Regulation of gastric secretion

proteins in stomach

cephalic & oral phase

distension

parasympathetic activation (via ENS)

strongest stimulus for HCl secretion,

+ pepsinogen, HCO_3^-, mucus

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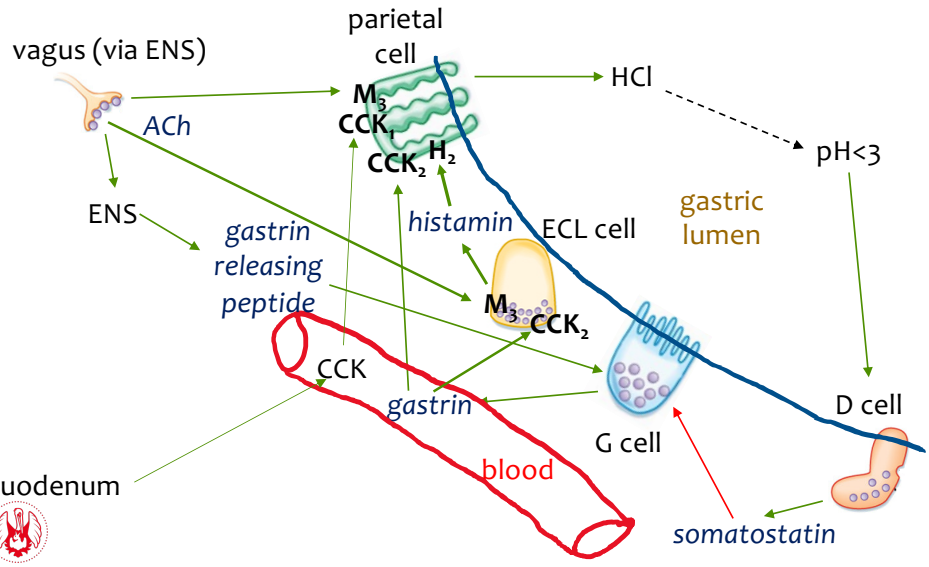
Regulation of HCl secretion



80

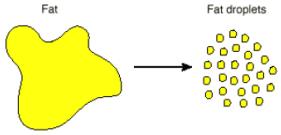
Regulation of pepsinogen secretion

- stimulation:
  - ACh (vagus, ENS) > CCK (duodenum) > histamin (ECL cells) > gastrin (G cells *via* bloodstream) > secretin (duodenum)
  - low gastric pH (likely *via* ENS stimulation)
- inhibition:
  - somatostatin (D cells)

81

Other digestion in stomach

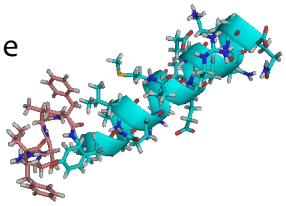
- saccharides
  - remnants of amylase activity, negligible
- lipids
  - emulsification (mixing movements)
  - gastric lipase: ~10% of all lipid hydrolysis, not essential



82

Migrating myoelectric complex (MMC)

- empty stomach rests ~75-90 min, then 5-10 min intense contractions of antrum with relaxed pylorus
- removes non-digested remnants (even large pieces)
- stimulated by motilin
  - polypetide (22 AA) hormone from small intestine
  - produced in hunger, perhaps stimulated by high pH in duodenum?



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Vomiting (emesis)

- protective reflex against toxicity x longer vomiting → metabolic alkalosis & dehydration
- vomiting center in medulla (next to cardiovascular & respiratory centers)
- stimuli (stomach/duodenum, larynx entry, inner ear):
  - mechanical (distension, irritation)
  - injury, pain
  - chemical (toxins, emetics - chemoreceptors in stomach/duodenum & bottom of the 4th chamber)

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Vomiting

- usually preceded with nausea, sometimes anorexia, autonomic reactions (salivation, sweating, cold skin,...)
- reverse peristalsis
  from the middle of small intestine to larynx
- forced inspiration against closed glottis -
  ↓ intrathoracic pressure, ↑ abdominal (diaphragm)
- strong contraction of abdominal muscles & diaphragm
  (except its middle part – that would compress LES)
- relaxation, then closure of pylorus, relaxation of LES and finally UES (glottis closure, ↓ breathing)

85

Integrated response to meal: small intestinal phase

- regulation of gastric emptying
- ↓ gastric HCl secretion
- interruption of MMC
- small intestinal motility
- ↑ pancreatic secretion
- gallbladder contraction
- sphincter of Oddi relaxation
- absorbtion

