Medical Committee
The University of Jordan

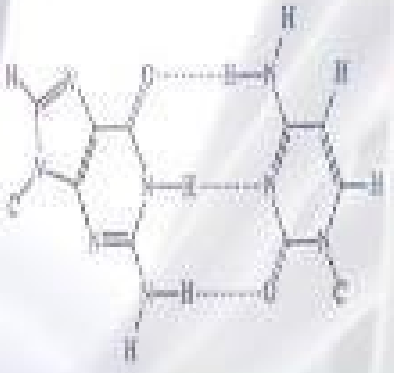
SLIDE SHEET

Done By: Ala'a Shaban

Sheet number: 23

DR.NAME: Dr. Nafeth

Biochemistry



Majida Al-Foqaraa'

Metabolism of Proteins & Amino Acids

We will have **four** lectures about **protein** and **amino acid** metabolism, we will talk about proteins and how we deal with them in our body; how we degrade them, to what proteins are degraded and how we deal with the degradation products.

Proteins are polymers of amino acids so the degradation process of proteins involves the breaking down of these proteins into their corresponding amino acids. Therefore, after breaking them to their amino acids, we will deal separately with those amino acids and how each of them will be degraded.

Degradation process of amino acids involves two main phases related to their structure because they're composed of two constituents that are different from each other:

- **The amino group:** A major part of each amino acid. By itself it is important in nitrogen metabolism.
- **The carbon skeleton:** It consists from carboxylic group with α- carbon and a side chain (involves carbon units).
  There is a specific metabolic pathway that deals with the amino group by itself and for the rest of the amino acid there is a specific metabolic pathway that deals with each amino acid and its corresponding carbon skeleton.
  So we will talk about proteins and how they are degraded to their amino acids then how we will deal with the amino group by itself and how we will deal with each carbon skeleton for each amino acid.

Structure wise amino acids are not different from each other as all of them are composed of a backbone and a side chain but function wise they are different.

Digestion of Proteins:

What is proteins digestion?

Breaking down **proteins** by **enzymes** to their corresponding **amino acids**.

What are these enzymes?

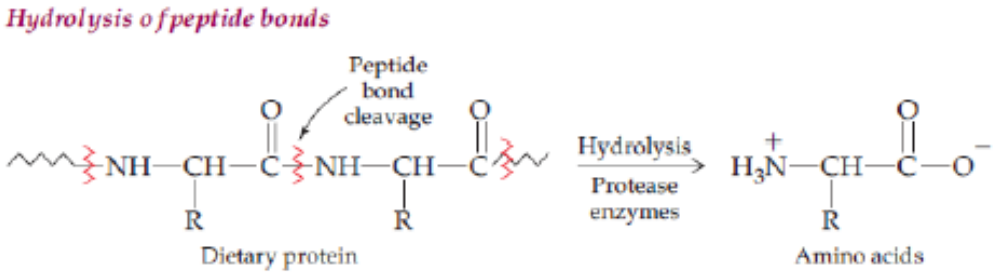
Proteases.

Proteases break down proteins by which type of reaction?

Hydrolysis reaction.

Proteins are formed by a condensation reaction that joins (condenses) two amino acid together by taking a hydrogen from one and a hydroxyl group from the another getting

out water. So adding water back by a hydrolysis reaction will degrade the proteins to their corresponding amino acids.



Where does the digestion process of protein begin?

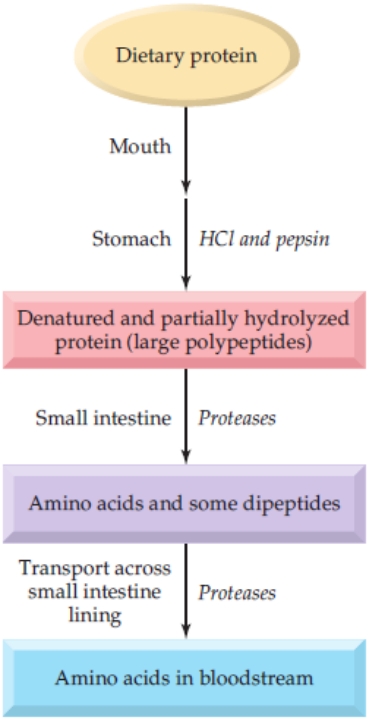
Mechanical digestion (for any substance digestion) begins in the mouth by grinding food to achieve a kind of denaturation of proteins and to make any constituent of food smaller in size. Chemical digestion ((for proteins)) starts in the stomach whereas in carbohydrates it starts in the mouth.

