Primary Cast Episode 26 - GIT & Metabolism Physiology

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Guest: Dr Lou Gabauer

1. **Gastric Secretion**
   What factors regulate gastric secretion?
   Can divide this answer into either neural and hormonal or do it via stages i.e. cephalic/gastric/intestinal. We have done it in order of what happens as you eat food because its easier to remember.
   Cephalic phase - mediated via the vagus nerve. The sight, smell or taste of food excites the vagus nuclei, which excites parasympathetic neurons in the stomach that release ACh onto parietal cells to stimulate secretion. Vagal efferents also stimulate gastrin release from G cells.
   Gastric Phase - food in the stomach triggers local receptors which activate post ganglionic neurons. These neurons stimulate parietal cells to produce acid.
   Intestinal phase - fats, carbohydrates and acid in the duodenum inhibit gastric acid secretion and pepsin secretion as well as motility by neural and hormonal mechanisms

   What does the parietal cell do?
   - Parietal cell is stimulated by histamine (from ECL cells) and gastrin (from G cells) as well as vagal efferents
   - H+ ions are pumped out by H/K/ATPase
   - Cl- ions follow to combine with H+ in the lumen

2. **Digestion of carbohydrates**
   Describe the enzymes required for the digestion of carbohydrates and their location
   - Mouth - salivary amylase
   - Duodenum - Pancreatic amylase
   - Brush border of the small intestine - oligosaccharidases i.e. lactase, sucrase, maltase, isomaltase
   - The final oligosaccharides are metabolised to one of the final hexoses (i.e. glucose, fructose) in the small intestine

   Please describe how carbohydrates are absorbed from the GI tract
   Two phases - first into the mucosal cell from the lumen, then into the ECF and blood from the cell.
   - Glucose and galactose undergo ‘secondary active transport’ with sodium via SGLT1 and SGLT2 co transporters. A low concentration of sodium inhibits transport.
   - Glucose and Galactose can also go via ‘facilitated diffusion’ into the cells via GLUT-2
   - Fructose can go via ‘facilitated diffusion into the cell via GLUT-5 and then GLUT-2 to blood

3. **Digestion and absorption of lipids**
   Describe the enzymes required for the digestion of lipids and their location.
   - Lingual lipase - active in the stomach on triglycerides
   - Pancreatic lipase - requires colipase for maximal activity, acts on triglycerides
   - Pancreatic bile-salt activated lipase - triglycerides, cholesterol esters, some vitamins and phospholipids
   - Cholesteryl ester hydrolase

   What other process is involved in the digestion of lipids?
   - Emulsification
   - Micelle formation - these are formed from bile salts, lecithin and monoglycerides surrounding fatty acids and cholesterol
   - Transport of lipids through the unstirred layer to the brush border of mucosal cells

   Please describe how lipids are absorbed through the GI tract
   - Two phases
   - First phase - lipids go into the intestinal mucosal cell and second phase into the interstitial fluid and thus into the capillaries and portal blood as free fatty acids (FFAs) or into lymphatics as chylomicrons
   - They move into the enterocytes via passive diffusion and carriers
   - They move out of enterocytes into the interstitial fluids depending on the size
     - <12 carbons goes directly into portal blood
     - >12 carbons are re-esterified to triglycerides or cholesterol esters & packaged in chylomicrons

4. **Digestion of Proteins**
   Describe the enzymes required for digestion of protein in the gastrointestinal tract and their location
   - In the stomach - pepsinogens are activated by gastric acid to produce pepsins and these cleave the bond between amino acids to yield polypeptides
   - Small intestine - proteins are digested by powerful proteolytic enzymes from the pancreas and intestinal mucosa. These include endopeptidases (trypsin, chymotrypsin & elastase - *which recognize specific amino acids in the middle of the peptide*) and exopeptidases which yield amino acids (*by recognizing and acting on one or two terminal amino acids*)
   - Brush border - amino, carboxy, endo and dipeptidases cleave peptides into amino acids

   How are proteins absorbed from the GI tract?
   - Two phases
     - 1 Into the mucosal cell
     - 2 Into interstitial fluid and then into capillaries and portal blood

- There are seven transport systems for moving amino acids into enterocytes: five require sodium co-transport and there are two sodium independent transporters
- Absorption of protein is rapid in the duodenum and jejunum and then slow in the ileum

How does protein absorption and digestion differ in infa nts and young children compared to adults?
Infants absorb more undigested protein, which results in passive immunity via absorption of antibodies. However, this also results in more food allergies in this age group.

