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Stomach

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1. States the functions of the stomach.
    a. Storage of ingested meal
    b. Inhibition of bacterial growth --> stomach acid
    c. Mixing contents of stomach
    d. Mechanical and chemical breakdown of food into small particles; some components solubilized
    e. Regulate rate of emptying into small intestine
    f. Provide intrinsic factor for vitamin B12 absorption (this is the only stomach function that is life critical, can survive w/o it)
2. Identifies the contents of the parietal (oxyntic) cell secretions.
    a. Found in fundus/body of stomach
    b. HCl
    c. Intrinsic Factor
3. Identifies the contents of the chief cell secretions.
    a. Found in fundus, body, antrum
    b. Pepsinogen
4. Describes the role of HCl in gastric digestion.
    a. Kills bacteria in food?
    b. Stimulates pepsin release
    c. Allows freeing of Cobalamin from food
5. States the effects of ingested protein on gastric acidity.
    a. Following sirloin steak
        i. Secretion rises for 1.5 hrs after meal
        ii. Acidity first decreases for an hour then rapidly rises as proteins buffering acid are depleted
    b. Sham feeding: secretion rises only during sham feeding then declines as soon as stimulus is removed
    c. Distension (saline w/o food) causes slight rise in acidity and slow decline
6. States the mechanism for activating pepsinogen.
    a. Synthesized and stored in chief cells.
    b. Release stimulated by vagal nerve and acid in stomach.
        i. Exocytosis
        ii. Responds to increased intracellular Ca2+
    c. Activated by cleavage at acid pH.
        i. Optimally active at pH 2
    d. Initiates digestion of protein.
        i. Proteolytic enzyme especially active on collagen
        ii. Endopeptidase acting on interal peptide bonds
7. Describes the digestion products of pepsin activity.
    a. Peptones
    b. Potent stimulators of gastrin and CCK release
8. Describes the relation between the stomach, intrinsic factor and pernicious anemia.
    a. Intrinsic Factor
        i. Glycoprotein (not easily digested) bound to Vitamin B12, cobalamin
        ii. Produced by parietal cells
        iii. Binds to receptors on ileal absorptive cells and internalized by endocytosis
    b. Cobalamin bound exclusively to animal protein
        i. Involved in methionine synthesis and FA metabolism
        ii. Release from protein requires acid pH thus can be deficient if chronically using PPIs
    c. Absorption of Cobalamin
        i. Food bound Cbl comes into stomach

ii. Acid pH frees Cbl
iii. Binds to R-proteins and IF
iv. Enters duodenum where proteolytic enzymes from pancreas release R protein
v. Cbl-IF complex forms
vi. IF-Cbl absorbed via receptor mediated endocytosis

