SHEET NO.

20

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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SCIENTIFIC CORRECTION :

GRAMMATICAL CORRECTION :

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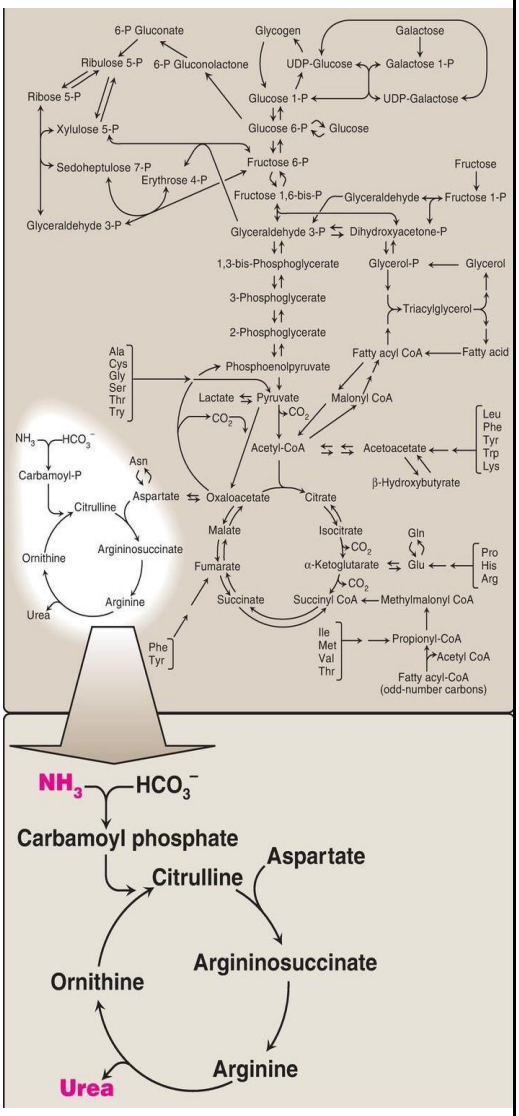
Amino Acids



- Proteins are different from fats and carbohydrates in that 1.they can't be stored within the body and 2.they can change their shape.
- After cleaving these proteins to their monomers (which are amino acids), your body deals with the amino acids through two phases:
- **The first phase:** A portion excreted in the urine, but most as urea
  The first phase of any protein metabolism is to deal with the amino group (by removing the nitrogen and you'll get ammonia) and then through many processes, this amino group will be excreted in the urine as urea (The body can excrete the amino group as free ammonia however this amount is very little because it's toxic so the body converts the ammonia into urea and then excrete it in the urine)
- The rest of the protein structure (<u>the carbon skeleton</u> of the amino acids) will go to **the second phase:** it will be metabolized to carbon dioxide (CO_2) and water (H_2O) (by glycine serine), glucose, fatty acids, or ketone bodies by the central pathways of metabolism.

- In nitrogen metabolism, we must look at two things regarding proteins: Amino acid pool and how the body deals with the degradation of proteins (Protein turnover).

Amino Acid Pool

- The free amino acids which are found in the blood.
- **Sources** of amino acid pool:
  1. Breaking down of protiens that are inside the body (turnover, remodeling)
  2. Breaking down of ingested proteins (from our diet)
  3. Synthesis of non-essential amino acids