In order to digest proteins by breaking them down by enzyme we have to denature these proteins to their primary structure then we can cut them down by the enzymes.

How can the denaturation process achieved?

- **Increasing temperature:** e.g. Heating eggs denatures the tertiary structure of the proteins so they become less soluble and the hydrophobic parts will attach with each other to form solid aggregates and because most of the egg is proteins so it will become solid.
- **Changing PH.**
- **Mechanical agitation:** e.g. Cream with egg; we denature proteins by a fast movement then the hydrophobic regions are exposed so it becomes solid. So mechanically we can denature proteins and this is why we have teeth.

So the denaturation is a part of the digestion process as it should be achieved before the enzymes can break down the proteins.



By now the protein has reached the stomach, so what will happen in it?

Chemical digestion starts in the stomach by an enzyme called **Pepsin**; It is produced as **Pepsinogen** (inactive state), it is there in the stomach but we do not need it to function all the time; when we need it to function, it will be activated and converted to **Pepsin** (active state) by HCL so

when the person starts to eat this will stimulate the secretion of stomach HCL**.** After Pepsin is activated, it starts an **autocatalytic mechanism**; that means it drives the breaking down of the protein itself; so once we have Pepsin, it will start catalyzing the conversion of more Pepsinogen to Pepsin (HCL will remain so it will convert more pepsinogen to pepsin).

A lot of enzymes in our body are produced in an inactive state then they will be converted to their active state through **proteolytic cleavage**; a part of the inactive form is broken down by breaking down of certain peptide sequence of that protein to expose the active site so that enzyme will be active

We produce enzymes in their inactive state for one of two reasons:

- We do not need enzyme to function now.
- We have produced the enzyme in a certain place but it will work in another place.

Now the proteins have reached the duodenum in the intestines. Once the food intake process begins, the cells in the duodenum secrete two hormones: **Cholecystokinin** and **Secretin**. Cholecystokinin is the main Player while Secretin helps Cholecystokinin to perform function.

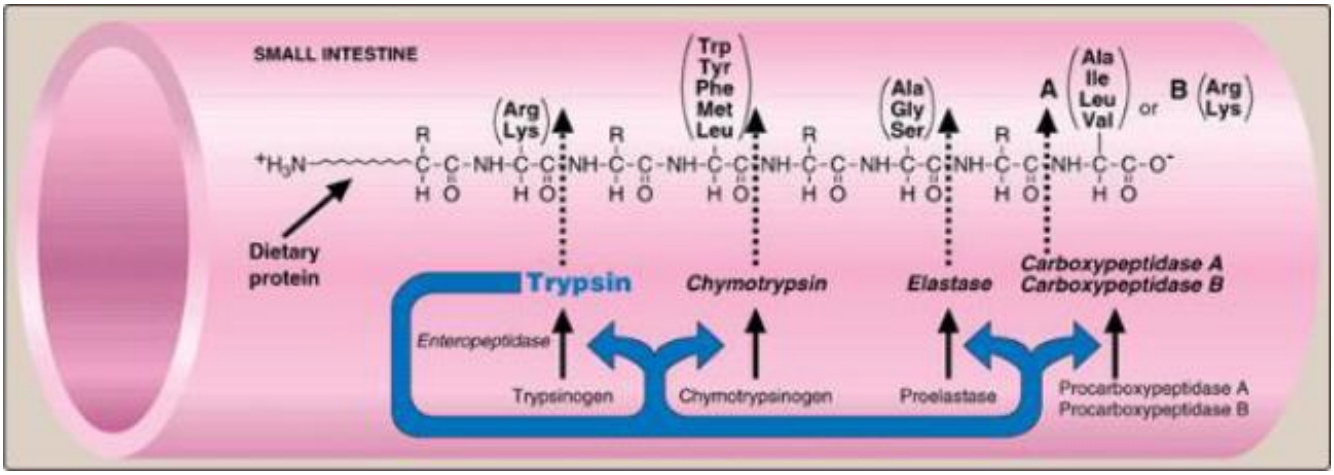
Cholecystokinin and **Secretin** when produced from the duodenum give two messages; one will go to the **pancreas** and the another one will go to the **gallbladder** to secrete their contents; bile from the **gallbladder** will help in lipids metabolism by degrading the lipids and help in absorbing lipids while **enzymes from the pancreas** help mainly in protein digestion.