5. **Glucose**

What factors influence glucose homeostasis?

- Glucose absorption from the intestine
- Uptake from the periphery - muscle, fat, brain, RBCs, liver
- Reabsorption in the kidney
- Gluconeogenesis in the liver - as determined by the actions of insulin and glucagon

What happens to glucose homeostasis in the absence of insulin?

- Hyperglycaemia due to a number of factors
    - decreased peripheral uptake of glucose into muscle and fat
    - reduced glucose uptake by the liver
    - increased glucose output by the liver and lack of glycogen synthesis
- The intake of glucose by the brain, GIT , kidney and RBCs remains unchanged

By what mechanism does glucose cause the release of insulin?

- Taken up by specific GLUT 2 transporter in beta cells of the pancreas
- Glucose is converted to pyruvate, then metabolised to glutamate via the citric acid cycle which primes insulin granules for release
- Production of ATP triggers (via K efflux) a Ca influx which causes the granules to be released

6. **Iron**

How is iron absorbed from the GIT?

- In the stomach, gastric acid causes a reduction of Fe3+ (ferric form) to Fe2+ (ferrous form) and formation of soluble complexes
- The duodenum is the major site of absorption
- Fe3+ is converted to Fe2+ by ferric reductase
- Fe2+ is transported into enterocytes via the apical membrane iron transported (DMT1)
- Dietary haeme is transported into the enterocyte by heme transporter
- Heme oxidase releases Fe2+ from heme
- Some intracellular Fe2+ is converted to Fe3+ and bound to ferritin

- The remainder binds to basolateral Fe2+ transporter ferroportin and transported to interstitial fluid aided by hephaestin (Hp)
- Then it is converted to the ferric form (Fe3+) and bound to transferrin

What factors reduce iron absorption from the GIT?

- Dietary factors - phytic acids in cereals, oxalates and phosphates bind to Fe to produce insoluble compounds
- Surgical factors - partial gastrectomy (via reduction of gastric acid), duodenal surgery or illness e.g. ulcers (via reduced site of absorption)
- Physiological - high iron stores, recent high iron diet, degree of erythropoiesis
- Drugs - antacids

How is iron transported?

Free Fe2+ (ferrous) bound to transferrin

7. **Calcium**

How does the body regulate plasma calcium?

- Works via a feedback loop
- 1,25-dihydroxycholecalciferol (1,25DHCC, from Vit D) increases Ca absorption in the GIT and kidneys
- PTH mobilises Ca from bone, increases Ca resorption in the kidneys and increased 1,25 DHCC in the kidneys
- Calcitonin (from thyroid) inhibits bone resorption, increases calcium excretion in the urine

How is the synthesis of 1,25 DHCC regulated?

- 1,25 DHCC is formed in the kidneys by 1-alpha-hydroxylase.
- Low Ca increases PTH which stimulates 1-alpha- hydroxylase and increases 1,25DHCC formation
- Low phosphate directly stimulates 1-alpha-hydroxylase
- High Ca/High PO4 inhibits 1,25 DHCC (increasing the inactive form 24,25DHCC instead)

8. **Water and Electrolytes**

Explain the mechanisms of absorption and secretion of water and electrolytes in the GIT

Absorption

- After meals, fluid is taken up due to coupled transport of nutrients e.g. glucose and water
- Between meals - NcCl enters across the apical membrane via the coupled activity of Na/H exchanger and a Cl/HCO3 exchanger
- In the distal colon, Na enters the epithelial cells via epithelial Na channels (eNAC) which is electrogenic