86

Filling the gut

- continuous processing by duodenum (despite irregular pattern of food intake)
- prevents injury to duodenum by acid
- strong contractions of antrum (strong muscles, middle oblique layer) against almost closed pylorus (prevents regurgitation - bile could damage stomach wall)
- stomach empties in ~ 3 hours

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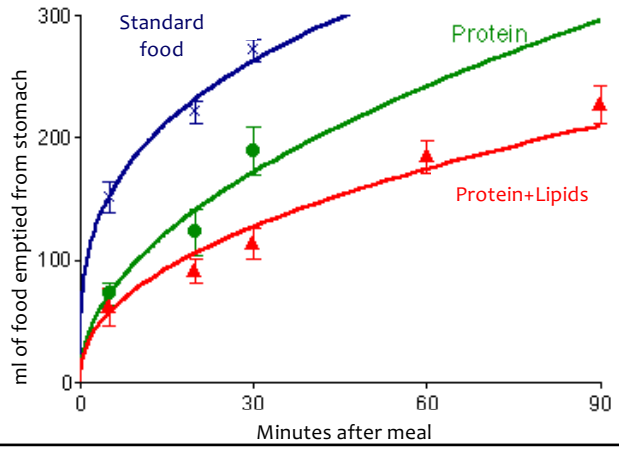
Gut filling depends on food composition

Intestine digests different nutrients at varying rates.
This "dictates" the rate at which it is filled

That 's why fats help prevent drunkenness: fat stays longer in the stomach, keeps alcohol there, alcohol resorption from stomach is slower than from gut



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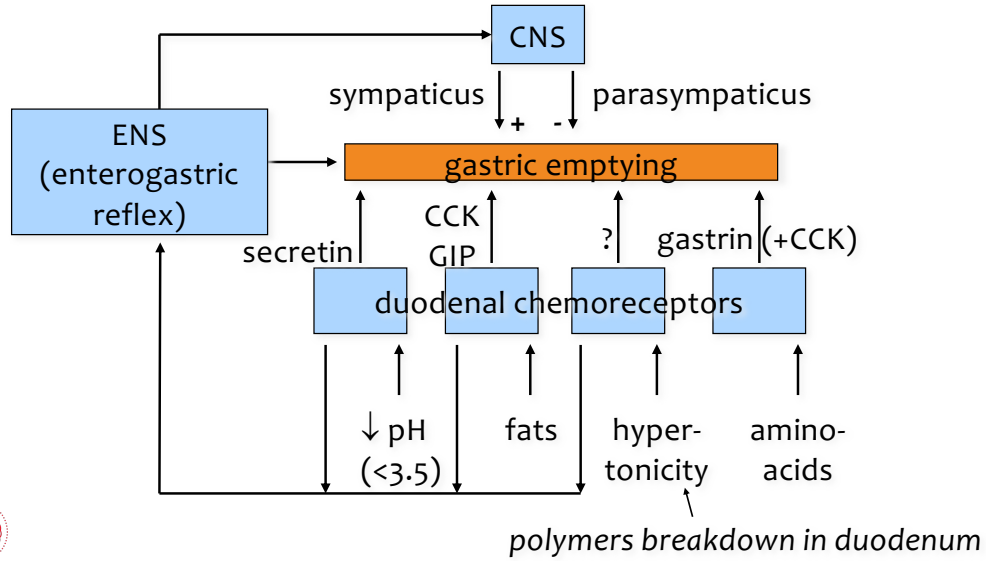
Regulation of stomach emptying



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Small intestine

- duodenum the first 5% of length,
  jejunum next 40, ileum the rest
- most of digestion in duodenum & jejunum,
  ileum not essential
- peristalsis simultaneously only in short segments (~10 cm)
  (except MMC)
- large internal surface area (~200 m^2)
  - length (5-7 m)
  - villi + crypts
  - microvilli
- pH ~7 (duodenum) to 7.2
  (HCO_3^- mainly from pancreas, also duodenal glands)

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Small intestine : segmentation

- alternating localized contractions of circular muscles
- mix chyme with intestinal fluid, contact with intestinal wall
- frequency determined by BER (~11-13/min duodenum, 8-9 end of ileum)
- BER run along the whole length, AP only locally - in these places segmentation contractions
- BER independent of innervation, contractility ↑ by PNS, ↓ by SNS (through ENS)