Pancreas is composed of two main parts: **endocrine** part and **exocrine** part. The endocrine part secretes **Insulin** and **Glucagon** from **Beta cells** in **Langerhans islets**. The exocrine part (has a duct for secretion, so they are not considered as hormones) secretes a number of enzymes that help mainly the protein digestion (work on protein degradation) and they aid in carbohydrates and lipid digestion.

Enzymes secreted from pancreas: **Trypsin**, **Chymotrypsin**, **Elastase**, **Carboxypeptidase A** and **Carboxypeptidase B**. These groups of enzymes are for breaking down proteins. All of them are produced from the pancreas but their action occurs in the intestines (they are produced from a place but their effect occurs in another place) so by logic they should be secreted in inactive state (**Zymogen form**) same way as **Pepsinogen**. To denote the inactive zymogen form of an enzyme, the name is modified by addition of the suffix "**-ogen**" or the prefix "**pro-**": **Trypsinogen**, **Chymotrypsinogen**, **Proelastase**, **Procarboxypeptidase A** and

Procarboxypeptidase B. Then, once they reach the intestines (Pancreas sends its secretions to the duodenum where), they will be activated we will talk about the activation process.

Enteropeptidase in the intestines is a product of the mucosal cells of the small intestines, it converts the **Trypsinogen** into **Trypsin** so the process of activating Trypsionogen is through Enteropeptidase. Once **Trypsin** is activated, it will start an **autocatalytic mechanism** to convert more **Trypsinogen** to **Trypsin** and it will convert **Chymotrypsinogen** to **Chymotrypsin**, **Proelastase** to **Elastase**, and **Procarboxypeptidases A** and **B** to their corresponding **active states**. So **Trypsin** is the main player because it converts all the other enzymes with itself to their active states.



We have reached here to small pieces of the protein as a result of the degradation processes, on the intestinal lining cells that secret enzymes; **aminopeptidases** and **carboxypeptidases**. **Aminopeptidases** remove an aminoacid from the **N-terminal side** of the small peptides while **Carboxypeptidases** remove an aminoacid from the **carboxylic side** of the small peptides, and they keep working until single aminoacids are left.

Absorption & transport of aminoacids & dipeptides:

As a result of the degradation process, there are **free amino acids** and **small pieces (di- and tripeptides)**. Free amino acids pass to the intestinal cells through **Na+-cotransport** while **di- and tripeptides** pass to the intestinal cells through **Proton-cotransport (H+-cotransport)**, so there are two different modes of absorption from the stomach to the intestinal cells. Once they are in the intestinal cells, **di-** and **tripeptides** will be broken again by the enzymes found within these cells to **free amino acids** so all the results of proteins degradation become **free amino acids**. You

cannot get to your blood out of the absorption process except free amino acids; only free amino acids will be translocated to the blood.