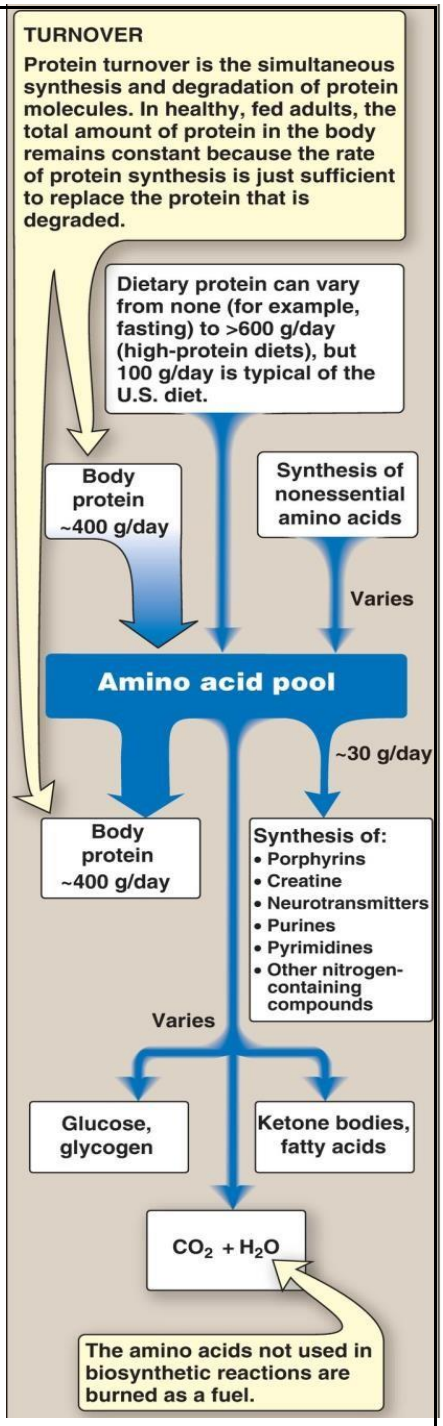
Remember:
1.Turnover (remodeling): all structures within the body are continuously built up (synthesized) then degraded
2.Essential amino acids: we can't produce them in the body, we get them from diet

- **Depletion** of amino acid pool:
  1. Break them down (to produce energy)
  2. Synthesis of body proteins
  3. Synthesis of <u>nitrogen-containing compounds,</u> such as:
     a) Purines and Pyrimidines which are nitrogenous bases in DNA and RNA
     b) Neurotransmitter like choline, Gamma aminobutyric acid, adrenaline, noradrenaline, dopa, serotonin, and nitric oxide
     c) Creatine
     d) Porphyrins
     e) Heme (four pyrrole rings that contain nitrogen)

(The only source of nitrogen inside the body: is amino acids)

- Free amino acids in the blood (amino acid pool) = ~ 90-100 g (protein = ~12 kg in a 70-kg man)
- In healthy, well-fed individuals, we notice that the amino acid pool is in a steady state (the sources of it equals the depletion), and the individual is said to be in a nitrogen balance

  When someone is in a positive nitrogen balance, give them less nitrogen
  When he is in a negative nitrogen balance, give them more nitrogen to deal with their condition
  (Positive nitrogen balance: intake of nitrogen > loss of nitrogen
  Negative nitrogen balance: loss of nitrogen > intake of nitrogen)



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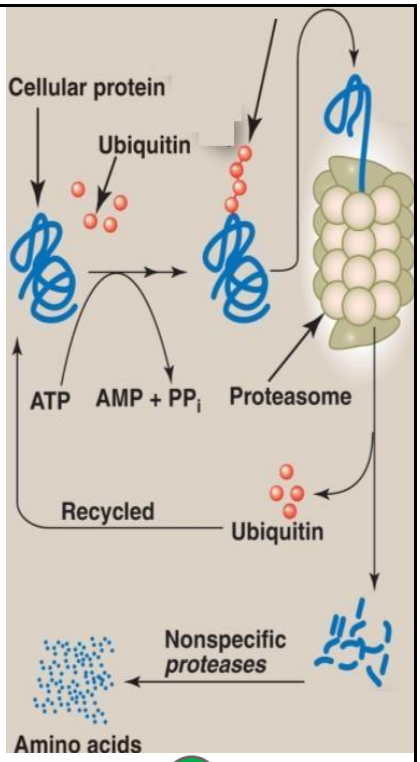
Protein Turnover (Remodeling)

