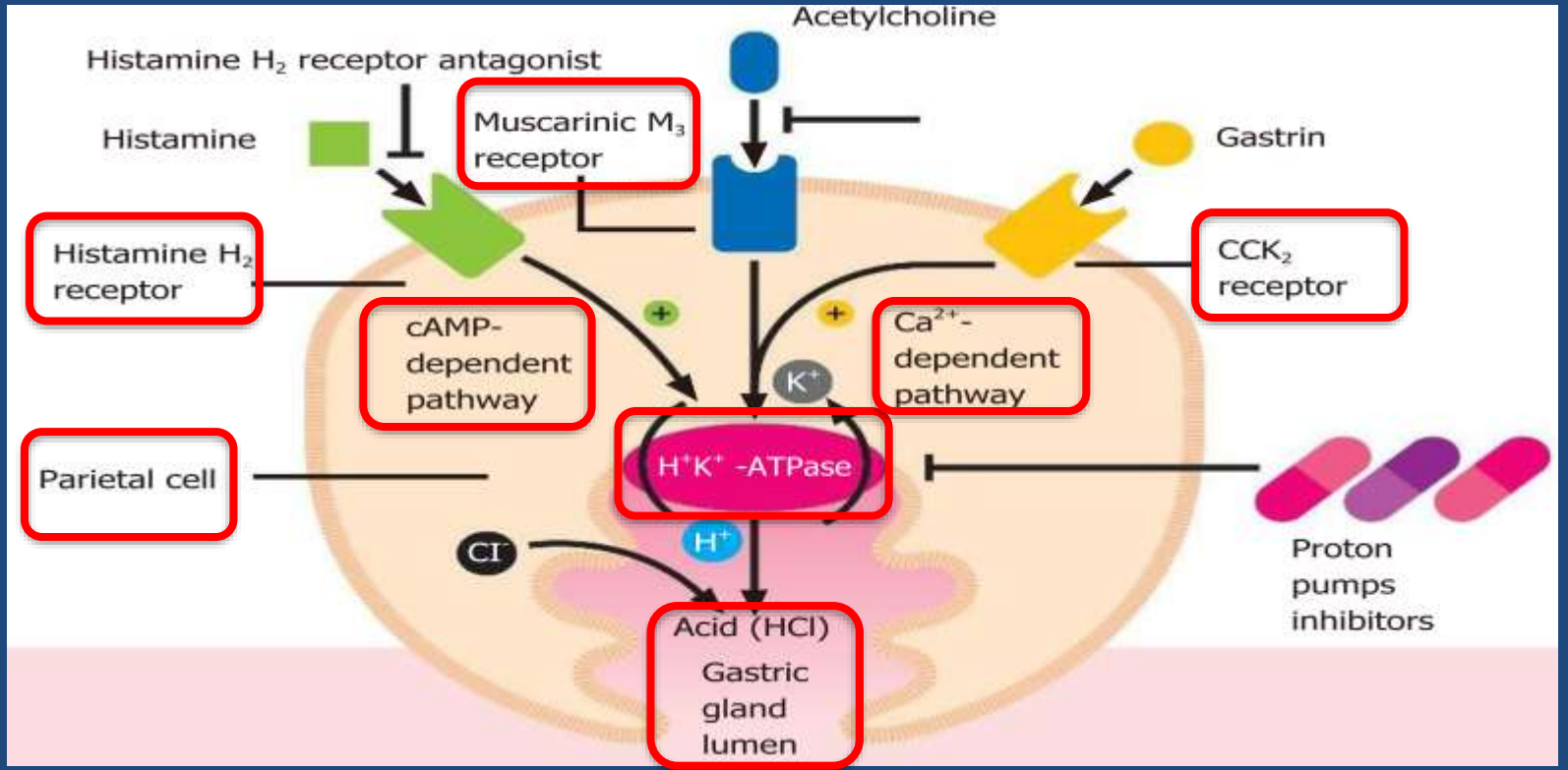
3. Molecular control pathways of Gastric Acid Secretion

Molecular control pathways of Gastric acid

- cAMP Pathway (Histamine)
  - Activates adenylate cyclase → ↑ cAMP → activates Protein Kinase A (PKA) → inserts H^+/K^+ ATPase into membrane

- Ca^{2+} Pathway (ACh, Gastrin)
  - Activates IP_3/DAG pathway → ↑ intracellular Ca^{2+} → stimulates acid secretion

Control of Gastric acid secretion



Pharmacological Options for Acid Suppression

Class	Drug	Mechanism	Onset	Use
Antacids	$MgOH_2$, $AlOH_3$	Neutralize acid	Immediate	Symptomatic relief
Sucralfate	—	Protective mucosal barrier	—	Stress ulcers
Misoprostol	—	PGE_1 analog, increases mucus	—	NSAID-induced ulcers (pregnancy caution)
H2RAs	…tidine	H2 receptor antagonist	Rapid (within 1 hr)	Mild GERD, adjunct to PPI
PPIs	…prazole	Irreversible inhibition of H^+/K^+ ATPase	1–2 hrs, max effect 3–4 days	GERD, PUD, ZES

