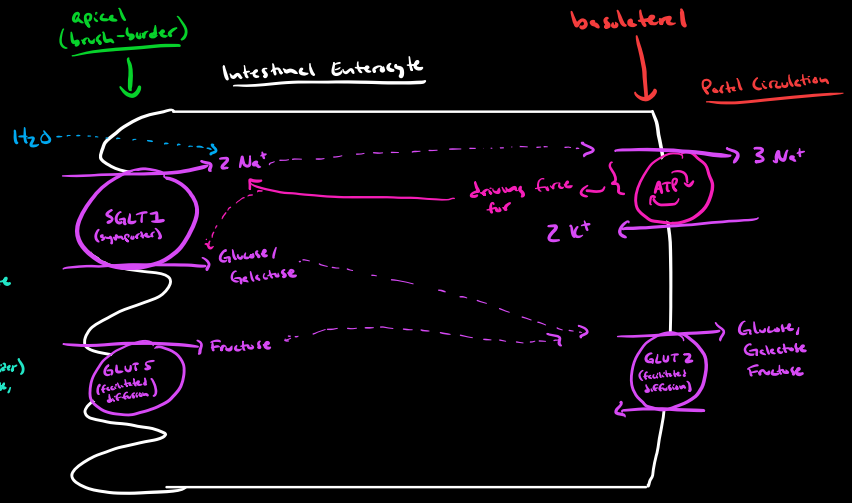
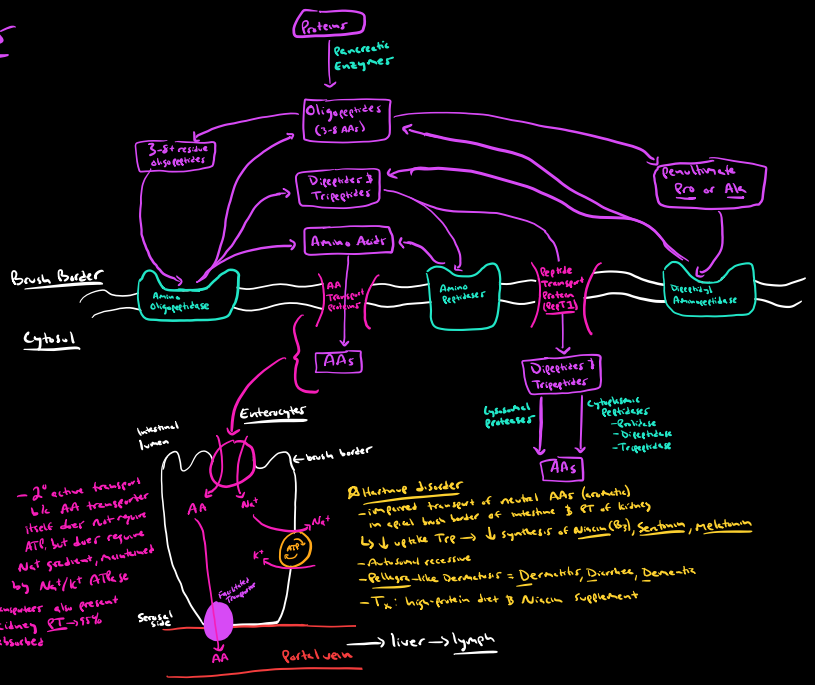
Carbohydrates



Proteins



- 2° active transport b/c AA transporter itself does not require ATP, but does require Na^+ gradient, maintained by Na^+/K^+ ATPase