- Degradation and building up of proteins differ from one protein to another (why? Because of the diffrences in the structure between proteins, and the structure guides the degradation)
- Rate of protein turnover: the total amount of protein in the body remains constant (hydrolysis and resynthesis of 300–400 g of body protein daily)

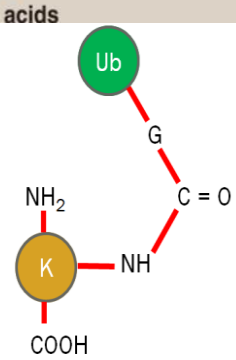
  In healthy individuals, the amount of degradation should equal the amount of synthesis. Otherwise, they have negative nitrogen balance or positive nitrogen balance
- The rate of protein turnover varies:
  a) Shortlived proteins (regulatory proteins and misfolded proteins, minutes or hours)
  b) Long-lived proteins (days to weeks, majority of proteins in the cell)
  c) Structural proteins (months or years) (example: collagen)
- Protein degradation has 2 ways:
  a) ATP-independent degradative enzyme system of the lysosomes (acid hydrolases, nonselective, autophagy and heterophagy)
     Lysosome: is not specific in general, non-selective, it has hydrolases and the environment in it is acidic, so whatever the structure that enters it, hydrolases will start breaking down proteins, carbohydrates, nucleic acid and lipids and it is independent of ATP (it doesn't need energy)
  b) ATP-dependent ubiquitin (Ub)–proteasome system of the cytosol (selective, damaged or short-lived proteins)
     Ubiquitin proteasome system: is ATP dependent (it needs energy), it is selective for certain proteins and it should have a mark in it to tell the body when to degrade the protein depending on the structure of the protein

Good job! You just finished the first part of the sheet ☺

Ubiquitin–proteasome system



- Notice the proteasome -in the figure- which is large, barrel-shaped macromolecule, has a hole inside it. The hole's walls have many enzymes which degrade proteins.
- The proteasome knows that this protein should be degraded through a mark linked to this protein. This mark is **Ubiquitin** which must be covalently bound to the protein.
- This ubiquitin is small, globular, nonenzymic, & highly conserved (has the same structure in all organisms).
- There should be 4 or more ubiquitin attached to the protein, to let the proteasome degrade it (at least 4).
- Attaching ubiquitin to the protein needs ATP and 3 enzymes for the 3 steps.
  - Enzyme 1: activates the protein to be degraded so the ubiquitin can be attached to it.
  - Enzyme2: conjugation (bring ubiquitin and targeted protein close to each other).
  - Enzyme3: ligates them (usually, we have it more than E1 and E2)



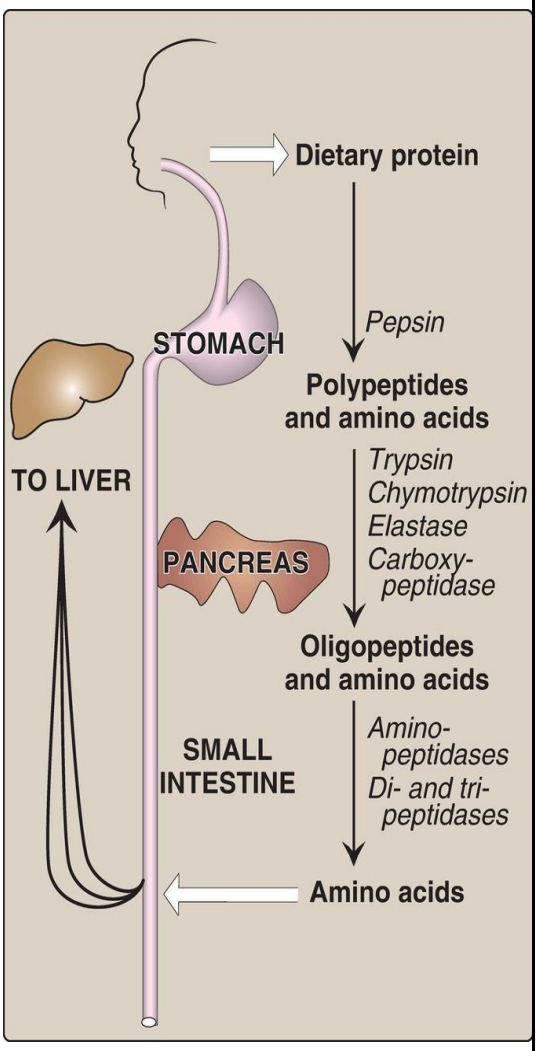
- For any protein to be degraded, it must be unfolded first (denaturation), then deubiquitination (Ub is recycled and used again), next, the enzymes inside the proteasome cut the protein into smaller pieces (short peptides), then in the cytosol, the proteases (aminopeptidases and carboxypeptidases) continue the cutting to get free amino acids that get into the amino acid pool in the blood.