9. Describes the role of the H+/K+ ATPase in secretion of gastric acid and how it is activated to turn on acid secretion.
    a. Mechanism of HCl Secretion
        i. Carbonic anhydrase in parietal cell makes H+ and HCO3-
        ii. H+ transported out into lumen in exchange for K+ via H+/K+ ATPase ("proton pump")
        iii. K+ recycled back out into lumen via K+ channel resulting in elevated K+ in gastric juices
        iv. Cl- exits passively through channel
            1) Basolateral membrane of cell has Cl-/HCO3- exchanger to pump bicarb created out and bring Cl- in to maintain intracellular homeostasis
            2) Na+/K+ ATPase also maintains intracellular balance like other cells
    b. H+/K+ ATPase is structurally and functionally similar to Na+/K+ ATPase and Ca2+ ATPase in muscle
        i. Catalytic alpha subunit
        ii. Glycoprotein beta subunit for targeting
        iii. Target of proton pump inhibitors (omeprazole)
            1) Weak bases that concentrate in low pH
            2) Activated by molecular rearrangement due to low pH
            3) Binds to cysteine residues in alpha subunit
            4) More potent than H2 blockers
    c. Activation of H+/K+ ATPase
        i. At rest, most is present within cell in tubules and vesicles in inactive form
        ii. Parietal cell stimulation leads to vesicles fusing with luminal membrane
        iii. Reversed with removal of stimulus
        iv. Receptors and Intracellular Messengers
            1) H2 histamine channels activate adenylate cyclase --> cAMP --> proton pump activation
            2) Gastrin and M3 muscarinic receptors activate phospholipase C --> Ca2+ --> proton pump
            3) Somatostatin acts on receptor couples to inhibitory G protein and inhibits adenylate cyclase
10. Describes the role of the enterochromafin-like cell in stimulation of gastric acid secretion
    a. Food leads to gastrin release
    b. CNS stimulation leads to acetylcholine release
    c. Gastrin from G cells and ACh both stimulate ECL cells to release histamine
        i. G cells release gastrin in response to amino acids or digested protein
    d. Inhibition by blocking gastrin release or activation of proton pump
        i. Somatostatin released from D cells in antrum/body in response to luminal acid (pH<3)
        ii. PGE from surface cells
        iii. Intestinal hormones collectively termed "enterogastrone"
11. Describes the types of molecules that are absorbed into the blood across the wall of the gastric mucosa.
    a. Ethanol because it is lipid soluble
    b. Salicylates because they are weak acids
12. States the effects of aspirin and bile acids on the gastric mucosal barrier.
    a. Barrier Components
        i. Mucus creates barrier that acids cannot dissolve as fast as it is created by pepsin
        ii. HCO3- neutralizes acid and creates gradient from pH 2 in lumen to pH 7 near surface mucous cells
        iii. Surfactant removes any penetrating acids
        iv. Tight junctions between epithelial cells
    b. Aspirin (NSAIDS) block effect of endogenous prostaglandins which stimulate secretion of gastric mucous and therefore can lead to degradation of mucosal barrier

c. Bile salts and lysolecithin if refluxed across pylorus can destroy the barrier as well

13. States the effect of vagal stimulation, gastrin, histamine and somatostatin on HCl secretion.
    a. Vagal stimulation leads to acetylcholine release from nerves
        i. ACh can directly act on M3 receptors to stimulates PLC-->Ca2+-->proton pump activation
        ii. Vagal stimulation can also stimulate ECL cells to release histamine
    b. Gastrin can either stimulate ECL cell histamine release or PLC activation in the parietal cell
    c. Histamine acts on H2 receptors to activate adenylate cyclase
    d. Somatostatin inhibits adenylate cyclase and therefore decreases HCl secretion
14. Describes the mechanism of potentiation between gastrin, histamine and acetylcholine in initiating gastric acid secretion.
    a. Potentiation is that the effect of combined second messengers is greater than the sum of the individual effects
    b. Therefore the efficacy of H2 blockers is higher than simply reducing the histamine response but also taking away the potentiated response
15. Describes the stimuli and possible pathways giving rise to the cephalic, gastric and intestinal phases of HCl secretion.
    a. Cephalic
        i. Sight, taste, smell chewing, stress --> vagus nerve --> enteric nerve plexus
        ii. Enteric nerve plexus releases GRP, ACh and stimulates ECL Cells
        iii. G-Cells release Gastrin which activates ECL Cells and Parietal Cells
        iv. ECL Cells release histamine
        v. Histamine and ACh directly activate parietal cell to secrete HCl
    b. Gastric
        i. Peptides, amino acids and distension activate
            1) G-Cells
            2) Vagal nerve stimulation --> Parietal cell activation
        ii. G-cells release gastrin to activate
            1) ECL Cells
            2) Parietal cells
        iii. ECL Cells release histamine to activate parietal cells
        iv. Parietal cells secrete HCl
            1) Activates D-cells to release somatostatin
            2) Buffered by proteins in meal
        v. Somatostatin inhibits G-Cells and Parietal cells
    c. Intestinal
        i. Luminal stimuli
            1) FA
            2) Acids
            3) Amino acids
            4) Hypertonic solutions
            5) Distension
        ii. Stimuli activates nerves and glands
            1) Glands release hormones
                a) Enterogastrone - hormone from gut
                b) GIP
                c) CCK - in response to fat
                d) Secretin - in response to acid
            2) Nerves and hormones inhibit parietal cell secretion and gastrin release
16. States the effect of luminal peptides on HCl secretion. --> increases HCl secretion
17. Identifies the stimuli that increase and inhibit gastrin release.
    a. Increase: Luminal acids and digested proteins
    b. Inhibit: somatostatin released in response to pH<3.0