Transporters also present in kidney PT → 95% reabsorbed

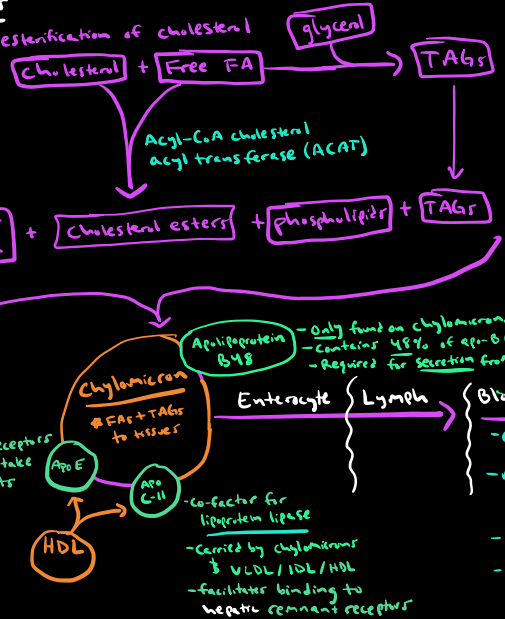
Hartnup disorder
- impaired transport of neutral AAs (aromatic) in apical brush border of intestine & PT of kidney
- ↓ uptake Trp → ↓ synthesis of Niacin (B3), Serotonin, Melatonin
- Autosomal recessive
- Pellagra-like Dermatitis, Diarrhea, Dementia
- Tx: high-protein diet & Niacin supplement

Most fat digestion occurs in duodenum
Most fat absorption occurs in jejunum

Fats

Micelles w/ LCFAs must use Carrier-mediated transport to get into enterocyte
- Fatty Acid Transport Protein 4
- Caveolin 1

- Enterocyter
  - Re-esterification of cholesterol



Intestine vs. Colon Salt & H_2O Absorption

- Crypts of Lieberkuhn - found in mucosa of both SI & LI
  - Contain different cells depending on location
  - Most concentrated in duodenum
  - In cell areas, can secrete isotonic NaCl
    - apical membrane - CFTR (Cl^-) channels
    - basolateral membrane - NKCC cotransporters
    - Na^+ & H_2O follow paracellularly & via AQP channels
- Fluid can either enter intestinal lumen or be absorbed via osmotic gradients

Small Intestine

- Under normal conditions, fluid moves rapidly in & out to achieve isotonicity by early jejunum
  - ↳ afterward, fluid absorbed isotonically using Starling
    - osmotic gradient in lateral spaces between enterocytes

- Na^+ absorption

Apical membrane	Basolateral membrane
- organic Co-transport	- Na^+/K^+ ATPase
- SGLT1	
- AA transporters	
- Na^+/H^+ exchanger (NHE3)	

- Creates Net transmural potential gradient of ~5mV in serosa vs. lumen

- Ca^{++}

Apical	Basolateral
- normal to ↑ $[Ca^{2+}]$	- Plasma membrane ATPase (PMCA)
↳ paracellular diffusion, non-saturable	- upregulated by Vit.D
- ↓ $[Ca^{2+}]$ → active transport via TRPV6 (ion channel)	- Na^+/Ca^{2+} antiporter (NCX1)
- regulated by Vit.D	

- inhibited by oxalate, phytate, dietary fiber, Mg^{2+}, PO_4^{3-}, tannins
  - ↳ soluble & PO_4^{3-} combine w/ Ca^{2+} → stones
- increased by acidic pH, Vit.D, estrogen, lactose

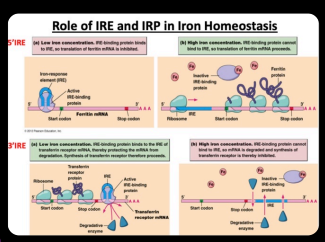
- Phosphorous
  - in plant seeds, storage form → phytate, only ~50% available to humans b/c don't have phytase
  - meats, seafood, dairy, eggs, cereal

apical
- Passive, paracellular
- Ba^{2+}
- Active Type 2b Na^+-P cotransporter
  - stimulated by Vit.D
  - driven by Na^+ down [ ] gradient, driven by Na^+/K^+ ATPase

