◉ Sheet ○ Slides

Subject :	Amino Acids-1
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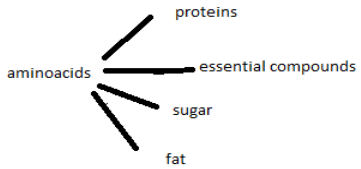
Amino acids metabolism

as you know we have 20 different amino acids ,what is good in our book that not all of them are explained(by talking about their metabolism and degradation).we have two types of aminoacids :The **essential amino acids** (that we cannot produce internally) like arginine (required for the young, but not for adults), histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine, and **the nonessential amino acids** that can be produced in our bodies .

so in this chapter we are going to talk about the absorption and digestion of the amino acids.

***comparison between the storage of different substances:**

as we know carbohydrates when taken in excess can be stored mostly in the liver ,and in the muscles .it takes up to 10% storage in the liver and 3% in the muscles .LIPIDS have unlimited storage as fats in the body .PROTEINS can't be stored in the body ,the proteins you take are used in the synthesis of your proteins that has been degraded, to build essential compound ,and if we have it in excess we can use it in energy .also it could be turned into fat and sugar .



so don't think that eating proteins will make you slimmer ,it won't as you read. it will be converted into fat .

amino acids can be divided into 3 different categories according to their products after metabolism :

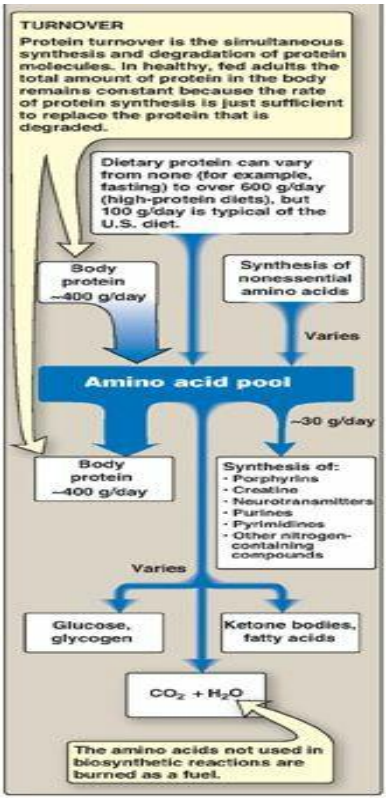
1-glucogenic: we can make glucose from the carbon skeleton of the amino acid .

2-ketogenic: we can make acetyl CoA, acetate , acetoacetate "ketone bodies"

3-both: you can make both glucose and ketone bodies.

Amino acid pool:

This pool is **supplied** by three sources: **1**) amino acids provided by the degradation of endogenous (body) proteins, most of which are reutilized; **2**) amino acids derived from exogenous (dietary) protein; and **3**) nonessential amino acids synthesized from simple intermediates of metabolism .Conversely, the amino pool is **depleted** by three routes: **1**) synthesis of body protein; **2**) consumption of amino acids as precursors of essential nitrogen-containing small molecules; and **3**) conversion of amino acids to glucose, glycogen, fatty acids, and ketone bodies, or oxidation to CO_2 + H_2O .



In healthy, well-fed individuals, the input to the amino acid pool is balanced by the output. That is, the amount of amino acids contained in the pool is constant. The amino acid pool is said to be in a steady state, and the individual is said to be in nitrogen balance. While on starvation this balance will be destroyed because the body is trying to over come the low glucose levels by breaking down some of the proteins to form amino acids that can

be converted into sugar thus leading to an increase in the output of the pool which is called negative nitrogen balance .Also ,the change can be on the other way by increasing the pool's input leading to positive nitrogen balance which mainly occur in children , pregnant women ,and people recovering from starvation .

Although the amino acid pool is small (comprising about 90–100 g of amino acids) in comparison with the amount of protein in the body (about 12 kg in a 70-kg man), it is conceptually at the center of whole-body nitrogen metabolism. So at any given time the pool will have 100g of amino acids .From the pool we need 30 g per day of amino acids to synthesize physiologically important compounds like porphyrine (like heme ,..) , creatine , neurotransmitters ,purines and so on.

The recommended uptake of the proteins is 60g per day while the average uptake varies from 50-100g per day ,and the high protein diet can reach up to 600g per day .The excess will be converted to give energy ,sugar ,lipids,...etc.

Protein turnover:

This process, called protein turnover, leads to the hydrolysis and resynthesis of 300–400 g of body protein each day as seen in the picture above. The rate of protein turnover varies widely for individual proteins. And it depends on :

1) protein's half lives:

- **Short-lived proteins** (for example, many regulatory proteins and misfolded proteins) are rapidly degraded, having half-lives measured in minutes or hours**. Long-lived proteins**, with half-lives of days to weeks, constitute the majority of proteins in the cell**. Structural proteins**, such as collagen, are metabolically stable and have half-lives measured in months or years.