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Intestinal reflexes

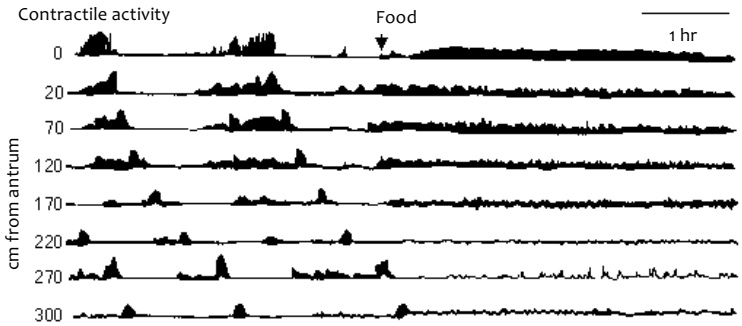
- local (e.g. peristaltic reflex) - ENS only
- mediated by both ENS & external innervation:
  - intestinointestinal reflex - excessive distension of one part of the gut relaxes the rest
  - gastroileal reflex - ↑ stomach activity → ↑ chymus movement through ileocecal sphincter
  - ileogastric reflex - ↓ stomach motility elicited by distension of ileum

95

MMC in hunger

- similar as in stomach; gradually from there → end of small intestine
- segmentations cease
- peristaltic waves include ~70 cm of gut
- every 70-90 min, the whole smaller intestine traversed by a series of MMP in 1-2 hr

"sweeps" non-digested remnants & prevents bacteria migration from colon



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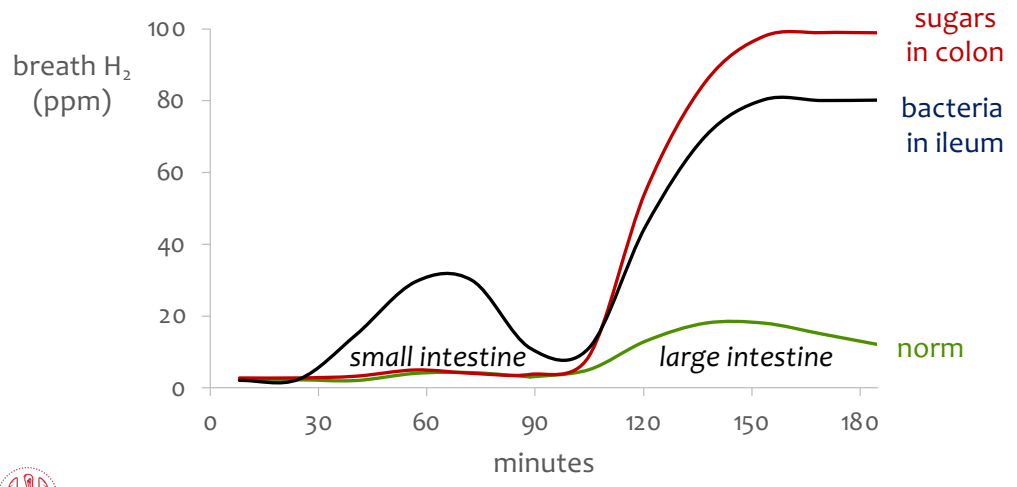
Weak MMC

- bacteria remain in small intestine → they grow (plenty of food)
- they release H_2 (no other source in humans)
  - only when they can use non-digested sugars (normally not present in colon)
  - elevated H_2:
    - either undigested sugar in colon (e.g. lactose intolerance, accelerated passage)
    - or bacteria go upstream to ileum
  - some H_2 gets in blood, from there to breath, can be measured

97

Breath H_2 test



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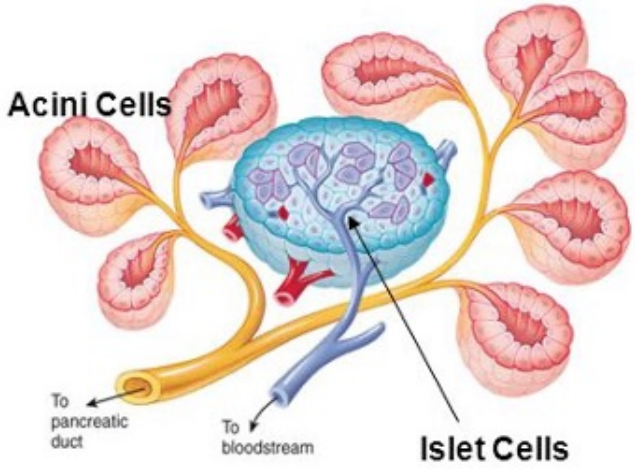
Contractions of muscularis mucosae

