**Proteins and Amino acids metabolism**

* We **don’t store** amino acids , there is no such storage protein .

Every protein is build up to do function

Any excess amino acids , if the body need to build proteins ,it will use them , if not it will degrade them and enter different metabolic pathways.

**\*\*Sources :**

1. essential AA from diet .
2. non-essential AA synthesized within the body from other AA or other sources like de novo .
3. protein degradation.

**\*\*destination :**

1. building up protein ( synthesis ).
2. they can be converted to other compounds such as glucose in gluconeogenesis .
3. nitrogen containing compound , e.x : heme "(porferin ring) which consist of 4 small nitrogen rings and iron in the middle".

-amino acids are the most important source for nitrogen .

-amino acids has special disposal system .

**\*\*Degradation of amino acid** :

We will look at the amino group as one unit "nitrogen has special disposal system", and the carbon skeleton has special disposal system.

Every AA has special metabolic pathway , and may group of them (around 3 amino acids) have the same pathway .

**two concept :**

* **amino acids pool "slide 3":**
* **pool:تجمُع**
* amino acid pool means: free amino acids in the body , not engaged with peptide bond with any other AA.
* Found in ; blood ,cytosol and extra cellular fluid .
* Generally for healthy people almost its amount is 100 g ,it is not that much however its central to all metabolic pathways .

\*its indicator to build or degrade proteins according to its amounts.

* The supply and destination of the pool is the same as AA .
* Humans live in **Nitrogen balance** which mean :

 Amount of N enter = amount of N use (get it out of the body or building protein).

- **protein turnover** **"slide 4"**:

-turnover: تجديد "بتحرق و بتجيب جديد!"

* All proteins broken down and re-synthesized (remodeling) .
* all proteins have saved half life but, generally every protein has half life in this half life it must be degraded and resynthesized again "the protein which work now in your body **NOT** the same protein that will do the same job in all of your life, it will be broken down and resynthesised again ☺" .
* protein remodeling depend on its half life (minutes, hours, days, weeks, years), **H**ow proteins differ in its half lifes ? generally speaking : according to the nature of their function>> for e.g. structural proteins will not remodel always, it will still for years, **COLLAGEN** is an example.

* How many the rate of turnover that happen per day for proteins??

300-400 grams/day.

rate : 200 and 300 g / day

* **two major pathways for proteins degradation :**
1. **lysosomes :**
* endocytosis on the cell membrane >> enter the cell in vesicles>>these vesicles unite with lysosomes>>> the proteins inside these vesicles will be degraded by acidic hydrolysis enzymes that are in lysosomes.
* Proteins comes from the same **cell membrane** or **EC** .
* They are ATP-independent

**2-proteasomes:**

* Take proteins that are **inside the cell**
* They are ATP-dependent .
* For protein degradation, a message must reach to the cell to tell proteasomes to degrade this certain protein

**\*\*Ubiquitin :** small globular protein **,** work as binding protein not as an enzyme, It's an AA



* It has ∝carbon, hydrogen, amino group, carboxylic group.

\*The arrows (in the picture above) refer to the binding sites of amino acids either at the carboxyl group or at the amino group .

* Glycine is a residue of ubiquitin will bind with lysine residue of the **target protein** (as in the picture below).
* **NOW** THE FIRST ubiquitin bind "look at the picture above",, **THEN** a Chain of ubiquitin will attach to each other "because the binding of the first ubiquitin and protein will trigger more ubiquitin to bind each other ( **polyubiquitination** ) ,,this is message for the cell in order to degrade this protein….(this is show in the picture at the next page ☺ ).



\*\*ubiquitination is ATP dependent "look at the picture above we use ATP and convert it into AMP and PPi " .

