DOCTOR 2020 | JU

METABOLISM

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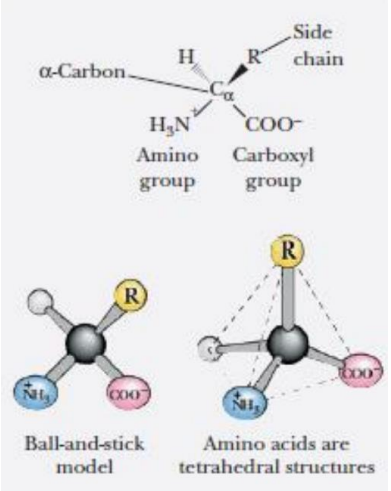
in this lecture we will start talking about the metabolism of amino acids.

The structure of amino acids

A carbon compound that has a central carbon atom called the **α carbon** and this carbon is connected to 4 different groups which are :

1- Carboxyl group
2- Amino group
3- Hydrogen atom
4- " R " group, which differs between amino acids



In protein structures we have only 20 amino acids, but there are other amino acids in our body that do functions other than protein synthesis.

The 20 amino acids are present in our body in 2 conformations : D&L (as an enantiomers).

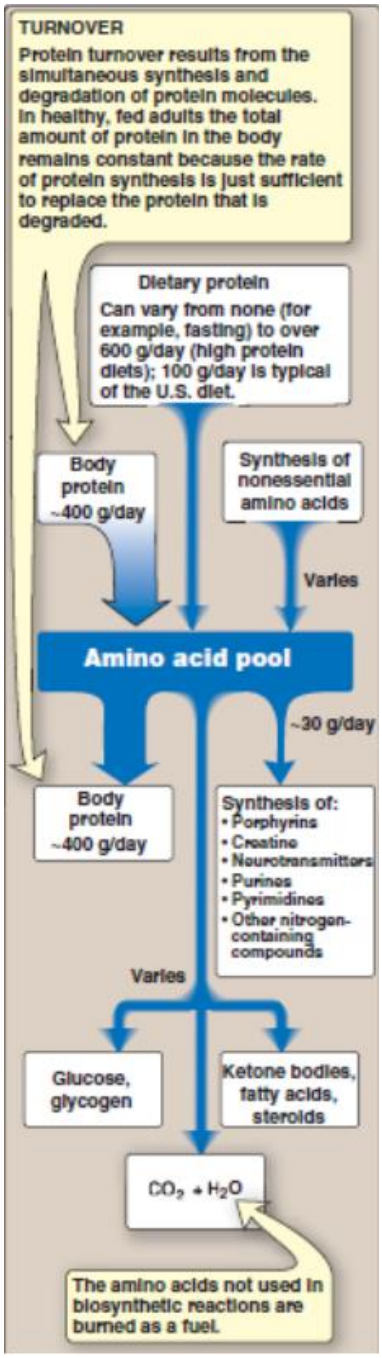
L : is the conformation present in proteins structures

Note : our cells can deal with **D** amino acids via a certain pathway we will get to it in later lectures

Peptides are made by the interaction of the **carboxyl group** of the first amino acid with the **amino group** of the second amino acid which forms **a peptide bond** and the free sides make up the C & N terminuses.

Amino Acid Pool

Amino acids can't be stored in cell (unlike sugars which can be stored as glycogen) so we have a fixed amount of amino acids in our body that is called " **Amino Acids pool** " which makes up about **90-100 grams** in our body, this pool can be supplied but also constantly consumed by different pathways so there is an " **in &out** " movement to maintain this pool.



Amino acids are an important source of nitrogen, and this nitrogen is released as **ammonia (NH_3)** which is a very toxic compound that may affect the **CNS** if it reaches toxicity concentrations in the blood, so we need to maintain a balance of amino acids.

Although almost 60% of our body is made up from water, but it can't dilute NH_3 to reach non-toxic concentrations (we will discuss the elimination of NH_3 in future lectures).

Sources of amino acids :

1- Exogenous: proteins / Amino Acids form **Diet**
2- Endogenous: protein **degradation** which is constantly taking place to eliminate misfolded, non-functional proteins or a protein that has finished its function.
3- Non-essential amino acids **synthesized** from metabolic pathway.

Amino acids depletion routes:

1- Synthesis of proteins
2- Amino acids consumed as precursors of nitrogen containing small molecules (ex : heme groups, hormones, etc.)
3- Conversion of Amino Acids to α-keto acids, glucose, glycogen, fatty acids, ketone bodies, or $CO_2 + H_2O$.

Note: degradation to CO_2 and H_2O happen when there is an excess of amino acids, because as we said they can't be stored.