- alter the shape of ridges & folds of mucosa, contract the villi (”milking" of the products of digestion to lymphatic passages), ”waving" of the villi
- improve contact of chyme with mucosa, mixing
- support lymph flow

99

Pancreas – essential for all digestion

- similar to salivary glands
  - acini
  - ducts
- ~1.5 l/d



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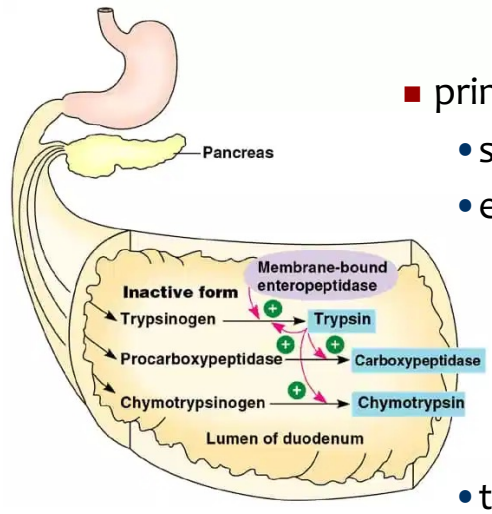
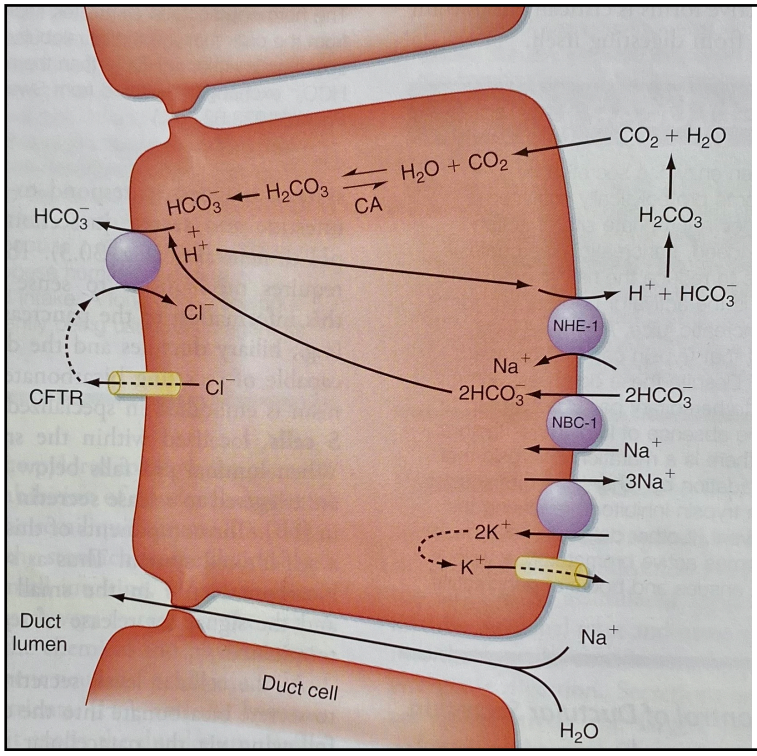


Pancreatic secretion

- primary (acini):
  - similar ions as in plasma
  - enzymes (all inactive):
    - trypsin, chymotrypsin, proelastase, procarboxypeptidase A & B
    - amylase
    - lipase
    - (deoxy)ribonuclease
  - trypsin inhibitors (trypsin activates all)
- ducts: H_2O, HCO_3^- (exchange for Cl^- - CFTR)

101



Pancreatic duct cell

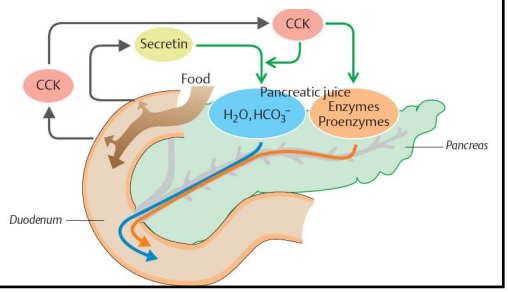
- extra HCO_3^- in blood from stomach
- carboanhydrase
- NBC1 = Na/HCO_3^- symporter 1
- NHE1 = Na/H exchanger 1