  Proteasome: unfolding → deubiquitination → cutting

- The degradation process is not random; as it depends on the half-life of the protein (long half-life → less degradation)
- There is a certain structure on the N-terminus end of the protein which tells the degradative enzymes if it should be degraded or not; Arginine, alanine bound to acetyl group (acetylated alanine) are destabilizing agents that force the protein to be degraded, on the other hand, serine is a stabilizing end that promotes the protein to stay alive.
- If the protein has PEST sequence (P:proline then E:glutamic acid then S:serine then T:threonine), then it has to be ubiquitinated and degraded.

Proteasome	Lysosome
ATP dependent	ATP independent
Specific	Not specific
Degrades intracellular proteins	Degrades extracellular (sometimes intra.) proteins surrounded by a cell membrane (endocytosis)

Dietary protein digestion

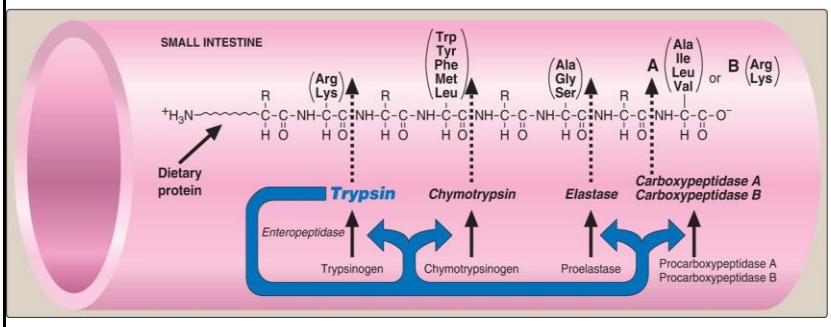


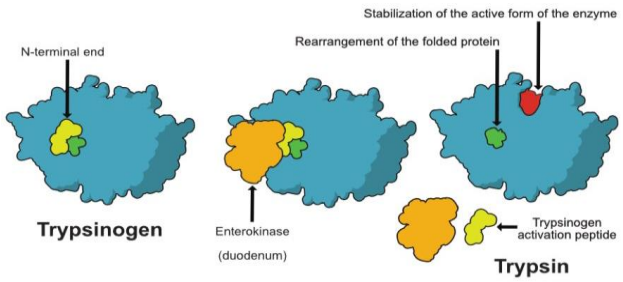
- American diet usually contains 70-100 g of proteins daily.
- All hydrolysis processes (carbs, lipids, proteins) begin in the mouth (physical)(mechanical force), but they differ in their chemical hydrolysis; carbs chemical digestion begins in the mouth (alpha amylase), lipids chemical digestion begins in the mouth (lingual lipase), proteins chemical digestion begins in the stomach then the small intestine.
- Stomach role: acidity (HCl) causes denaturation of the protein. Its pH is almost 1-2 but it is not strong enough to break peptide bonds although it converts pepsinogen to pepsin by cutting a certain peptide bond in pepsinogen BUT MAINLY, its function is to denature proteins.
- The stomach has the ability to convert small number of pepsinogen (because of its low strength in breaking peptide bonds), pepsin now is the one who takes the responsibility of converting other pepsinogens into pepsins which degrade proteins into smaller pieces according to the specificity of pepsin.
- Pancreas role: it secretes exopeptidases (act on terminal ends of the polypeptide chain N and C) and endopeptidases (act on peptide bonds inside the protein).
- When the stomach mixes its contents together, the sphincter that connects it to the small intestine opens a bit, so chyme in the stomach (mixed and digested food and fluids) will get into the duodenum (the first part of the small intestine) → the endothelial cells lining it send a message (secretin) to the pancreas stimulating it to secrete bicarbonate which neutralizes the acidity of the stomach → increasing the pH in the small intestine up to almost 6.8 (depending on the part of the intestine (each part has its own pH)).