* proteasome is like barrel shape, in the lining of this proteasome the degradation take place ; when message arrive>> protein will be a little bit unfolding >> enter proteasomes >> degraded to small peptides or free AA "that depend on the enzymes that are inside the proteasome" >> Proteases insides the cells will take care for small peptides to produce free AA >> ubiquitin then released to recycle and bind with other proteins that should be degraded .
* degradation isn’t random process >> SO if there is Serine on the internal residue of the protein has long half life period more than 20 hr, its degrading will be late,,, BUT if there is Aspartic acids residue proteins on the internal residue of the protein which have short half life around 3 min, its degrading will be early.

\*Pest short lived sequences are :

**P**roline **G**lutamic acid **S**erine and **T**herine

If You find them at the end of protein>> the protein generally will be short lived.

\*\***Digestion of proteins "slide 6":**

Its involve two phases :

1. mechanical phase : denaturation; once protein comes in primary structure and loses its quaternary structure .

2– chemical phase : also has denaturation, then breaking peptide bonds to produce free AA and short peptides .

##Digestion start at **mouth** (chewing), apply **mechanical force** which aids in denaturation of proteins .

**Note** : digestion of **carbohydrates** start at mouth "chemical and mechanical", when you make chewing, you apply a mechanical force which will aid for the denaturation process for **proteins**>> you are breaking the cells by mechanical forces which will lead to the **denaturation**.

* At **stomach** : which contain:

**HCl** :

1-when we put the protein in acid medium needed to change charges on AA so electrostatic attraction between basic and acid (salt bridges ) will break the protein, so it will lose its shape and denature .

2-And its convert the inactive pepsinogen to active pepsin "which will degrade the peptide bonds".

 \*then active pepsin convert pepsinogen to pepsin (autocatalytic activation ).

* **"Slide 7":**
* At **intestine** : ( enzymes in intestine come from intestine and pancreas)

-Pancreatic enzymes : (More Specific for degradation )

-Secretion mediated by cholecystokinin and secretin, when they secreted they induce the contraction of the pancreas so it will secrete its enzymes .

-Enteropeptidase enzymes found in the lining of small intestine (mucosal) ,once its secreted "after the activation to the pancreatic enzymes secretion" it activates trypsinogen (the common activator of all the pancreatic zymogens) by converting it into trypsin .

Trypsin once its activated,\* it will convert more trypsinogen to trypsin (autocatalytic activation).

and so it :

\*convert chemotrypsinogen to chymo trypsin

\*convert proelastase to elastase

\*convert procarboxypeptidase A and B to carboxypeptidase A and B

(Trypsinogen , chemotrypsinogen, proelastase, procarboxypeptidase A and B) all come from pancrease because of signals from cholecystokinin and secretin.

-They converted to their active form once trypsinogen activated by enteropeptidase.

**-**each enzyme cut at a certain point>> **Trypsin** will cut on carboxylic group after argenine and lysine .

(Just this what we need to memorize)…."look at the picture in slide 7".

- Result in free amino acids and small peptides .

-Amino peptidases secreted by small intestine , will break these small peptides .

-(aminopeptidase differ from carboxypeptidase in the function

Carboxypeptidase come to free carboxyl group and cut off the first amino acid while aminopeptidase come to free amino group and cut off the first amino acid).

\*In **intestine** we said we have free AA and small peptides:

-The free AA transport to intestinal lining cell by co-transport with **sodium**

-Peptides transport to intestinal lining cell by co-transport with **protons H+** .

>>Nothing exit to blood except the free amino acids form .

So di and tri peptides should be broken inside the intestinal lining cells to be converted into free amino acids.

-Cells in general conserve free AA out of the cells in less amount than free AA inside them, so it should be ATP driven "to make the amino acids inside the cell less than that outside it".

* **Absorption and transport of amino acids and dipeptides "slide 8":**
* **Absorption** of amino acids either from intestine or

**Re-absorption** after they secreted in the kidney .

* Each Groups of free AA (3-7) are gathered , having one system to be reabsorbed in intestine or reabsorbed in kidney .
* Example :

**COAL** system (**C**ystine **O**rnithine **A**rginine **L**ysine )

Note : ornithine is amino acid but not engaged in protein .