Getting out of these free amino acids from the **intestinal cells** to the **blood** is done through **transporters** and they need **energy** (**active transport**), we do **not** have 20 transporters one for each amino acid; we have transporters which can transport **only one amino acid** and we have transporters which can transport **groups of amino acids** (e.g. for two, four, seven... amino acids). We have **7 transporters** which **account** for the **twenty amino acids**; Those transporters are identical in their structure and function to the transporters which are present in the **kidney**; in the kidney there is a filtration of most of blood constituents and then there will be **reabsorption** of them including amino acids, in the urine we don't find proteins or amino acids; we can detect a few number of amino acids because the filtrated amino acids will be **reabsorbed** to the blood by **transporters** (**active transport**) which are the same to ones present in the intestines.

Because there are grouped transporters that transport as an example four amino acids, there is **no** selection or specificity in these transporters for any of their transporting materials; e.g. a transporters that transports Cysteine, Arginine (not sure), Serine, Lysine, there is **no** specificity which means if you have more cysteine, there will be less serine absorbed; the excess in one amino acid can decrease the absorption of another amino acid which is transported by the same transporter. Those transporters can be genetically deficient (problems in the transcripted genes); this problem appears in certain amino acids which can be absorbed in the body rather than other amino acids, it appears after filtration of amino acids in the kidney so there will be **no** reabsorption of these amino acids outside of the kidney so they will start building up in the kidney resulting in kidney stones; there is a famous genetically caused disease called **Cystinuria**; where Cysteines aggregate forming disulfide bridges resulting in kidney stones.

Then After reaching the blood, from there they will go to cells where there will be a degradation of the amino group separately and a degradation of the carbon skeleton separately.

Proteins are unlike fats and carbohydrate; as you can store carbohydrates, lipids and fats but you **cannot store proteins**; so if you have excess amino acid or protein

intake, you will not be able to store it in your body so either you will use those amino acids to **build up proteins**; so people who eat a lot of proteins should exercise to build up their muscles in body building, or you will **pass out** those excess amino acids; the amino group exit to the urea cycle passing out more urea, so you will not benefit of the high amounts of proteins in storing them. The high amount intake of proteins is important for children to build up their muscles and body. In adults if you are not combining protein intake with body building, you will not use those proteins.

Amino Acid Metabolism - overview:

How can you get amino acids and proteins into your body?

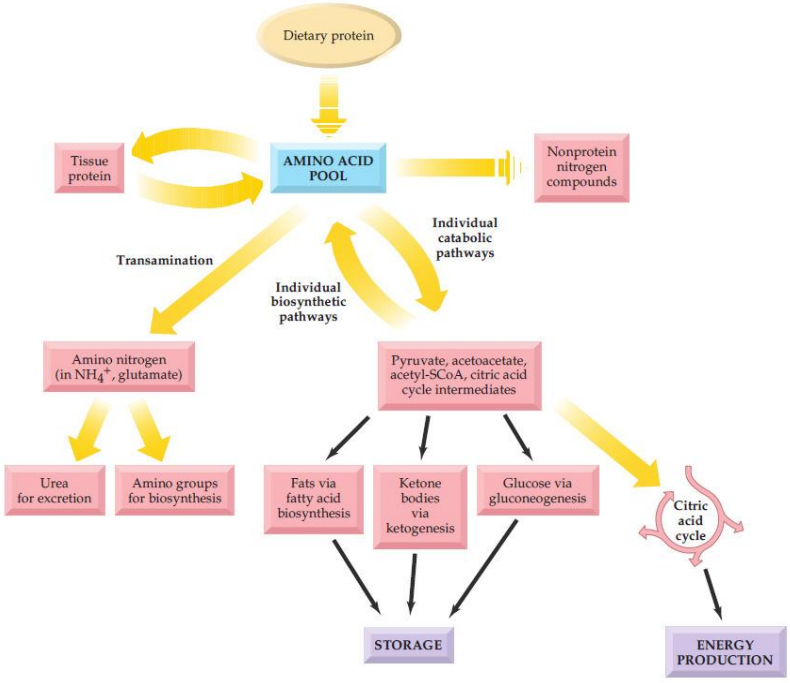
Main sources of amino acids for the body:

- **Food (Diet):** you take proteins into your body from food then they will be degraded to their amino acids and you will absorb them.
- **Degradation of our own proteins** that results in free amino acids.
- **Synthesis of amino acids:** there are essential amino acids that you have to get from outside (those are from diet) and there are non-essential amino acids that you can build it within your bodies.