102

Regulation of pancreatic secretion

presence in duodenum:		duodenal hormone:		secretion in pancreas:
acidity	→	secretin (S cells)	→	HCO_3^-
peptides (aminoacids) lipids (free fatty acids)	→	CCK (I cells)	→	enzymes

vagus



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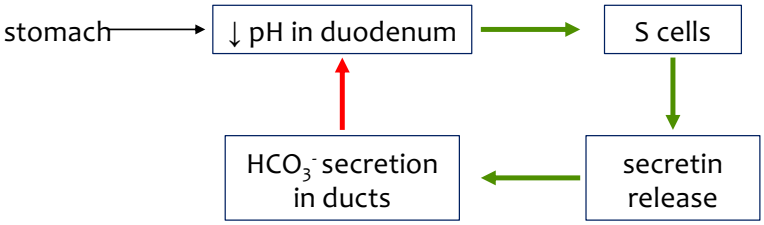
Řízení pH v duodenu

- at pH<4.5, S cells (duodenum and jejunum) release secretin into the blood
- secretin activates CFTR in pancreatic ducts
- HCO_3^- from blood (↑ due to HCl formation in the stomach) and by carboanhydrase



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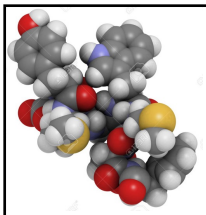
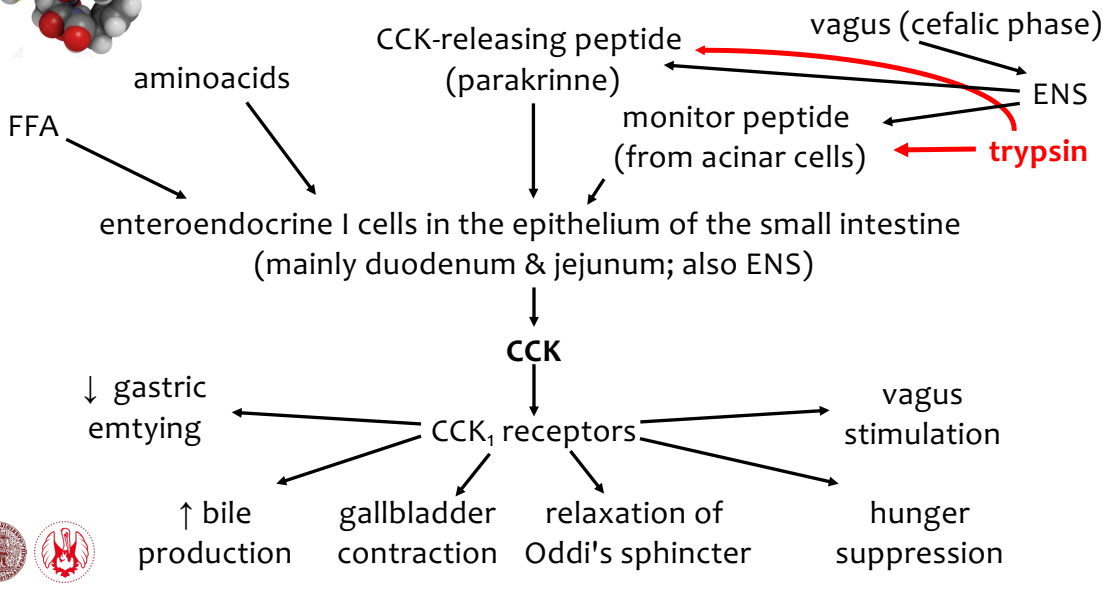


Cholecystokinin (pankreozymin)



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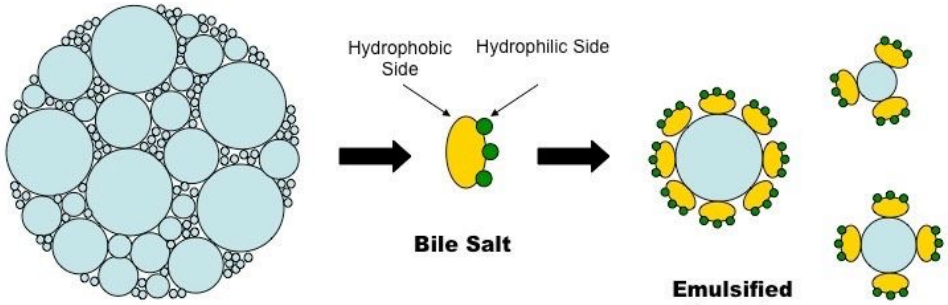
Bile (gall)