Protein Turnover

- It is the process in which the rate of protein synthesis is sufficient to replace the degraded protein.
- Each day, 300–400 g of body protein is hydrolyzed and resynthesized
- In healthy adults, the total amount of protein in the body remains constant.

This process varies widely between different proteins because of their functions so for example, Collagen is a structural protein so it can live long (months to years)

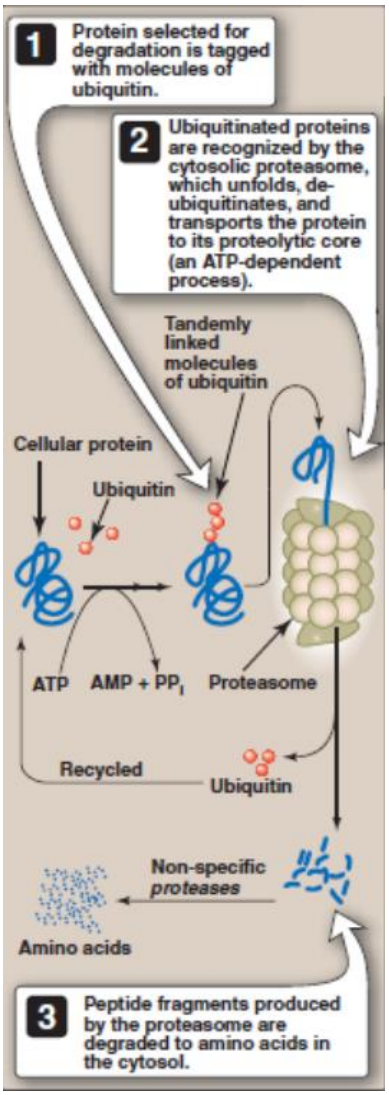
But enzymes they live shorter because they have a certain function, it has to be degraded at some point to stop its action.

The half-life of a protein is highly related to its structure, ex : structural protein have certain amino acids sequence on a certain position which might prolong its life spam.

- **Note** : there is something called the **mode of expression** that affects protein turnover, it means how and when this gene is expressed.
  So for example, **housekeeping** genes are considered as **constitutive genes** they are constantly expressed, but there are certain proteins that are only synthesized under certain condition and stimulators, so they are called **induced proteins** , such as insulin and glucagon , which **regulate** metabolic pathways.

PROTEIN DEGRADATION MECHANISMS

1) The **ATP-dependent ubiquitin-proteasome** system (for intracellular proteins)



it uses proteosomes that is composed of proteins so in fact it's not an organelle, it's just a machine , the protein that is degraded should be **labeled** with a protein called ubiquitin (not an enzyme) and notice that several ubiquitin molecules are attached to the degradable protein, that's why it's called **poly-ubiquitination**.

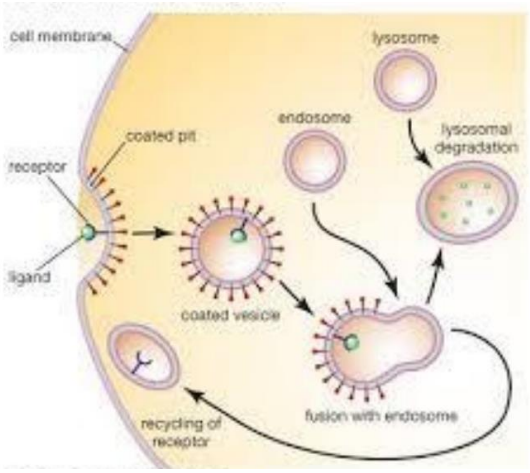
After tagging it's going to be guided to the pores of the proteosome ,

Notice that after entering the proteosome the protein is degraded into smaller peptides but not individual amino acids, so those are further degraded by non-specific **proteases** into amino acids.

- The process of ubiquitination needs ATP but the process of hydrolyzing the protein doesn't require energy, so this system is considered as ATP dependent pathway.

Note : ubiquitin is recycled

2) The **ATP-independent** degradative enzyme system of the **lysosome** (for extracellular and cellular membrane proteins)



extracellular proteins are taken by receptor mediated endocytosis and degraded by lysosomal enzymes, which are acid hydrolases enzymes that work on a pH around 5, the cytosol is around 7, and this pathway doesn't need ATP.

Digestion of dietary proteins

Protein consumption varies between individuals, but in a normal American diet 70–100 g/day of proteins are consumed.