Secretion

- Cl- secretion occurs continuously in the small intestine and colon
- Cl uptake occurs via Na/K/2Cl co-transporter and is secreted into the lumen via Cl channels (CFTR = cystic fibrosis transmembrane conductance regulator)
- Water endogenous secretions is approx 7L per day, intake is 2L and the amount reabsorbed is 8.8L. Balance is in the stools approx 200ml

9. Exocrine pancreas

List the enzymes secreted from the exocrine pancreas and give at least 3 examples of the substrates that these enzymes work on

- Trypsin- proteins, polypeptides
- Chymotrypsins - proteins, polypeptides
- Elastase - elastin and some proteins
- Carboxypeptidase A and B - proteins and polypeptides
- Colipase - fat droplets
- Pancreatic lipase - triglycerides
- Bile salt acid lipase - cholesterol esters
- Pancreatic alpha amylase - starch
- Ribonuclease - RNA
- Deoxyribonuclease - DNA
- Phospholipase A2 - phospholipids

Describe the regulation of pancreatic juice secretion

- Primarily under hormonal control
- Secretin acts on the duct to cause production of copious amounts of alkaline pancreatic juice, which is poor in enzymes. Exerts effects via cAMP. Also stimulates bile secretion.
- As the flow of pancreatic juice increases is becomes even more alkaline because the exchange of HCO3- for Cl- in the distal duct is inversely proportional to flow
- Cholecystokinin (*aka moves the gallbladder*) acts on acinar cells to cause release of zymogen granules and pancreatic juice rich in enzymes. Also relaxes the sphincter of oddi. Secrete by I cells in the mucosa of the upper small intestine.
- Acetylecholine (The rest and digest transmitter) also stimulates the release of zymogen granules. ACh is also involved in vagal nerve mediated pancreatic secretion via the sight/smell of food.

Describe the composition of pancreatic juice

Cations, anions, bicarb (HCO3-), digestive enzymes - released as proenzymes which are activated by brush border enzymes

BONUS Q: (no previous viva)

What hormone is secreted by delta cells of the pancreas?
Somatostatin: (the quick stop).

- Half life of 3 minutes, stimulated by food intake.
- Decreases the motility of upper GIT, reduces secretion and absorption of GIT and inhibits glucagon and insulin release by the pancreas.
- Extends the period of time over which food nutrients can be absorbed from the GIT into blood.
- Inhibits growth hormone (which is where the name comes from).

10. Liver

List the principal functions of the liver

- Bile formation (500ml/day)
- Synthetic function - makes proteins, coagulation factors, albumin
- Inactivation/detoxification - drugs, toxins, circulating substances
- Nutrient/vitamin absorption/metabolism/control - amino acids, lipids, fat soluble vitamins
- Immune function - especially against gut organisms, via the Kupffer cells/macrophages in the sinusoidal epithelium

How is bilirubin produced in the body?

- Formed by the breakdown of hame from haemoglobin
- Heme is converted to biliverdin and then on to bilirubin

How is bilirubin metabolised?

- Bound to albumin in the circulation
- Dissociates in the liver and free bilirubin enters the liver cells via OATP (Organic Anion Transport Polypeptide)
- Conjugated within liver cells - by glucoronyl-transferase located in the smooth ER to convert bilirubin into bilirubin-diglucoronide which is the water soluble form
- This soluble form is transported against the gradient to the bile canaliculi and then into the intestine (small amounts <5% leak back into the blood)
- Intestinal bacteria acts on the bilirubin-diglucoronide it to convert mostly to urobilinogens and unconjugated bilirubin which are excreted by the gut
- Some bile pigments/urobilinogen and unconjugated bilirubin are reabsorbed in the portal circulation, where most are then re-secreted. This is what is referred to as the enterohepatic circulation
- Small amounts of urobilinogen are excreted in the urine and stercobilin is excreted in the faeces

Describe the composition of bile

- 97% water
- Bile pigments - conjugated bilirubin and biliverdin
- Bile salts - colic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid

- Inorganic salts
- Others: cholesterol, fatty acids, lecithin, fat