- produced in liver
- primary bile acids (cholic and chenodeoxycholic) by cholesterol oxidation catalysed by cytochrome P450
- lipid emulsification (bile acids ⟶ salts - amphiphilic)



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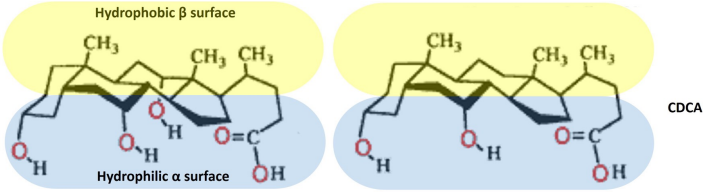
Bile acids (steroid)

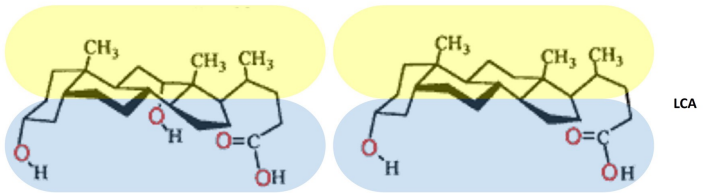
- toxic to many bacteria
- conjugated (in liver) with aminoacids taurine or glycine ⟶ soluble bile salts

cholic acid



- deconjugated by bacteria
  (sparing taurine & glycine before defecation)

chenodeoxycholic acid



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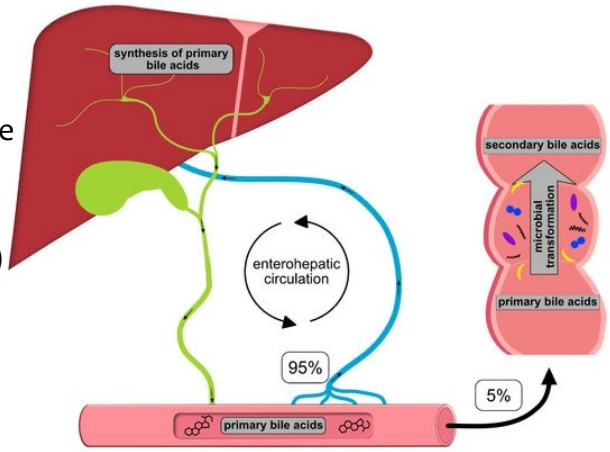
Enterohepatic circulation of bile acids

- minimal overflow into the colon and arterial blood
- 3-4x/d
- apical Na/bile acid co-transporter (ASBT) + basolateral organic solute transporter (OST) α+β in distal ileum enterocytes
- dysfunction ⟶ diarrhea (osmotic)
- recycling of lipid xenobiotics (↑ damage)



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Small intestinal enzymes

dipeptides —*dipeptidases*→ amino acids

maltose —*maltase*→ glucose + glucose

lactose —*lactase*→ glucose + galactose

sucrose —*sucrase*→ glucose + fructose

di- & monoglycerides —*lipases*→ fatty acids + glycerol

nucleotides —*nucleotidases*→ nucleosides —*nucleosidases*→ sugars + bases

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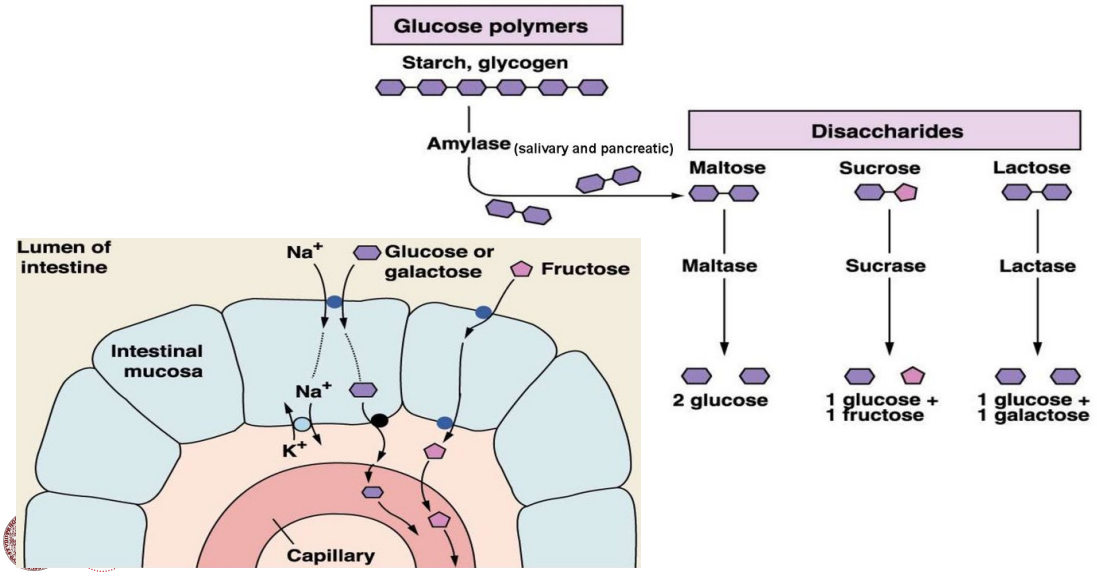
Carbohydrate assimilation