* When one amino acid concentration increase, the absorption of other amino acids in the same group will decrease .
* This is problem when people take specific free AA in body building in large amounts than normal so this will affect the absorption of other systems .
* Genetic deficiency to some absorption systems of AA

ex : **cystinurea** ; cystine not absorbed or reabsorbed in kidney

it affect 1 : 7000 birth

almost common inherited genetic diseases of amino acids ,so the release of cystine through kidneys , they didn’t reabsorbed , that will make bonds and form cystine which form kidney stones .

* **General scheme for amino acid catabolism "slide 9":**
* **Removal of the amino group :**

If I need N → Use nitrogen in synthesis of new nitrogen containing compounds

 If I don’t need N → Passage of nitrogen into the urea cycle to make urea → secreted in urine

**\*Nitrogen containing compounds**:

NO ; work in nervous systems

Hormons

Neurotransmitter as glutamate

NAD+

Heme

purine & pyrimidine bases of DNA

 All are synthesized inside the body

* **Degradation of the carbon skeleton :**

Incorporation of the carbon atoms into compounds that can enter the citric acid cycle or glucose formation .

\*carbon portion of the amino acid is converted to TCA cycle compounds or for gluconeogenisis.

* **Catabolism of The Amino Group "slide 10" :**
* two ways to remove amino group from amino acid :
1. **transamination**:Removing the amino group and replacing it by "double bond with oxygen (( =O )) " on alpha carbon. Which then called keto acid.

\*aminotransferases (transaminases) remove amino group from AA and put it on keto acid SO the AA become>> keto acid, and the keto acid become>> AA .

\*most common keto acid in TCA ; alpha-ketoglutarate ,when we put amino group it becomes glutamate.

\*pyruvate (3C) is a keto acid when we put amino group become alanine.

\*Almost every AA has specific transaminase and may group of AA share the same transaminase.

\*aminotransferases are all reversible , that mean if AA increases the reverse reaction occur to preserve the balance of the amino acids.

**Most important examples** :

Alanine transaminase and Aspartate transaminase ( ALT & AST ).

ALT is more **specific** for liver disease ; is found mainly in liver , when increase its good indicator that problem in liver .

AST is more **sensitive** for liver disease ; is found in large amount , you can detect it better however it’s found in other sites

\*All aminotransferases require the coenzyme **pyridoxal phosphate** coenzyme (a derivative of vitamin **B6**), which facilitate the transfer of amino group to the ring of pyridoxal phosphate and become pyridoxamine phosphate then donate the amino group to an exist keto acid .

Oxaloacetate in TCA is keto acid once amino group is added, it becomes aspartate.

Pyridoxal phosphate is the key co-enzyme in all the aminotransferases .

1. **Oxidative deamination of amino acids** "**slide 12**":

e.g. : Glutamate DH Removing the amino group from **(glutamate)** and release it as free ammonia NH3 or as ammonium ion NH4+ by **Glutamate DH**.

* Glutamate is the only amino acid that undergoes rapid oxidative deamination.
* Most of aminotransferases transmit the amino group from one AA to Keto acid

-As we said the most common keto acid that we use is:

alpha-ketoglutarate ,when we put an amino group, it becomes glutamate .

* **THE Most keto acid that used by aminotransferases is: alpha-ketoglutarate ,which becomes glutamate,,, so most of AA that go through aminotransferases reactions will produce glutamate, because of that; Glutamate has specific pathway so we extract amino group from glutamate as free ammonia or ammonium ion.**
* Ammonia is very toxic shouldn’t be in the body and shouldn’t be moved through blood , for that we have urea cycle because urea is less toxic and can go through blood then to kidney and secreted .
* Glutamate DH rxn Remove the amino group and release it as free ammonia and give you alpha-ketoglutarate , and alpha-ketoglutarate go to other aminotranferases in order to receive amino group to give glutamate .
* This reaction can go backward by combination of ammonia with alpha-ketoglutarate to give glutamate .
* When removing amino group (oxidative deamination) ,using NAD+ as co-factor .
* When adding amino group (reductive amination ),using NADPH .