How do we use those amino acids?

The destinations of those amino acids:

- **Using these amino acids for Synthesis of proteins**.
- **Precursors:** synthesizing nitrogen containing compounds; amino acids are the common source of nitrogen as it is heavily needed in our body; it is involved in synthesis of many things in our body to the extent that we can't live without Nitrogen. We get Nitrogen from amino acids by removing the amino group and using its Nitrogen.
- **Conversion** of amino acid to other compounds for **energy purposes** as in gluconeogenesis where they are converted to give glucose.



Amino Acid Pool:

What does "**Amino Acid Pool**" mean?

It is a term that tells about all the free amino acids within the body, they can be found inside the cells, interstitial fluid and in the blood; any space in the body you can find in it amino acids. Collectively, all those free amino acids are called "Amino Acid Pool".

They are used as what we have already said for synthesizing proteins and nitrogen containing compounds or for conversion into molecules which can result in energy.

In healthy adult there is a **Nitrogen balance** which means that there is always a balance between the thee sources of free amino acids and their three destinations (the supplied amount equal the used amount), this pool amount is 100 g; you think it is an unimportant little amount but **50% of the body dry weight** (weight of the body without water) is for protein, so the protein is very main and important in the body for all processes specially for enzymes; so even if it is a small amino acid pool, it is central to all body processes.

Protein Turn-over:

Don't think that the protein which you are using in your body is there forever; it keeps in a **remodeling process**; any protein within your body will be degraded and synthesized again in place to serve the function, **proteins are different from each other** in their degradation processes and their half-lives, some of them are degraded rapidly then resynthesized; some of them live for seconds, minutes, some for hours and some for years; it differs depending on the function of the protein, how its synthesis is complicated and whether the cells corresponding to it will be still active or not; so there are many things corresponding to protein synthesis or degradation.

How much proteins are you remodeling (breaking down and resynthesizing) each day?

300-400 g daily.

How do we degrade our own proteins?

We have two main processes responsible for protein degradation:

- **ATP independent:** doesn't need energy, **lysosomal pathway.**
- **ATP dependent:** needs energy.

How does the degradation process by lysosome happen?

Lysosome is an organelle within the cell, a vesicle comes to this lysosome then there will be a fusion between the lysosome and the vesicle so the content of the vesicle will

be released to the lysosome and the degradation starts, this process does not need energy.

Because there should be a vesicle that comes from the cell membrane to fuse with lysosome so lysosome breaks down proteins which are mainly **extracellular** (their origin from outside the cell). The vesicle don't go to lysosome from intracellular origin except when the cell is dying in apoptotic process which is not a living healthy-state process. So lysosome is responsible for breaking down extracellular proteins.

How **intracellular** proteins will be degraded?

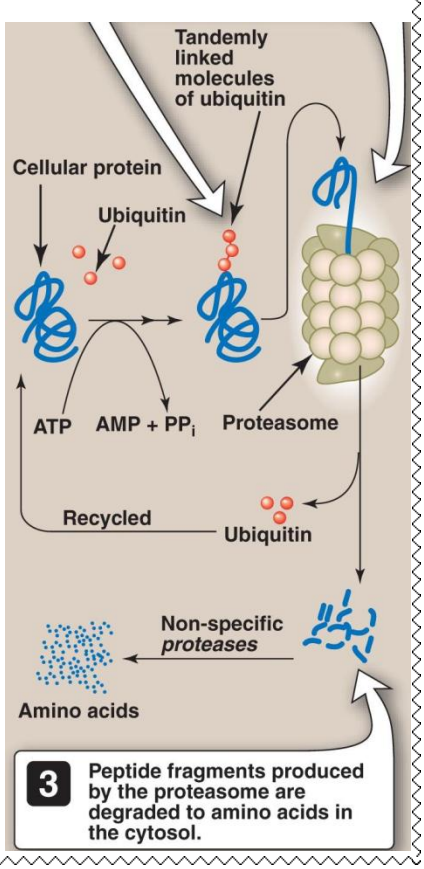
Through an ATP-dependent process in a structure called **Proteasome**. Proteasomes are responsible for breaking down intracellular proteins.