Molecular control pathways of Gastric acid

- Advanced molecular insights
  - 1. H^+/K^+-ATPase (Proton Pump)
    - A P-type ATPase with α and β subunits
    - Target of PPIs and Vonoprazan
  - 2. Proton Pump Trafficking
    - Resting parietal cells store pumps in tubulovesicles
    - Upon stimulation, vesicles fuse with the apical membrane → pump insertion → acid secretion
    - Actin, Rab11, and H^+/K^+-ATPase recycling are key in this vesicle trafficking

Control of Gastric acid secretion

- **Vonoprazan**: A Novel gastric acid suppressant
  - A Potassium-Competitive Acid Blocker (P-CAB)
  - Directly blocks H^+/K^+ ATPase at the K^+-binding site, unlike PPIs which require acid activation

Feature	Vonoprazan	PPI
Target	K^+ site on proton pump	H^+/K^+-ATPase (sulfhydryl binding)
Activation	Active as given	Requires acid activation
pKa	~9.4 (stable)	Weak bases, degrade at neutral pH
Duration	~24 hours acid control Especially at night time	~12–16 hours
pH Stability	Stable in acid	Unstable in acid

Control of Gastric acid secretion

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Feature	Vonoprazan	PPI
Onset	1–2 hours	Depends on generation of PPI (average – hours and less rapid than Vonoprazan)
Acid suppression	More potent	Less potent
CYP metabolism	Minimal	Extensive (e.g., CYP2C19 polymorphisms affect PPIs)
Meal dependence	No	Yes

4. Disorders related to Gastric Acid Secretion

Disorders related to Gastric Acid Secretion

- 1. Gastroesophageal Reflux Disease (GERD)
  - Pathophysiology
    - Dysfunctional lower esophageal sphincter (LES) permits reflux of gastric contents
    - Chronic exposure causes esophagitis, Barrett's esophagus, and risk of adenocarcinoma
  - Symptoms
    - Heartburn
    - Regurgitation
    - Dysphagia
    - Chronic cough/laryngitis

Disorders related to Gastric Acid Secretion

- 2. Peptic Ulcer Disease (PUD)
  - Causes
    - H. pylori infection (80–90% of duodenal ulcers)
    - NSAID use
    - Smoking
    - Alcohol
  - Pathophysiology
    - Disruption of mucosal defense by acid and pepsin

Disorders related to Gastric Acid Secretion

- 3. Zollinger–Ellison Syndrome (ZES)
  - Pathophysiology
    - Gastrin-secreting tumors (gastrinomas) → excessive acid → refractory ulcers

Disorders related to Gastric Acid Secretion

- Hypochlorhydria & Achlorhydria
  - 1. Autoimmune Atrophic Gastritis & Pernicious Anemia
    - Pathophysiology
      - Autoantibodies against parietal cells and intrinsic factor
      - Loss of acid → impaired B12 absorption
    - Complications
      - Megaloblastic anemia
      - Increased risk of gastric cancer

Disorders related to Gastric Acid Secretion

- Hypochlorhydria & Achlorhydria
  - 2. Chronic PPI Use: Safety Considerations
    - Risks (with long-term use >1 year)
      - Malabsorption: B12, calcium, magnesium, iron
      - Enteric infections: C. difficile, Salmonella
      - Rebound hypersecretion
      - Renal complications, osteoporosis (debatable)

Disorders related to Gastric Acid Secretion

Disorder	Acid Status	Key Features
GERD	↑	Heartburn, regurgitation
PUD	↑	Epigastric pain, H. pylori
ZES	↑↑	Multiple ulcers, diarrhea
Atrophic Gastritis	↓	B12 deficiency
Chronic PPI Use	↓	Nutrient deficiencies

Take-home Message

Gastric acid and GI disorders
Take-home message

- 1. Gastric Acid: Essential Yet Potentially Harmful
  - Hydrochloric acid (HCl) is secreted by parietal cells in response to gastrin, histamine, and acetylcholine
  - It plays vital roles in
    - Protein digestion (via activation of pepsinogen to pepsin)
    - Defense against pathogens
    - Facilitating absorption of iron, calcium, and vitamin B12

Gastric acid and GI disorders
Take-home message

- 2. Dysregulation of Acid Secretion Is Central to Many GI Disorders
  - Hypersecretion (↑ Acid) Leads To
    - Gastroesophageal Reflux Disease (GERD)
    - Peptic Ulcer Disease (PUD)
    - Zollinger–Ellison Syndrome (ZES)
  - Hyposecretion (↓ Acid) Associated With
    - Chronic PPI use
    - Autoimmune atrophic gastritis
    - Pernicious anemia

Gastric acid and GI disorders
Take-home message

- Balance of acid secretion and mucosal defense is crucial for GI health
- Helicobacter pylori and NSAIDs remain major preventable causes of PUD
- Gastric acid suppressing drugs must be used wisely
- Chronic acid suppression has real risks—evaluate indications regularly
- A novel gastric acid suppressing drug: Vonoprazan is now emerging with promising evidences from molecular level to clinical experiences

Thank you