- Mg^{2+}
  - ~50% stored in bones
  - rest in muscle & soft tissues (61% in ECFV)
- used as cofactor for ATP-driven reactions (esp. neurotransmission & muscle contraction)

apical
- Passive, paracellular (non-saturable)
- Active transcellular via TRPM6 & TRPM7

- Fe^{2+}
  - heme-iron: ferrous (Fe^{2+}), non-heme iron = ferric(Fe^{3+})
  - Can only absorb Fe^{2+} @ brush border
  - absorption promoted by: Acidity, Vit.C, cysteine
  - absorption inhibited by: Phytates (cereals), oxalate (leafy greens), copper deficiency, gastrectomy
  - Ferritin mRNA has cis-acting 5'-IRE (↑[Fe] → Fe binds IREBP → 5'-IRE free to ↑ translation → ↑ storage; ↓[Fe] → IREBP free to bind 5'-IRE → Blocks translation → ↓ storage)
  - Transferrin Receptor mRNA has 3'-IRE (↑[Fe] → Fe binds IREBP, not IRE → IRE not protected by endonuclease → ↓ translation → ↓ Fe uptake; ↓[Fe] → IREBP free to bind IRE → Stabilizes mRNA (IRE @ tail end) Protects from endonuclease cleavage → ↑ receptor translation → ↑ uptake)

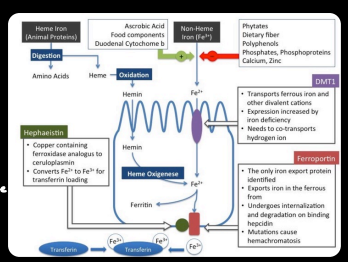


- Once in circulation, peripheral cells uptake iron from blood w/ transferrin receptor 1-mediated endocytosis

apical
- Heme-Fe^{2+} → Heme Carrier Protein (HCP)
  - SLC transporter family
  - ↳ then delivered Heme-Fe^{2+} to Heme Oxygenase inside cell
  - ↳ Fe^{2+} released → 2 options
    - Stored as Fe^{3+} w/ ferritin (for temporary storage)
      - if ATP (Fe^{2+}) → overwhelms ferritin → Hemosiderin formation (Fe^{3+} deposits)
    - transported through circulation via ferroportin
- Non-heme Fe^{3+} → Duodenal Cytochrome B (CYTB) on brush border
  - reduces Fe^{3+} → Fe^{2+} → DMT1
  - enhanced by Vit.D

HFE protein inhibits transferrin receptor @ ↓[Fe^{2+}]
↳ @ ↑[Fe^{2+}] → HFE protein dissociates → ↑ Fe^{2+} uptake
Mutations in formation, hepcidin, & molecules that promote hepcidin secretion (↓HFE, BMP) → ↑↑ Fe^{2+} absorption
↳ Hemochromatosis
- Most common cause = HFE mutation
  - HFE = hemochromatosis autosomal recessive
- Hereditary Hemochromatosis: autosomal recessive
  - all types involve dysfunctional hepcidin pathway → ↑ iron transported from enterocyte → blood

basolateral
- ferroportin 1 takes up Fe^{2+} for transport out
  - mainly expressed by enterocytes & macrophages
  - inhibited by hepcidin
    - hepcidin decreased by Erythropoietin & hypoxia
- Hephaestin = Cu-containing ferroxidase
  - homologous to Ceruloplasmin
  - oxidizes Fe^{2+} → Fe^{3+}
- ↳ Fe^{3+} binds transferrin in interstitium → circulation
  - ~3.8mL of transferrin-bound iron delivered to bone marrow → incorporated into Hb (must be reduced again to Fe^{2+})
- Storage sites for Fe storage = liver & spleen
- @ Hepcidin used in enterocyte
- @ Ceruloplasmin used in most body cells
  - synthesized in liver
  - contains 6-8 Cu^{2+} molecules
    - ↳ Cu^{2+} deficiency → anemia



