GI Physiology

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Liver

**Functional Anatomy**

- impt function is a filter between blood coming from GI tract and blood from rest of body
- blood from intestines reach liver via portal vein
- portal vein $\Rightarrow$ sinusoids between plates of hepatic cells $\Rightarrow$ central vein $\Rightarrow$ coalesce to hepatic veins $\Rightarrow$ IVC $\Rightarrow$ hepatic artery blood also empties into sinusoids
- bile is formed on the other side/adjacent to each plate of liver cells in bile canaliculi:
  - bile canaliculi $\Rightarrow$ intralobular bile ducts $\Rightarrow$ interlobular bile ducts $\Rightarrow$ R or L hepatic duct $\Rightarrow$ join outside liver = common hepatic duct
- common hepatic duct joins with cystic duct (from GB) $\Rightarrow$ common bile duct $\Rightarrow$ (usually) joins with main pancreatic duct prior to $\Rightarrow$ enter duodenum at duodenal papilla (surrounded by sphincter of oddi
- sphincter of oddi:
  - usually closed
  - to open:
    - gastric contents into duodenum $\Rightarrow$ CCK release $\Rightarrow$ gastrointestinal hormone relaxes sphincter
- in each hepatic lobule, plates of hepatic cells = 1 cell thick
- microcirculation:
  - large gaps found between endothelial cells allow movement of blood contents into hepatocytes and vice versa
    $\Rightarrow$ sinusoids = highly permeable
  - Kupffer cells (phagocytes) anchored to endothelium of sinusoids and project into lumen
- transit time across lobule from portal lobule $\Rightarrow$ central hepatic vein $\Rightarrow$ 8.4 secs
Hepatic Circulation

- functional unit of liver = acinus
- each acinus found at end of vascular stalk containing (akin to aveoli or grapes on a stalk):
  - terminal branches portal vein
  - hepatic arteries
  - bile ducts
- acinus is surrounded on periphery by hepatic veins
  - thus blood flows from central to peripheral outwardly
- acinus divided into zones:
  - zone 1 = central - well oxygenated
  - zone 2
  - zone 3 - peripheral - least well oxygenated . susceptible to anoxic injury
- liver has 100,000 acini
Functions of Liver

1. Metabolic:
   - CHO
   - Lipid & cholesterol
   - Protein & plasma protein production
   - fat soluble vitamins
2. Endocrine
3. Detoxification / Metabolism of drugs and xenobiotics
4. Immunologic
5. Coagulation
6. Acid Base
7. Bile formation
8. Reservoir for blood
9. Urea formation
10. Storage function
11. Haematopoiesis

1. Metabolism

CHO
- CHO metabolism:
  - glycogen metabolism (glycogenlysis, glycogen synthesis + storage)
  - GNG
  - conversion of galactose \( \Rightarrow \) fructose \( \Rightarrow \) glucose
- glucostat function:
  - buffering of BSL: removes glucose post prandial, and returns it when needed
  - low BSL \( \Rightarrow \) opposite reaction ie production of glucose from non-glucogenic precursors

Lipid Metabolism
- synthesis of most lipoproteins
- synthesis of large amounts cholesterol & phospholipids:
  - 80% cholesterol made \( \Rightarrow \) bile acids
  - 20%\( \Rightarrow \) lipoproteins eg LDL
- conversion of CHO & protein \( \Rightarrow \) fat:
  - occurs almost exclusively in liver
  - then transported in lipoproteins \( \Rightarrow \) adipose for storage
- FA \( \beta \) oxidation for liver energy and other organs
- ketone production:
  - neutral fats split into glycerol + FA
  - FA \( \Rightarrow \) \( \beta \)-oxidation \( \Rightarrow \) acetyl CoA \( \Rightarrow \) citric acid \( \Rightarrow \) 9 kCal/g fat
  - liver cannot utilise all acetyl CoA formed \( \Rightarrow \) 2 acetylCoA condense (deacylase enzyme) \( \Rightarrow \) acetoacetylCoA
  - CoA removed \( \Rightarrow \) acetoacetic acid \( \Rightarrow \) \( \beta \)-hydroxybuturic acid & acetone
  - ketone bodies distributed to rest of body where reconverted to acetylCoA for citric acid cycle energy eg heart