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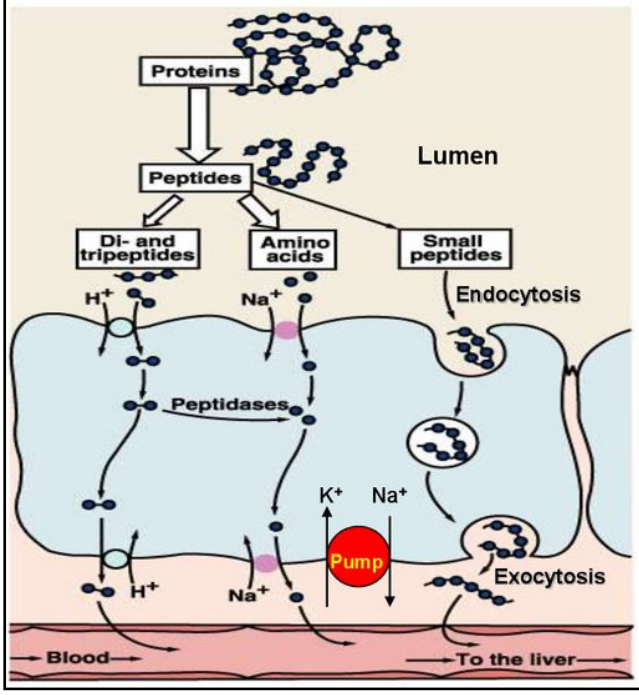
Protein assimilation



- some small proteins by endocytosis
- AA & di- & tripeptides by Na-dependent secondary active transport

112

Emptying of ileum

- ileocecal sphincter (valve) normally closed (e.g. because of bacteria)
- opened by distension of end of ileum (local reflex)
- closed by distension of proximal colon (local reflex)

115

Integrated response to meal: colonic phase

- water & ions absorption
- HCO_3^- secretion - neutralization of acids formed by the intestinal flora
- mucus - protection, lubrication
- absorption of vitamins B & K formed by colonic microorganisms
- storage of unnecessary residues (typically 15-30 hours, but up to 30% can remain for up to a week)

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Large intestine

- mainly mixing, only ~5% of movement is peristalsis
- mixing more difficult with ↑ density
- haustrations, swing movement, mass movement

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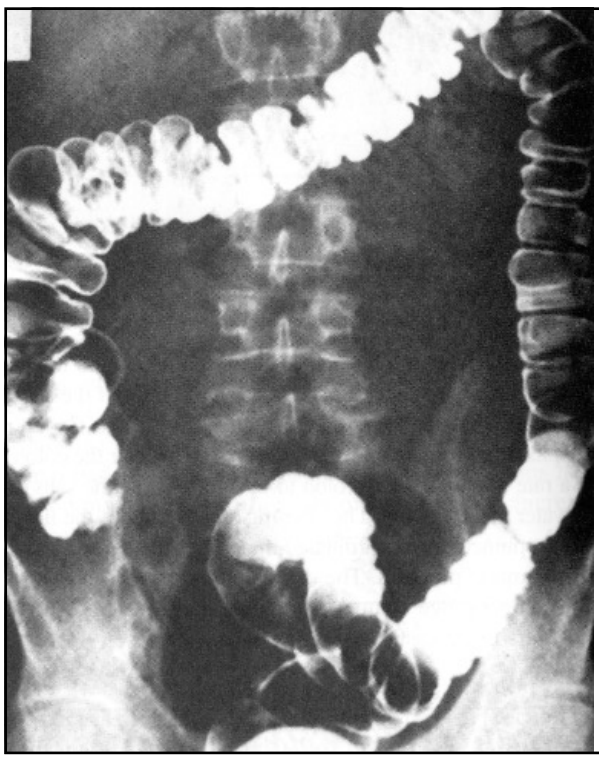