- Cl^- absorption
  - ~5mV potential gradient due to Na^+ absorption
    - ↳ drives ↑ Cl^- flux via "leaky" epithelial junctions (paracellular)

- K^+ absorption
  - as [K^+] rises in lumen as fluid is reabsorbed
    - ↳ creates transmucosal gradient
      - ↳ drives K^+ absorption paracellularly

Divalent Metal Transporter 1 (DMT1/SLC)

- Intestinal transporter responsible for absorbing:
  - Iron
  - Manganese
  - Nickel
  - Zinc
  - Cadmium } Toxic
  - Lead
- DOES NOT transport:
  - Ca^{2+}
  - Mg^{2+}

Colon

- Colonic epithelium effectively secretes K_2HCO_3 in exchange for NaCl absorption
  - ↳ excessive diarrhea → ↑↑ secretion of K_2HCO_3
    - ↳ Metabolic acidosis & hypokalemia
- Significantly decreased absorptive capacity for electrolytes & H_2O due to:
  1. Shorter length
  2. Smaller surface area (no villi)
  3. Tighter epithelial junctions (no paracellular transport)
- Colonic bacteria produce Short Chain Fatty Acids (SFCA) from Soluble Fiber
  - ↳ ↑ NaCl & H_2O absorption via Sodium Monocarboxylate Transporter (SMCT1)
    - transports SFCAs & Na^+ across apical membrane of colonocytes
  - ↳ antibiotics → destroy colonic bacteria → ↓ SFCA production → ↓ Na^+ & H_2O absorption → diarrhea

Pernicious Anemia

- autoimmune disorder where antibodies attack parietal cells
  - → ↓ intrinsic factor → Vit. B_{12} deficiency
    - ↳ impairs RBC growth → macrocytic anemia (MCV > 120, normal = 100-120)
  - → ↓ HCl secretion → ↑ pH → ↑ Gastrin release by G cells

Minerals

Iron

- Iron absorption must be tightly regulated b/c mostly recycled and found in [↑] in dietary sources
  - only lose iron via:
    - natural shedding of skin & mucosa
    - Blood loss (menstruation/GI bleeding)
    - Sweat
- Iron readily absorbed in ferrous (Fe^{2+}) state
  - by stomach promotes Fe^{2+} absorption b/c ↓pH ($↑H^+$) promotes $↑Fe^{2+}$ (ferrous state)
- absorbed on apical surface of enterocyte in duodenum

2 forms:

- Heme iron
  - Complexed w/nonpolar heme group
    - ↳ readily absorbed via receptor-mediated endocytosis
  - Iron = Fe^{2+}
  - found in red meat
- Non-heme iron
  - Unbound/free
  - Fe^{2+} or Fe^{3+}
  - Poorly absorbed due to charge
    - ↳ requires divalent metal transporter 1 (DMT1)
      - coupled H+ absorption w/ Fe^{2+} (NOT Fe^{3+})
      - Acidic pH of GI lumen keeps iron in Fe^{3+} state
        - ↳ Duodenal Cytochrome B (DcyB; iron-reductase)
          - reduces $Fe^{3+} \rightarrow Fe^{2+}$
          - Vit. C cofactor

- once Fe^{2+} absorbed by enterocyte...
  1. storage as Fe^{3+} in Apoferritin
  2. Shuttled across basolateral membrane into systemic circulation
     - Fe^{2+} transported across membrane via Ferroportin
       - ↳ oxidized to Fe^{3+} via Ferroxidase (aka HAEG/Hephaestin Complex)
         - Ferroxidase = transmembrane protein
         - binds Fe^{2+} in blood → Fe^{3+}
       - ↳ Fe^{3+} binds Transferrin → Liver → dispersed to body
         - Transferrin = Fe^{3+} binding protein