Protein Metabolism
- =essential function for life
- deamination of aa’s \( \Rightarrow \) needed prior to energy utilisation

By Adam Hollingworth
formation of urea as part of alanine cycle
plasma protein production:
  • acute phase proteins
  • albumin - most significant
  • clotting factors
  • steroid binding & other hormone binding proteins
  → (liver makes all proteins except Immunoglobulins)
• interconversions between different amino acids

2. Endocrine
• 25 (OH) cholecalciferol production:
  • (OH)\(_2\)D - created in skin from UV light
  • 25-(OH)\(_2\)D - created in liver by hydroxylation
  • 1,25 (OH)\(_2\)D - created in kidney by hydroxylation
• synthesis of hormone precursors
• inactivation of hormones
• EPO production - especially fetal

(OH)\(_2\)D \(\Rightarrow\)

3. Detoxification
• detox of substances from gut or elsewhere e.g. steroids, hormones, toxins etc
• biochemical:
  • cytochrome P450 enzymes in hepatocytes:
    - phase I reactions (oxidation, hydroxylation)
    - phase II reactions (esterification)
• metabolites secreted into bile for elimination

4. Immunologic
• liver = largest organ in tissue macrophage system (RES)
• RES function:
  • Ag processing & presentation (MHC-2)
  • phagocytosis in tissues of bacteria & cell debris
  • removal of bacteria, old red blood cells, debris in blood
  • secretion of cytokines
• blood reaching liver from intestine via portal vein contains large amount of bacteria
• Kupffer cells
  • = part of RES:
  • line venous sinusoids
  • very effective at eliminating bacteria from portal venous blood (~99%)

5. Coagulation
• most of coag proteins & protein C & S

6. Acid Base & Liver
• liver can be NET producer or consumer of H⁺
• CO2 production:
  • from complete oxidation of substrates
  • liver VO₂ = 20% of whole body \(\therefore\) produces 20% of body CO2 \(\Rightarrow\) lungs
• Metabolism of acid anions:
  • endogenous:
    • lactic acid
    • ketones
  • \(\Leftrightarrow\) metabolism of these does not = NET ↑H⁺ ie metabolism of lactate uses H⁺ produced when it was made
• exogenous:
  - eg acetate & gluconate (plasmalyte), lactate (ringers), citrate (transfusions)
  - metab of these anions consumes H+ $$\Rightarrow$$ NET production of bicarbonate anions
• amino acid metabolism:
  • incomplete metab $$\Rightarrow$$ fixed acid production
  • results in av NET production of 70% of total daily fixed acids
• metabolism of ammonium (NH4+):
  • conversion of NH4+ $$\Rightarrow$$ urea produces a H+ ion

7. Bile
• bile =
  • water
  • bile salts:
    - steroid compounds made in liver from cholesterol
    - conjugated with glycine or taurine
    - excreted as salts with Na or K
    - diff types:
      • primary = formed in liver
      • secondary = made in colon by bacterial action on primary acids
  • bile pigments - biliverdin & bilirubin
  • alkaline electrolyte solution (similar to pancreatic juice)
• 500ml secreted each day
• some contents of bile are reabsorbed in intestine & returned liver
  $$\Rightarrow$$ enterohepatic circulation
• function of bile acids
  • facilitate lipid absorption from small intestine via:
    - emulsification (surface tension ↓ function) - cause fat to break up into minute particles
    - lipid micelle formation (water soluble):
      • bile acids (& phospholipids) are amphipathic
      • above critical micelle concentration $$\Rightarrow$$ all bile salts create micelles ie hydrophyllic on outside, hydrophobic on inside
      • lipids, cholesterol, Fa, fat soluble vits collect in centre of micelle
      • then transported across brush border of enterocytes
    - without bile acids $$\Rightarrow$$ 40-50% fat appears in faeces
  • major excretory route for lipid soluble waste products