How does the degradation process by proteasome happen?

For a Protein to be degraded, there should be a mark (signal) on it telling the proteasome: "please degrade me! :p", otherwise; the process will be randomly occurring, so in order to make the process sharp you have to mark the proteins to be degraded.

How does this marking occur?

The protein to be degraded will be attached to a small globular protein known as **Ubiquitin**; which has a glycine amino acid that attacks a lysine residue within the protein to be degraded and makes a bond with it; once the Ubiquitin attaches to the protein of interest, another Ubiquitin can attach to the already bound Ubiquitin and then another Ubiquitin attaches so there will be Polyubiquitins bound to the protein and the process is called **polyubiquitination**; polyubiquitination is responsible for proteasome binding; for the proteasome to attach to a protein and break it down, the protein should have ubiquitins. This process of attachment is a **ligation** process, you are connecting proteins together so you need to spend **ATP** (1 ATP has two high energy bonds; firstly you break the phosphodiesteser bond resulting in pyrophosaphate released, then you break the pyrophosphate bond, so two high energy bonds are spent to attach each ubiquitin).



This is the protein of interest that enters the protesome which has a **barrel shape** that is empty from inside, the linings of this barrel-shaped structure are **enzymes** that can break down proteins (it only identify proteins only when attached to ubiquitins); the proteins are degraded to small pieces then

ubiquitin will be recycled again to be used with another proteins. Small pieces will be further broken down into free amino acids through non-specific proteases; aminopeptidases or carboxypeptidases within the cell.

What makes the ubiquitin to bind the specific protein not another one?

This selection process is long and still not cleared; however researches are going on to identify all the markers that identify the protein to be degraded or not; one of them is the oxidation (free radicals which lead to oxidation of certain proteins) this will give a message to the ubiquitin to bind these proteins, another marker is the misfolding; any misfolded protein will be degraded by the same mechanism.

There is a research to find if there is a character within the protein to determine the half-life and studies have been done on the **N-terminal side** of the protein; they found that the proteins having serine at their N-terminal side are usually long-lived with a half-life of 20 hours but if the N-terminal side is aspartic acid; the proteins are usually short-lived with a half-life of around 3 minutes, proteins which in their N-terminal side have **Proline**, **glutamic acid**, **serine**, and **threonine** (**PEST**) as a group will be very short-lived proteins. These are examples about how the N-terminal side can determine the life of the proteins.

General scheme for amino acid catabolism:

When we have free amino acids resulted from the degradation of proteins, we remove the amino group of these free amino acids then there will be a usage of the nitrogen in of the amino group. Nitrogen is central of the body; it is used for the synthesis of **nitrogen-containing compounds** such as **nitric oxide (NO)** that is used in the central nervous system, Nitrogen used also for the **synthesis of some hormones** like **Epinephrine** and **Norepinephrine** which contain nitrogen, also for the **synthesis of some neurotransmitters** which contain nitrogen, in the **synthesis of NAD^+** which is involved in the energy metabolism and converted to NADH, in the **synthesis of Heme** which contain iron in the center connected to four pyrrole rings each of which contain nitrogen, and for the **purines and pyrimidines syntheisis** that are used for DNA and RNA synthesis, without Nitrogen we cannot synthesize these nitrogen-containing compounds so we cannot live without nitrogen. Excess nitrogen that is not used to make precursors go to the liver to make Urea.

So we get Nitrogen from the amino group of the amino acids then we are left with the carbon skeleton which can be broken to give citric acid cycle components so it is used in energy metabolism, or it can be used to make glucose-related material such as **Pyruvate** or **Oxaloacetae** which through the glucuneogenic pathway make glucose.

"Whatever your mind can conceive and believe, the mind can achieve regardless of how many times you have failed in the past"
Napoleon Hill