- Regulation
  - ↑[Fe] in blood → liver releases hepcidin
    - hepcidin binds to ferroportin → ferroportin degraded
      - ↳ ↓[Fe] release

Copper

- Regulated/controlled by metabolism & excretion in liver
  - not by uptake, like ↑ iron
  1. Absorbed into enterocyte in duodenum & stomach
     - High-affinity Copper transport Protein 1 (Ctr1)
     - DMT1
       - ↳ ↑↑[Cu] → Ctr1 saturation → ↑[Cu] uptake via DMT1 → ↓ uptake of other divalent ions like Zn^{2+}, Fe^{2+}, etc.
     - Cu^{2+} absorption inhibited by:
       - ↑ fiber
       - ↑ Zn^{2+}
  2. Once inside enterocyte...
     - binds to Metallothionein (MT)
       - MT = important regulator of heavy metals in body
         - transports ions to basolateral membrane
  3. Member P-type ATPase (ATP7A)
     - transport Cu^{2+} from cell → blood
  4. In blood (portal vein)
     - Cu^{2+} binds to albumin → transported to liver
  5. In liver, Cu^{2+} complexes w/other proteins to form ceruloplasmin
     - ↳ ceruloplasmin excreted or dispersed
       - excreted w/bile via common bile duct
       - transfer back into blood → dispersed throughout body

- Wilson's disease - defective enzymes in liver responsible for metabolizing/excreting Copper → ↑[Cu^{2+}] in blood
  - ↳ Copper toxicity → oxidation → ROS → oxidative damage
- Menke's disease - defective Copper transporter → Copper deficiency
  - most commonly due to ATP7A defect, X-linked → global loss of function
    - ↳ activity of lysyl hydroxylase (collagen), ceruloplasmin, dopamine β-hydroxylase
  - "kinky"/"steely" hair, stunted growth, abnormal skin pigmentation, mental deterioration

Zinc

- required for immune function & tissue regeneration
  - utilized as cofactor by metalloproteinases that hydrolyze collagen & elastin to form scars
- Absorbed via DMT1
  - absorption inhibited by ↑↑[Zn^{2+}] or [Fe^{2+}]
- Binds to MT (metallothionein) → sequestered for storage or transported to blood
  - ↑Zn^{2+} → upregulates MT form
- In blood, binds to plasma proteins (albumin, α2-macroglobulin) → liver → dispersal

Deficiency → Acrodermatitis Enteropathica - mutated ZIP4 transport protein
- autosomal recessive

Toxicity → ↑MT → ↑MT can bind Copper → Copper deficiency → iron deficiency

Manganese

1. Absorbed via DMT1
2. Transported to basolateral membrane
3. Transported to blood via iron exporters (ferroportin → transferrin)
   - in blood, binds albumin or α-2-macroglobulin → liver → dispersal