Bilirubin Metabolism & Excretion
• bilirubin made in tissues from breakdown of Hb:
  • rbc life span ~120 days, Hb 150g/l, total Hb = 750g
  • daily breakdown = 750/120 = ~6g/day
• rbc removed
  • mostly by spleen (liver & BM too)
  • abnormal rbc's recognised by RES macrophagues $$\Rightarrow$$ Hb break down
• 10% rbc breakdown in circulation:
  • Hb dissociate into α + β dimers - bind to haptoglobin
  • haem binds to haemopexin
  $$\Rightarrow$$ to prevent excretion in urine & assoc iron loss
• breakdown products of Hb:
  • haem $$\Rightarrow$$
    - degraded by macrophage haem oxygenase to yield:
      • iron released: Fe++ $$\Rightarrow$$ Fe++++ $$\Rightarrow$$ into body iron pool
      • biliverdin $$\Rightarrow$$ reduced to bilirubin $$\Rightarrow$$ release into circulation
• carbon monoxide - only endogenous source of CO
• bilirubin bound to albumin in circulation and flows to liver
• bilirubin able to dissociate from albumin ⇒ free bilirubin enters liver via organic anion transporting polypeptide (OATP) (facilitated diffusion)
• in hepatocyte cytosol: conjugated to glucuronic acid (catalysed by glu-cur-on-yl transferase)
• glucuronic acid ⇒ bilirubin glucuronide (more water soluble than bilirubin)
• bilirubin glucuronide transported against gradient by active transport into bile canaliculi
• small amount of bilirubin glucuronide escapes into blood ⇒ bound less tightly to albumin ⇒ excrete in kidneys
• in intestine:
  • intestinal mucosa :
    - impermeable to conjugated bilirubin
    - permeable to
      • unconjugated bilirubin
      • urobilinogens
  • 50% bilirubin glucuronide broken down by gut bacteria into urobilinogens
• urobilinogens:
  • excreted in stool (most)
  • reabsorbed (some):
    • excreted again via liver into intestine
    • 5% circulation ⇒ urine

Jaundice
• =free or conjugated bilirubin accumulates in blood ⇒ yellow jaundice (icterus)
• hyperbilirubinaemia may be due to:
  • ↑ed production of bilirubin ie haemolytic anaemia
  • ↓uptake of bilirubin into hepatic cells
  • disturbed intracellular protein binding or conjugation
  • would see ↑free bilirubin on testing
  • disturbed secretion of conjugated bilirubin into bile canaliculi
  • intra-extra-hepatic bile duct obstruction
  • would see ↑conjugated bilirubin (bilirubin glucuronide)

Glu-cur-on-yl transferase Activity
• works on many other substances than just bilirubin
• eg steroid hormones and various drugs
• drugs can upregulate this enzyme system eg barbituates, antihistamines, anticonvulsants

8. Reservoir for blood
• Norm liver blood volume ~500ml ie 10% circulating volume
• ↑RAP ⇒ ↑liver blood volume up to 1litre 2nd to back pressure
• liver able to mobilise ~350mls blood to circulation with acute SNS stimulation

9. Urea Production
• levels must be carefully controlled as is toxic to CNS & freely permeable across bbb
• liver only organ which complete urea cycle is expressed:
  • converts circulating ammonia ⇒ urea ⇒ excreted in urine
• ammonia created from:
  • colon
  • kidneys
  • breakdown rbcs (less)
  • metabolism of mm (less)
• ammonia enters hepatocyte mitochondria ⇒ converted to carbamoyl phosphate ⇒ reacts with ornithine ⇒ citrulline
• citrulline cytoplasmic reactions ⇒ produce arginine ⇒ dehydrated to
  • urea - small molecule diffuses back into sinusoidal blood ⇒ kidneys for excretion
  • ornithine - recycled for another cycle
• hepatic encephalopathy:
  • from ↑level of circulating ammonia
  • result from:
    - loss functional hepatocytes
    - shunting of portal blood around hardened liver
  • attempt to ↓ammonia load coming from liver using lactulose which traps luminal ammonia in
    ionized form

10. Storage Functions
• stores:
  • glycogen - glucostat function
  • triglycerides
  • lipid soluble vitamins:
    - A - enough for 10 months
    - D - enough for 4 months
    - E
    - K
  • folic acid,
  • B12 - enough for 1 yr
  • iron - except for iron in Hb, liver = greatest store of Fe in form of ferritin
  • copper
• blood capacitance function with volume 450mls

11. Haemtaopoiesis
Evaluation of Liver Function

- tests used to delineate:
  - hepatic function
  - hepatic damage
  - specific markers of liver disease