OMG! You rock, you just finished the second part of the sheet ☺

Digestion by pancreatic enzymes

The process of digestion inside the small intestine is much more and huge compare to the stomach where only pepsin works.
What's happening here?
We have many enzymes that work inside small intestine to cut the protein to different parts (free amino acids), so what we absorb and deliver into the cell is only free amino acids.





Note: if these enzymes are followed by Pro, it makes the enzyme inactive and lose its specificity to this piece.

Enzyme	Specificity
Trypsin	C-terminal to R, K, but not if next to P
Chymotrypsin	C-terminal to F, Y, W but not if next to P
Elastase	C-terminal to A, G, S, V, but not if next to P
Pepsin	N-terminal to L, F, W, Y, but not when next to P

What happens once the Chymo reaches the small intestine?

- Secretin tells the Pancreas to deliver the Bicarbonate HCO3- to adjust for the acidity inside the small intestine, also the cholecystokinin as a hormone is released from the endothelial cells in small intestine and it tells pancreas to start releasing their pancreatic enzymes.
- So we have many enzymes from pancreatic fluid which secreted from pancreas with a pancreatic duct on common bile duct on duodenum, which are proenzymes, inactive enzymes, they are zymogen, how will they be activated?
- Ex: Enteropeptidase (enterokinase) binds to Trypsinogen, and remove 6 amino acids from N-terminus (which blocks the active site), and when we remove it, there will be detachment for those hexapeptide and the active site will be open now, and it can do its function.
- After converting trypsinogen to trypsin, Trypsin has a capacity, it also converts all other pancreatic enzyme (zymogen) to their active enzymes, ex: proelastase → elastase, procarboxypeptidase A + B → carboxypeptidase A + B, chymotrypsinogen → chymotrypsin. So it is responsible for converting.
- Every piece that is removed by Trypsin, must have Lys or Arg, so Trypsin can do its function.

Digestion abnormalities

- If there's a problem in pancreas itself, we will have digestion abnormalities.
- Causes of deficiency? chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas.
- Symptoms: undigested protein (with feces), steatorrhea (presence of fatty content inside the feces), fatty is degraded in intestine by pancreatic lipase.
- Celiac disease: immune-mediated damage to the small intestine in response to ingestion of gluten (wheat, rye).

Digestion of oligopeptides (small pieces of amino acids) by small intestine enzymes

- Aminopeptidase (exopeptidase) which cuts those pieces of amino acids from N-terminal, take one amino acid at a time.
- What is left? Either free amino acids or small pieces (dipeptide + tripeptide).