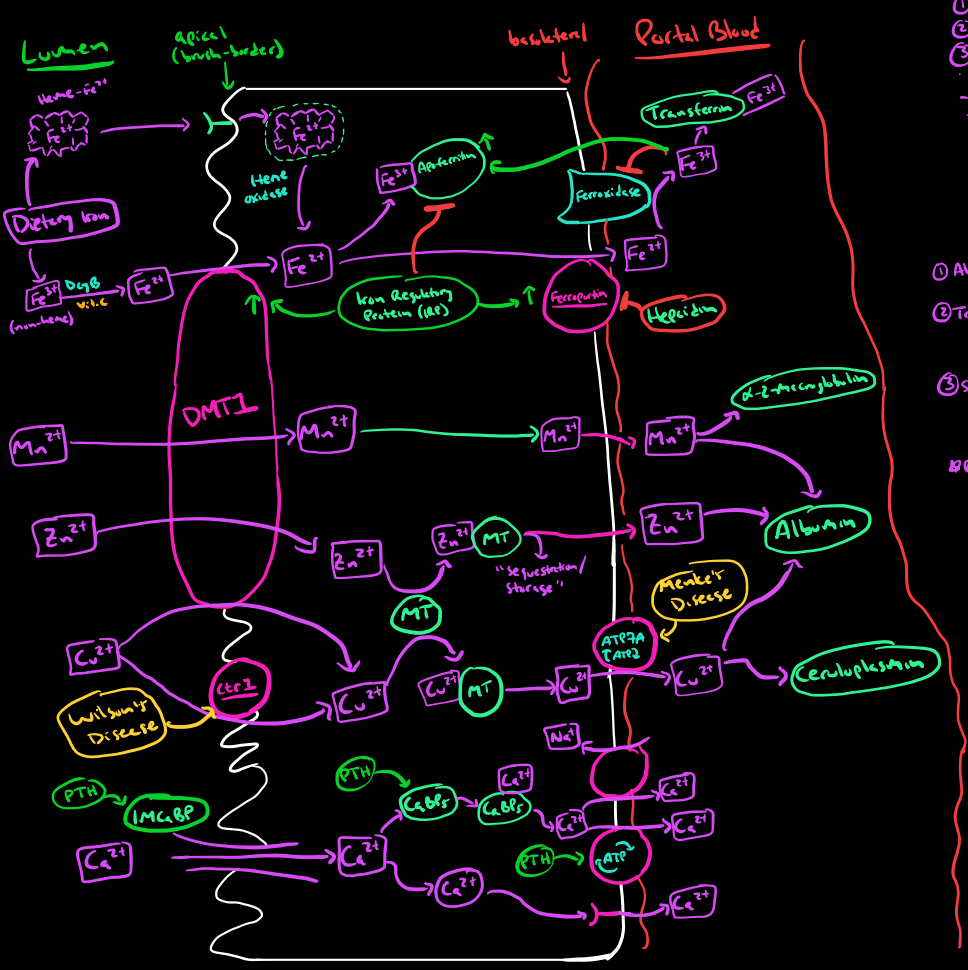
- important for metabolism of proteins & fats; supports immune system, regulates [glucose]
- Cofactor for Arginase (urea cycle), pyruvate carboxylase (gluconeogenesis)
- works w/ vit K to promote clotting
- Cofactor for Superoxide dismutase (front line defense against free radicals)

Toxicity → neurological problems
- Seizures
- Parkinson-like symptoms

Calcium

1. Absorbed via Ca^{2+} channel
   - Channel activated by Intestinal Membrane Ca^{2+} Binding Protein (IMCaBP)
2. Transported through cytoplasm via:
   - vesicles
   - Ca^{2+} binding proteins (CaBP), aka Calbindins (different types exist)
3. Secreted across basolateral membrane via:
   - Ca^{2+} ATPase
   - Ca^{2+}/Na^+ exchanger
   - vesicle exocytosis

- Regulation by PTH
  - ↓[Ca^{2+}] → ↑ PTH → ↑ formation of active $Vit.D_3$ ($1,25\text{-dihydroxycholecalciferol}$; $1,25\text{-(OH)}_2\text{-D}_3$) → ↑ protein synthesis of IMCaBP, Calbindins, Ca^{2+}/Na^+ ATPase



	Site of Absorption	Key Proteins
Carbohydrates	Enterocytes (small intestine)	SGLT1, GLUT5, GLUT2
Proteins	Enterocytes (small intestine)	PepT1
Fats	Enterocytes (small intestine)	FATP4 and caveolin 1
Iron	Duodenum	DMT1, DcyB, ferroportin
Copper	Duodenum	DMT1, Ctr1, MT, ATP7A
Zinc	Duodenum	DMT1, MT
Manganese	Duodenum	DMT1

Primary sites of absorption mnemonic
Dude Is Just Feeling Ill Bro
Duodenum - Iron (Fe^{2+})
Jejunum - Folate
Illeum (terminal) - B_{12} & Bile Salt