- aminotransferases:
  - =intracellular enzymes eg AST (<50), ALT (<30)
  - elevation ~ liver cell damage
  - limited by fact that other organs also contain same enzymes eg heart, brain, skel mm, kidneys

- alkaline phosphatase (ALP) (30-120)
  - usually indicates cholestasis from any cause
  - can be intra or extra hepatic
  - found in canalicular & sinusoidal membranes of liver
  - NB ALK is also derived from:
    - Bone: raised levels = Pagets/osteomalacia/bony mets
    - Placenta in pregnancy

- albumin (30-50)
  - good indicator of hepatocyte function
  - better use n chronic liver disease
  - albumin half life = 20days

- coagulation factors:
  - short half life ie better for acute Ax
    - most = hours
    - fibrinogen = 4days
  - INR best function
  - failure to correct INR with vit K signifies sig hepatic disease

- bilirubin (<30):
  - haemolysis => ↑unconjugated bili (indrect bili)
  - cholestasis & hepatocellular dysfunction => ↑conjugated bili

- Gamma GT (<50 male; <30 female)
  - microsomal enzyme which can be induced by:
    - alcohol - useful screen for alcohol abuse
    - enzyme inducing drugs eg phenytoin

- αFP = marker for primary liver carcinoma
- ANF = 75% with chronic active hepatitis
- INR:
  - invitro test of extrinsic pathway
  - tests liver ability to produce vit K dependant clotting factors
  - not particularly sensitive

- BSL -
  - will ↓in end stage liver disease
  - sign of fulminant disease

- MEGX:
  - measure this metabolite of lignocaine after a standard dose
  - experimental use only
**GI Secretions**

**Mucus**
- mucins = high molecular weight glycoproteins
- secreted by
  - Brunner’s glands in duodenum
  - surface epithelial cells throughout GIT
  - Goblet cells in mucosa of small & large intestine
- main functions:
  - lubricate whole GIT
  - physical barrier/protect against pH changes

**Saliva**
- secretions may be:
  - serous
  - mucous
  - mixed
- parotid = serous
- sublingual & smaller glands = mucous
- submandibulary = mixed
- saliva production:
  - as saliva flows out of ducts:
    - Na & Cl extracted
    - K & HCO3 added
    - ducts impermeable to water ⇒ removal of Na ⇒ hypotonic saliva
      ⟹ as speed of saliva creation ↑s less time for Na extraction ∴ less hypotonic
- composition:
  - slightly hypotonic compared to plasma
  - electrolytes: Na 15, HCO3 50-70, K 30 mmol/L
  - alkaline - neutralise gastric acid reflux
  - proteins - low
  - α amylase from parotid gland ⇒ CHO digestion
  - lingual lipase from tongue mucosa glands ⇒ fat digestion
  - mucins - lubrication
  - immunity for oral cavity = lysozyme & IgA
  - blood Ag’s
  - supersaturated solution of Ca to stop teeth dissolving
- Rate of excretion = 5ml/hr @ rest ie 1-1.5L/day:
  - 2/3 from parotid
  - 1/4 from submandibular
- glands innervated by autonomic ns:
  - PNS = (most impt) ↑volume serous (parotid) & mixed (submandibular)
  - SNS = little influence on volume but ↑s proteinaceous content
- function:
  - facilitate swallow
  - keep mouth moist
  - solvent for tasting
  - aids speech
- keeps teeth clean
- antibacterial
- buffer to keep oral pH at ~7

**Gastric Fluid**
- secretion ~2.5L/day up to ~150ml/hr when stimulated
- fluid = isosmotic
- H+ 100, Na 40, Cl 150, K 10, HPO4, SO4
- pH 1-2
- body & fundus of stomach:
  - parietal (oxyntic) cells ⇒
    - HCl - sterilse meal & hydrolysis of dietary macromolecules
    - intrinsic factor - impt for later B12 absorption
  - chief (zymogen, peptic) cells ⇒
    - pepsinogens - precursor of pepsin for protein degradation
    - gastric lipase - fat digestion
  - Enterochromaffin like cells (ECL cells) ⇒ histamine secretion + motilin
  - surface mucus cells ⇒
    - mucus
    - trefoil peptides - stabilise mucus bicarb layer
    - HCO3 secretion
- antral cells:
  - G cell ⇒ gastrin
  - D cell ⇒ GIH (somatostatin)