In mouth :

In the mouth digestion **will not** take place because:

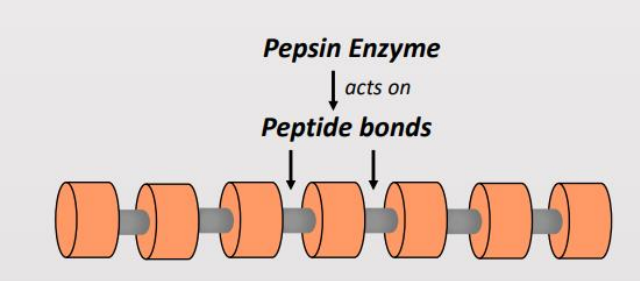
1- the **duration** spent there is short
2- the **structure** of the polypeptide is large and complex so there are no enzymes to digest those molecules.

In stomach :

Is the stomach proteins will face an acidic environment due to HCl which is secreted by **parietal** cell in the stomach, which decreases the pH to be from 2-3.

HCl has several functions such as :

A- Denaturation of proteins (taking away their 3D shape) , the purpose of this denaturation is to **unfold** the protein into a chain of amino acids, so it becomes easier to degrade by enzymes)



B- activate **pepsinogen** (which is an inactive zymogen) into pepsin, this enzyme is secreted by the stomach's **chief cells**, if it's synthesized as active protein it will degrade the cells that it was synthesized in , so it's released as a zymogen to act in the place of function.

C- This acidic environment works as a **sterilizer** for pathogenic microbes that may enter the stomach.

Pepsin is going to catalyze the partial digestion of the protein, but it will not give us single amino acids.

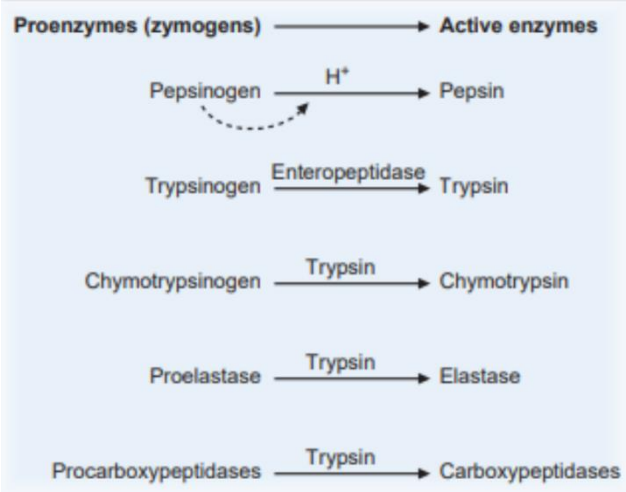
Note : Pepsin + HCL + the partially degraded protein, is called the **chyme**.

In intestine (duodenum specifically) :

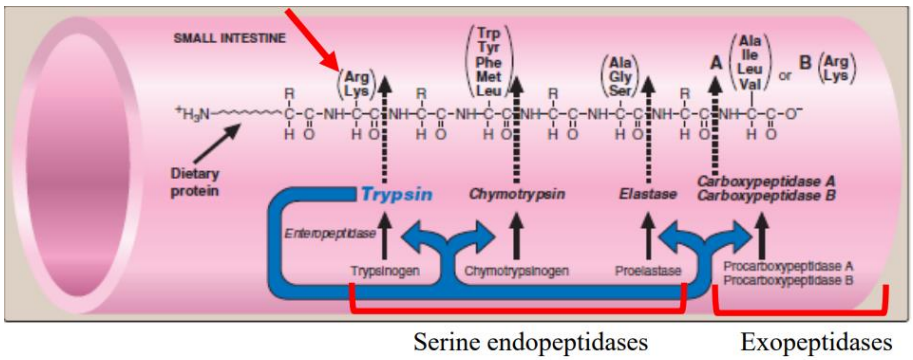
This chyme will move to the **duodenum** where **inactivation of pepsin** takes place because of the increase in pH which reaches around 6.

At this time other enzymes will be secreted by the pancreas which are also produced as zymogens for the same reason mentioned above.

Pancreatic enzymes in the duodenum :



1- **trypsinogen** which is cleaved into trypsin , it's activated by an enzyme called **Enteropeptidase**, once it's active it will convert other zymogens into their active form such as the ones in the slide.
2- **Carboxypeptidase A & B** they cut next to the C terminus (exopeptidases)
3- **Serine endopeptidases** : they are named like that because serine is involved in the active site during catalysis, and " endo " because they cut in the middle of the peptide, and those include trypsin, chymotrypsin and elastase.



(the positions of cleavage for these enzymes are not required)

Note : **Amino peptidase** is an **intestinal** enzymes (not pancreatic) that cuts after the n-terminus.

Q) Why do we have all these enzymes and not a single enzymes that runs the whole process?