Haustrations

- similar to segmentation, but more marked & in anatomically pre-defined locations of circular muscle layer
- governed by BER from interstitial cells (~6/min)
- usually no AP
- stronger contractions (e.g. ACh) by prolonging BER

118

Swing movements of large intestine

- longitudinal muscles, mixing
- controlled by myenteric potential oscillations (lower amplitude, higher frequency than slow waves)
- have APs on their top, APs elicit contractions
- contractions are stronger when APs more frequent (e.g. ACh)

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Mass movement

- 1-3x/day (usually after meal)
- wave of strong contraction
- moves content to larger distances (most of colon length)
- colon remains contracted for a while
- overall movement is slow (max 5-10 cm/hr)
- controlled by ENS
- SNS blunts movements, PNS stimulates haustrations of proximal parts & expulsive movements of distal parts

120

Reflexes of large intestine

- colono-colic - distension of one part relaxes the rest (partly SNS)
- gastro-colic - filling of stomach increases frequency of mass movements
  (SNS, PNS, CCK, gastrin)
- similarly duodeno-colic

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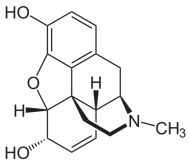
Opioids

- endogenous opioids (met-enkephalin, leu-enkephalin, β-endorphin, dynorphin) & their receptors richly expressed in GI tract (ENS) → possible physiol. function, but uncertain
- morphine mostly in colon:
  - stronger contractions, but↓ forward movement → ↑ H_2O reabsorption
  - mainly local (μ receptors)
  - partly also central (μ a κ effect)
- also↓ gastric emptying



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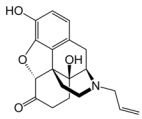
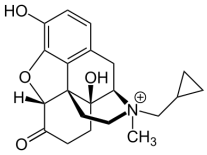
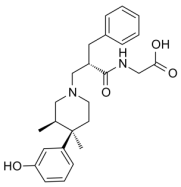
How to handle opioid inhibition of motility?

- selective inhibition of peripheral μ-receptors (analgesia is mediated by central receptors)
- classic: naloxone – inhibits periph. & central
- recent: methylnaltrexone, alvimopan – mainly periph. action, restore motility without reducing analgesia







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Rectum & anal channel

- Rectum usually (almost) empty (retrograde contractions return content to sigmoideum, until there is too much of it)
- Just before defecation mass movement in sigmoideum fills rectum → ↑ pressure → reflex relaxation of inner sphincter (smooth muscle) & contraction of outer sph. (skeletal muscle controlled intentionally via pudendal nerves)
- Stretch receptors in rectal wall can adapt - urge to defecate can temporarily subside id suppressed

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Defecation

- reflex controlled from sacral spinal cord, modulated from higher levels (conscience, will)
- efferent branch - ACh parasympathetic fibers in pelvic nerves
- highly propulsive contraction of descending colon & sigmoideum
- relaxation of both sphincters (outer voluntary)
- inspiration pushes the diaphragm downwards
- contraction of expiratory muscles with full lungs & contraction of abdominal muscles increase abdominal pressure (up to 200 mmHg)

125

Satiety

- distension inhibits intake
  - ↓ stomach size (bariatric surgery) ⟶ ↓ meal sizes
- cholecystokinin ~ "satiety hormone"
  - ↑ by nutrients
  - inhibits food intake (CCK receptors v CNS)
- glykémie
- glucagon-like peptide 1 (GLP-1)
- peptide YY (PYY)

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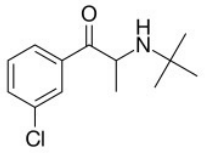
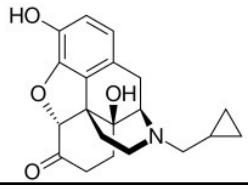
Pharmacotherapy of obesity

- not only GIT, but also physiology of adipose tissue & CNS regulation of food intake

- Mysimba (bupropion + naltrexone)
  - bupropion:
    - ↓ dopamine and NA reuptake
    - ↑ hypothalamic proopiomelanocortin anorexigenic axis → suppresses appetite
  - naltrexone:
    - ↓ μ-opioid receptors
    - ↓ β-endorphine binding
    - ↓ feedback inhibitory mechanism that would reduce proopiomelanocortin production





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