**Regulation of Secretion**
- 3 phases of gastric secretion:
  - cephalic phase -
    - anticipatory prior to food arriving
    - vagal mediated
- gastric phase
- intestinal phase

3 primary stimulators of secretion:
- G cells in antrum:
  - release gastrin hormone
  - stim for release:
    - vagal ⇒ gastrin releasing peptide (GRP) = neurotransmitter from enteric nerve endings
      ⟷ ie atropine does not affect it as GRP not ACh involved
    - oligopeptides in gastric lumen
    - stretch
    - Ca
    - adrenaline
  - inhibitors for release:
    - gastric acid
    - GIH
    - secretin/GIP/glucagon/calcitonin
- gastrin action:
  - via blood ⇒ fundus of stomach where actions include activating:
    - Chief cells ⇒ pepsinogen & lipase
    - parietal cells ⇒ HCl, intrinsic factor
    - ECL cells ⇒ histamine release
      ⟷ histamine - provides ↑ed stim for ↑parietal cell release via H2 receptors
  - trophic action ⇒ ↑growth of GI mucosa
- ACh from enteric nerve endings in fundus ⇒ parietal & chief cell release

overall inhibitors of secretion:
- ↑acidity of gastric fluid ⇒ D cells release of GIH (somatostatin) ⇒ inhibition of G & ECL cells
- contents in duodenum: CHO, fat & acid
- drugs: PPIs, H2 blockers

Overall stimulators:
- cephalic phase:
  - vagal output ⇒ ACh release & GRP release
  - emotions
  - hypoglycaemia, alcohol, caffeine
- gastric phase:
  - presence of meal in stomach
  - stretch receptors in stomach
  - meal buffers acidity of stomach which impairs GIH mediated autoregulation of gastric secretion ⇒ ↑secretion
- intestinal phase:
  - ↑GIH release ⇒ termination of secretion
Parietal Cells
- highly specialised:
  - mitochondria ++
  - H,K,ATPase aka proton pump:
    - move H+ ions out of parietal cell against conc gradient of >1 million
- activation of parietal cell ⟹
  - @rest proton pumps in intracellular tubovesicles
  - activation ⟹ proton pumps move to apical membrane (canaliculi)
  - pumps begin secreting H+ + Cl
  - OH reacts with CO2 ⟹ HCO3 (carbonic anhydrase) ⟹ secreted into blood in exchange for Cl
  - Cl passed through cell and secreted with H as HCl
- 3 agonists of parietal cell:
  - gastrin
  - ACh
  - histamine - ↑cAMP
- agonists work in synergy .: if stop one pathway has ↑ed effect on other eg H2 antagonists

Bile
- =primary hepatic secretion
- contains:
  - bile salts
  - HCO3
  - excretory bile pigments (bilirubin + biliverdin)
  - cholesterol
  - inorganic salts
  - fatty acids
  - lecithin
  - alk phosphatase
  - steroids
  - heavy metals
  - drugs
- all concentrated to 100-200 in gall bladder water
- pH ~8
- 0.5L enters duodenum/day
- produced continually but stored in GB
• secretion controlled by -ve feedback from recycled bile salts
• function:
  • bile salts ↓ surface tension
  • assist with emulsification of fats
  • phospholipids & monoglycerides ⇒ form micelles with outward facing hydrophilic surfaces

**Pancreatic Juice**
• alkaline watery secretion with high HCo3 content
  ⇔ bile, intestinal juice & pancreatic juice ⇒ alkaline or neutral ⇒ neutralise gastric acid
  duodenum = pH 6-7 ⇒ jejunum = neutral
• 1500ml secreted/day
• contents:
  • amylase
  • trypsinogen
  • trypsin inhibitor
  • phospholipase A2
• contents action: trypsinogen ⇒ trypsin ⇒ activate phospholipase A2 ⇒ digestion of proteins

• control of secretion under hormonal control:
  • secretin ⇒
    - ↑ flow of HCO3 rich fluid but low in enzymes & Cl
    - (also ↑ bile secretion)
  • CCK: ↑ enzyme release but ↓ ed volume
  • ACh (vagus): ↑ enzyme release but ↓ ed volume