Because every enzymes cuts after certain amino acids (specifity), because the "R" group alters the binding of the enzyme to the substrate (the certain site for cleavage)

Absorption of amino acids and small peptides

After all these enzymes, we end up with single amino acids or at most di-tri peptides , so now these molecules are ready for absorption (transport of these molecules from the lumen → enterocytes → portal circulation → liver)

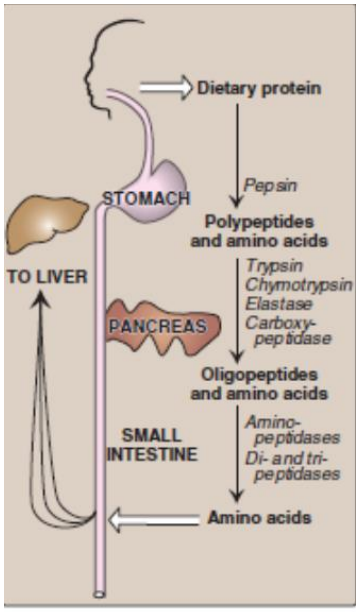
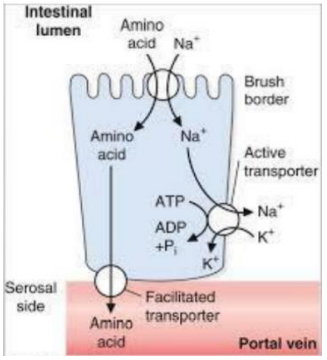


Figure 19.4



Recall that enterocytes are polar cells; with a brush border and a baso-lateral surface.

- Na^+-dependent transport system will be used to transfer single amino acids only (not di or tripeptides).
- Di and tripeptides enter via a proton transport system , and when they enter the cell they will be hydrolyzed to single amino acids.

these molecules concentration increases inside the enterocyte , so the **concentration gradient** will lead to the transport of these amino acids to the **portal** vein using **facilitated diffusion** (with no need of energy).

When amino acids reach the body cells, each amino can have its own transporter or a single transporter can be shared between different amino acids, that depends on the amino acid itself.

Clinical applications

1- Pancreatic illness (chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas, etc.).
Recall that the pancreas is an endocrine and an exocrine gland because it causes systemic and local effects , you noticed that a ton of digestive enzymes come from the pancreas, so in case of illness digestive enzymes for lipids, carbs and proteins will be decreased , therefore there would be less digestion→so these substances will stay in the lumen without any absorption→ these molecules will be excreted with feces.

Osmotic pressure will be increased (due to the difference of protein concentrations) i.e. water will get from cells to the lumen, which causes diarrhea.
the most obvious molecules seen with feces are lipids, because they are hydrophobic so they are separated easily from feces and the appearance of such lipids is called **steatorrhea (really important to know)**.

2- Celiac disease :
it has high prevalence nowadays because :

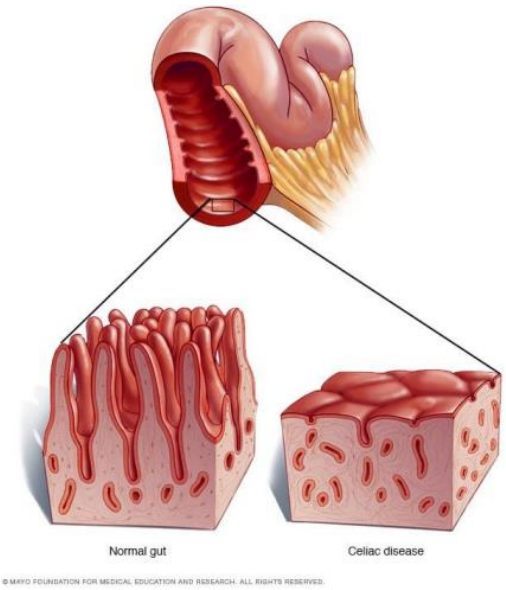
- in the past it was undiagnosed
- The modern lifestyle specially the diet has affected the spread of celiac

Gluten is present among a lot of products not just wheat , gliadin will be recognized as a foreign object which will induce an immune response that will **destruct intestinal cells** , normally enterocytes are replaced every **3 days** but in the case of celiac those cells will be destructed in less that 3 days.

Notice the figure → , the difference between normal gut and celiac gut, the brush border of enterocytes provides higher surface area for absorption and higher concentration for enzymes and transporters but this structure has changed due to frequent destruction of enterocytes that affects absorption and causes malabsorption which happens only when consuming gluten.

But digestion won't be affected in this case, because most digestive enzymes come from the pancreas that is not affected by celiac.

- The treatment is to have gluten-free diet



Note : Maltase, iso-maltase, amino peptidase and lactase are digestive enzymes that come from the intestine, but they are just few enzymes compared to the quantity of the pancreatic enzymes, so digestion is not affected that much.

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