Amino acid and small peptide intestinal absorption

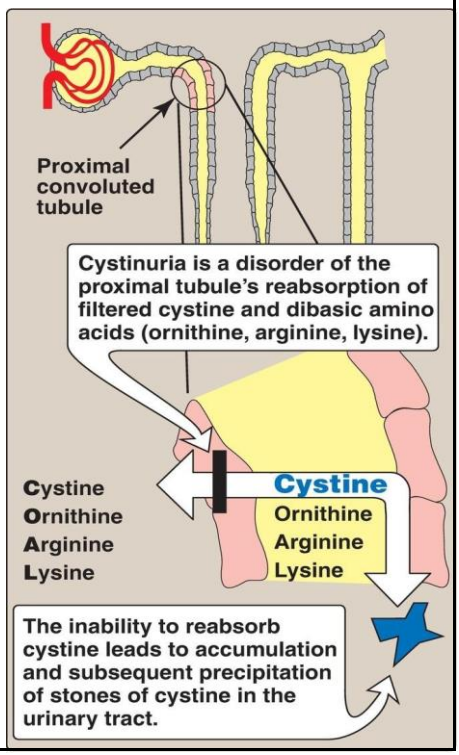
How this process occurs?

- Most free amino acids: Na^+- dependent secondary active transport, so the Na+ will come along with amino acids, if we have Na^+ co transport, there should be Na+/k+ pump at any intestinal cell, to keep concentration of Na+ for transporting.
- Recap: Na+/K+ ATPase which pumps Na+ out and K+ in.
- At least seven different transport systems, for absorption amino acids to inside intestinal cells, and these transporters can carry more than one amino acids and there is overlapping amino acid specificities, which means that one amino acids transport in more than transporter system.
- Skin, GIT, RT and GUT → facing outside environment.
- GIT and Renal → absorption
- Kidney filters out 180 liters each day then reabsorption of a lot of that amount, and what is left in the urine 1-1.5 liter per day.
- Reabsorption of free amino acids occurs through transporters which are the same transporter inside the small intestine.
- We use that when finding a genetic defect which is affecting one of the transporters inside GI tract, so we suspect a defect in the kidney.

- If there's an accumulation of amino acids in the kidney, as a consequence, lots of amino acids are released and stones, because amino acids can connect together, Cystines can connect together, so sometimes you will build up things as Ca+2 and other thing over amino acids because they will create a nucleus for things to be built on it. The more amino acids you have, you will have kidney stones.
- Di- and tripeptides: get inside intestinal cell through a proton-linked peptide transporter (PepT1) – proton co transport. Inside the intestinal cell, there are peptidases which break down Di and Tri into free amino acids which will only transport from the inside intestinal cells to the blood stream in a facilitated diffusion
- Free amino acids are released into the portal system: Na^+-independent transporters
- These amino acids are either metabolized by the liver (BCAA) or released into the general circulation
- Liver metabolizes all amino acids except branched chain amino acids that have a huge amount of energy, so they are metabolized in muscles mainly.

Absorption abnormalities

- Small intestines and kidney proximal tubules
- Defect consequences?
- Cystinuria: inherited; defective COAL (responsible of transporting 4 amino acids, one of them is Cystine which is the oxidized cystine, Ornithine, Arginine, Lysine); 1 in 7,000; the most common genetic error of amino acid transport
- Clinically: kidney stones (calculi), hydration, drink water to let these especially Ca+2 get solubilized in water and get out with the urine.
- Hartnup disorder: defective neutral amino acid transporter (NAAT, tryptophan)



Bro, you're amazing! You just finished the last part of the sheet 🎉

You should be proud of yourself 🌚

صفحة فاضية عشان إذا كنت حاسب الشيت ٩ صفحات تنبسط إنهم طلعوا ٨ وبس

دعواتكم
وإذا في أي غلط سامحونا وابعثولنا لنعدله

✨وبتركم مع الحل لكل مشاكل الدنيا✨

"وَمَن يَتَّقِ اللَّهَ يَجْعَل لَّهُ مَخْرَجًا وَيَرْزُقْهُ مِنْ حَيْثُ لَا يَحْتَسِبُ
وَمَن يَتَوَكَّلْ عَلَى اللَّهِ فَهُوَ حَسْبُهُ إِنَّ اللَّهَ بَالِغُ أَمْرِهِ قَدْ جَعَلَ اللَّهُ لِكُلِّ شَيْءٍ قَدْرًا"