**Intestinal Fluid**
• highly viscous fluid which lies on surface of duodenal epithelial cells trapping alkaline fluid ↓ protecting from gastric acid
• jejunum + ileum = isoosmotic NaCl solution
• produced by:
  • duodenum = Brunners glands
  • jejunum & ileum = intestinal crypt cells
• aminopeptidases, amylase, phosphatases for digestion released from intestinal cells

**GI Regulators**

**Gastrin**
• see prev under gastric fluid

**CCK**
• secreted by cells of upper small intestine - I cells
• major actions:
  • stim pancreatic enzyme secretion
    - augments secretin
  • trophic effect on pancreas
  • motility:
    - inhibits gastric emptying
    - ↑ tone pyloric sphincter preventing duodenal reflux into stomach (with secretin)
motility of small intestine & colon
contraction GB
relaxation sphincter Oddi
stim for release:
  - peptides, aa, fats in duodenum
  - ie +ve feedback loop until contents move on
half life = 5mins

Secretin
secreted by S cells in mucosa of upper small intestine
5min half life
actions:
  - ↑watery, HCO3 pancreatic secretion
  - ↓gastric acid secretion via inhibition of Gastrin
  - contraction pyloric sphincter
secretin by:
  - products of digestion
  - acid bathing mucosa op upper small intestine

GIP
made by K cells of mucosa of duodenum & jejunum
↑secretion by:
  - glucose & fat in duodenum
action:
  - inhibit gastric acid & motility (but only in large non physiological doses)
  - ↑insulin secretion (physiological levels)

Motilin
secreted by enterochromaffin cells & Mo cells in stomach, small intestine & colon
action to produce contraction of smooth mm in stomach & intestines
major regulator of migrating motor complexes (MMCs)
control GI motility inbetween meals
erthyromycin binds to motilin receptors
ingestion of food inhibits it
circulating levels ↑ at intervals ~100mins

Somatostatin (GIH)
secreted from
  - D cells in pancreatic islets
  - D cells in GI mucosa
↑secretion by:
  - acid in lumen
action to:
  - inhibit secretion of gastrin, VIP, GIP, secretin, motilin
  - inhibit pancreas exocrine secretion
  - ↓Gi motility
  - ↓absorption of glucose, aa, TGs
Physiology of Swallowing

- afferent limb = pharyngeal receptors ⇒ CN
  - 5 trigeminal
  - 9 glossopharyngeal
  - 10 vagus

- swallowing centre =
  - reticular substance of medulla
  - lower portion of pons

- efferent limb ⇒ pharyngeal musculature via CN
  - 5 trigeminal
  - 7 facial
  - 10 vagal
  - 12 hypoglossal

Phases

- divided into 3 stages:
  - oral
  - pharyngeal
  - oesophageal phases

Oral

- voluntary
- food moves from mouth to pharynx by up & back motion of tongue against hard palate
  - stylopharyngeal mm

- sensory receptors of glossopharyngeal (IX) stimulated ⇒ involuntary coordinated movements of remaining phases

Pharyngeal

- involuntary
- resp inhibited for 1-2 seconds ⇒ food pass into upper oesophagus

- closed areas:
  - nasopharynx by soft palate
  - laryngeal inlet by
    - adduction of vocal cords & aryepiglottic folds
    - epiglottis swings down
    - larynx raised

- food bolus then pushed into oesophagus by pharyngeal contraction & opening of upper oesophageal sphincter (UES)

Oesophageal

- bolus food propelled to stomach by peristaltic contractions
- once in oesophagus:
  - UES contracts
  - oesophageal sphincter relaxes

- primary slow peristaltic waves:
  - pressure 20-60mmHg
  - velocity 2-4cm/s
  - initiated by swallowing centre via vagus nerve
  - gravity promotes movement of fluid > solids

- secondary peristaltic waves:
  - mediated by enteric nervous system of oesophagus
  - stretch receptors in oesophageal wall stim by distension ⇒ activating intrinsic n.s.
Gastric Motility & Emptying

- motility:
  - receptive relaxation of fundus & upper portion of body
    - vagally mediated triggered by oesophagus & pharynx
  - peristalsis begins in lower body ⇒ mixing & grinding
    - controlled by gastric BER
  - stomach contractions (antral systole) occur every 20 seconds lasting up to 10secs
    - facilitate mixing
    - movement of contents fundus ⇒ antrum
  - lower portion body of stomach has stronger waves (50-70cmH20) needed for propulsion

- Control:
  - hormonal:
    - ↑ed emptying:
      - Histamine (H2 receptors) ⇒ ↑cAMP
      - Motilin
      - Ach (M1 receptors)
      - gastrin - receptors on parietal cells
    - ↓ed emptying:
      - PGs - esp PGE - inhibit gastric acid secretion by inhibiting histamine secretion
      - GIP, secretin, CCK + GIH
  - Neural:
    - methods:
      - local autonomic reflexes involving cholinergic neurons
      - vagal induced ↑gastrin/acid secretion/pepsin secretion
  - mechanism of change in emptying rate:
    - neural:
      - osmolality receptors in duodenum:
        - hyperosmolar ⇒ ↓gastric emptying
    - neural & hormonal:
      - fats, CHO, acid in duodenum ⇒ ↓emptying

Transit Time

- liquids ~2hrs
- solids:
  - high calorie slower than low calorie
  - hyperosmolar slower than hypoosmolar (via duodenum sensing)
  - CHO few hours < proteins slower < fats slowest
- gastric emptying delayed by:
  - pain/stress/anxiety
  - drugs eg opioids
  - labour
  - DMs
  - IBD
  - hypothyroid
  - post operative: likely 2nd to ↓CO or redistribution of CO away from viscera
Factors Preventing Reflux of Gastric Contents into oesophagus

Lower Oesophageal Sphincter

- central role
- not an anatomical sphincter
- macroscopically indistinguishable from rest of oesophagus
- = distal 2-5cm oesophagus :
  - ↑ intraluminal pressure ~30cmH20
  - higher no of nerve cells
  - extends below & above diaphragm
    - intrathoracic part exposed to more -ve pressure
- opens reflexly with swallowing (and coordinated with respiration)
- without spincter:
  - intragastric pressure = 5-10 cmH20
  - thoracic oesophageal pressure = -5cmH20
  - passive reflux
- gastric barrier pressure = LESP - IGP

Factors Contributing to prevent reflex

- LES tone
- external mechanical factors
- flap-valve mechanism
- hormonal
- drugs

LES Tone

- ↑ smooth muscle in inner circular layer mm in LES zone due to?:
  - ↑ nerve cells
  - ↑Ca uptake and utilisation
- neural input:
  - vagal mediated = reflex ↑mm tone with ↑intragastric pressure
    - abolished with atropine
  - SNS = ↑tone by α stim or β blockade

External Mechanical Factors - ‘Pinch Cock’

- oesophageal compression by crurae of diaphragm (phreno-oesophageal ligament)
- transmitted abdo pressure compressing oesophagus

Flap Valve Mechanism

- sling fibers of stomach wall create flap valve mechanism
- acute-oesophageal angle
- diaphragmatic crurae contribute to causing pinch-cock

Hormonal

- ↑ LES tone: gastrin, motilin, secretin, CCK, histamine
- ↓ LES tone: progesterone (pregnancy), PGs, VIP, GIP, glucagon

Drugs

- ↑ LES tone: dopamine antagonists, antihistamines, βblockers, α agonists, antacids, NMBs
- ↓ LES tone: atropine, dopamine, IV induction, inhalational, opioids, cricoid pressure (via reflex from pharyngeal receptors)
Physiology of Nausea & Vomiting

Definitions
- Vomiting =
  - Active reflex
  - Usually involuntary
  - Associated with nausea
- Regurgitation = Return of oesophageal contents
- Reflux = Gastric content backflow
  - Both together =
    - Passive pressure effects
    - Need all of:
      - Pressure gradient
      - Channel
      - Content
    - Usually involuntary
- Nausea = Unpleasant experience +/- Associated with vomiting.
  - Symptoms:
    - Salivation
    - Bradycardia
    - Yawning
    - Pallor
    - Sweating
  - As control centres close to each other in brainstem

Vomiting

![Diagram of the factors involved in the control of vomiting, with the probable sites of action of anti-emetic drugs. The cerebellum may function as a second relay or gating mechanism in the link between labyrinth and CTZ (not shown). (CTZ = chemoreceptor trigger zone; H₁ = histamine H₁; M = muscarinic; D₂ = dopamine D₂; 5-HT₃ = 5-hydroxytryptamine₃). (Based partly on a diagram from: Borison et al. 1981)
afferent limb
  › inputs from:
    - CTZ (see below for triggers)
      • located in area postrema in lat walls 4th ventricle ie outside BBB
      • responds via neurotransmitters: ACh, 5HT, Histamine, DA
    - vestibular apparatus/cerebellum ⟹
      • afferent to vomit centre 2 routes:
        › directly
        › via CTZ eg dopamine (CTZ blocker) does not block motion sickness
    - higher centres – pain/smell/sight
    - organs eg
      • heart via vagal
      • testes,
      • GI tract - mucosal irritation/distension via SNS & PNS (vagal) afferents

© generally most common trigger is bowel or brain

induction of vomiting coordinated response from 1+1 areas:
  › vomiting/emetic centre – reticular formation of medulla [MAIN]
  › chemoreceptor trigger zone (CTZ) –
    - very close integration with emetic centre
    - neurotransmitters vital ie ACh, 5HT, Histamine, DA

• efferent to:
  › CN 5, 7, 9, 10, 12 to upper GIT
  › Spinal nerves to diaphragm, abdo muscles

CTZ
• CTZ activated by:
  › CSF & blood borne emetics eg chem. toxins & drugs
  › 5HT neurotransmitter from afferent nerves from stomach & small intestine receives input from vestibular apparatus
  › higher centres – smells, emotions, pain
  › ↑ICP
  › endocrine disturbances
  › radiation & chemotherapy
• CTZ cannot initiate vomiting alone
• CTZ very close physically to resp centre ∴ difficult to full abolish vomit without effecting RR
• vomiting action comes via efferent nerves from emetic centre (not CTZ)

Vomit Reflex

Sensors
• higher centres
• vestibular
• stomach - chemo & stretch receptors
• other organs

Processing
• CTZ
• emetic centre

Efferent
• vagal
• corticospinal tract ⟹ abdominal muscles
**Physical Mechanism of Vomiting**
- autonomic premonitory symptoms ⟹
- breathing deepens & inspired breath held ⟹
- glottis closed & soft palate elevated to close nares ⟹
  - this vagal protective reflex is lost under GA
- UES & LES tighten ⟹
- abdo mms & diaphragm vagally contract forcefully ⟹ ↑intra-abdo pressure via
  - valsalva effect
  - compressing stomach between abdo wall & diaphragm
- UES & LES suddenly relax ⟹ gastric contents forcefully expelled up & out
  - hyoid bone & larynx raised ⟹ pulls cricooesophageal sphincter open

**Consequences of Vomiting**
- wound dehiscence
- intraocular bleeding
- anorexia
- aspiration
- dehydration
- alkalaemia
- hypokalaemia
- raised ICP = valsalva
- acidosis - only if prolonged ⟹ shock
- Mendelson’s syndrome =
  - chemical pneumonitis post aspiration during GA
  - hypoxia 2-5hrs after aspiration ⟹ APO
  - risk higher if pH <2.5 & aspirated contents >25mls

**Risk of Vomiting in Pregnancy**
- enlarged uterus ⟹ ↑intra-abdo pressure (further worsened by lithotomy position)
- ↑gastrin levels ⟹ ↑acidity and ↑volume of gastric contents
  - but also ↑tone LES, and ↓pyloric tone
- ↓motilin levels ⟹ ↓speed gastric emptying & ↓LES tone
- general ↓gastric emptying:
  - narcotics/sedatives
  - pain
- progesterone ⟹ ↓LES tone

**Clinical Use of Anti Emetics Using Pathways**
- H1 receptor antagonists: ⟹ motion sickness, PONV
  - cyclizine
  - promethazine
- D2 receptor antagonists: ⟹ GIT, cytotoxics, radiation, uraemia
  - metoclopramide
  - phenothiazines eg prochlorperazine
- muscarine receptor antagonists ⟹ motion sickness
  - hyoscine
- 5-Hydroxytryptamine (5-HT3) receptor antagonists ⟹ PONV, cytotoxics, radiation
  - serotonin
- cannabinoids ⇒ cytotoxics
  - nabilone