2) mode of expression:

-constitutively expressed protiens : continuous synthesis like structural protiens ,actinfilaments and microtubules.

-inducable protiens : the body synthesize them when needed under a stimulus.

protein degradation:

- Damaged and misfolded proteins must undergo degradation .

-Oxidized proteins that got oxidized by exposure to variety of oxidants undergo degradation .

There are two major enzyme systems responsible for degrading endogenous proteins:

1-ATP INDEPENDENT degradative enzyme system of the lysosome:

Lysosomes use acid hydrolases to nonselectively degrade intracellular proteins (“autophagy”) and extracellular proteins (“heterophagy”), such as plasma proteins, that are taken into the cell by endocytosis.(Mainly degrade extracellular protiens and membrane protiens)

This mechanism start by : binding the ligand to its recptor > invagination of the membrane to the inside forming a coated veiscle > forming an endosome > the endosome starts uptaking protons to decrease its PH by proton pump > then fuse with the lysosome > the acid hydrolases get activated by the acidic environment > before they start digestion they start a separation process by which the ligand detaches from its receptor and the ligand takes the digestion site , and the receptors take a different site were they can be recycled and used again.

2-ATP DEPENDENT ubiquitin- proteasome system of the cytosol: (degrade intracellular protiens)

it is controlled by a proteolytic enzyme complex called proteasome that recognize proteins that has been tagged with a flag which is Ubiquitin,a small, globular, nonenzymic protein that is highly conserved across eukaryotic species .Ubiquitination of the target substrate occurs through

isopeptide linkage of the α-carboxyl group of the C- terminal glycine of Ub to the ε-amino group of a lysine on the protein substrate by a three-step, enzyme-catalyzed, ATP-dependent process.

*proteins which are damaged, inactive, and misfolded will be tagged to be taken by a complex of a proteolytic enzyme (proteosome) which is made of globular protiens aligned in a barrel shaped structure , inside the proteosome the action of ATP depended proteolytic enzyme takes place .proteins that have been chemically altered by oxidation or tagged with ubiquitin are preferentially degraded. The half-life of a protein is also influenced by the amino (N)-terminal residue. For example, proteins that have serine as the N-terminal amino acid are long-lived, with a half-life of more than 20 hours, whereas those with aspartate at their N-terminus have a half-life of only 3 minutes. Additionally, proteins rich in sequences containing proline, glutamate, serine, and threonine (called PEST sequences after the one-letter designations for these amino acids) are rapidly degraded and, therefore, have short half-lives.

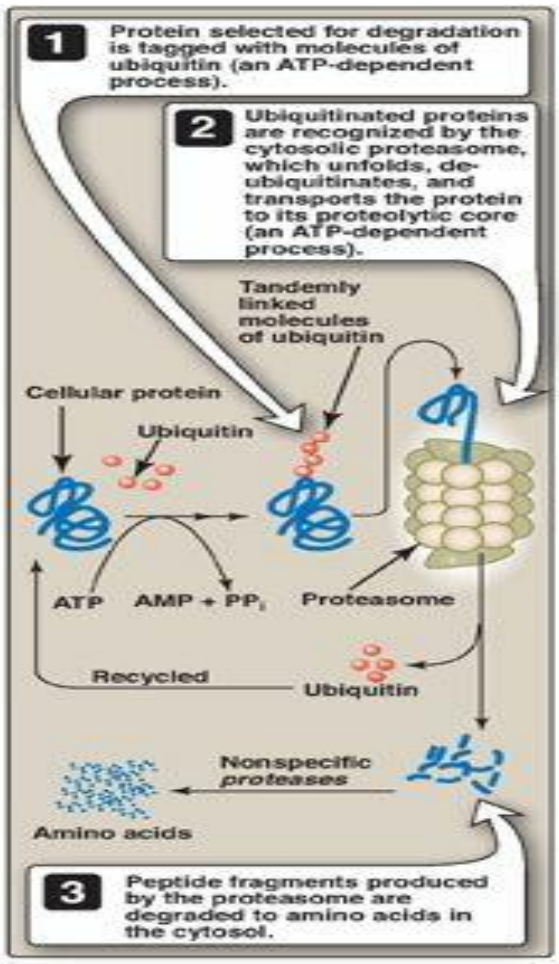
* Ubiquitination is a process that tags the damaged protein and when it is fixed the proteosome will be able to recognize the damaged protein that will lead to the unfolding of the protein , the removal of the Ubiquitin and the degradation of the protein into small fragments that will be degraded in the cytosol by a nonspecific proteosome to single amino acid .

-it degrades endogenous proteins .

-it involves ubiquitin to help to recognize the damaged protein .

-it involves poly Ubiquitination , more than one Ubiquitin molecule is added to the target protien.

- Ubiquitin is recycled and used again.



The intake of the dietary proteins (exogenous) :

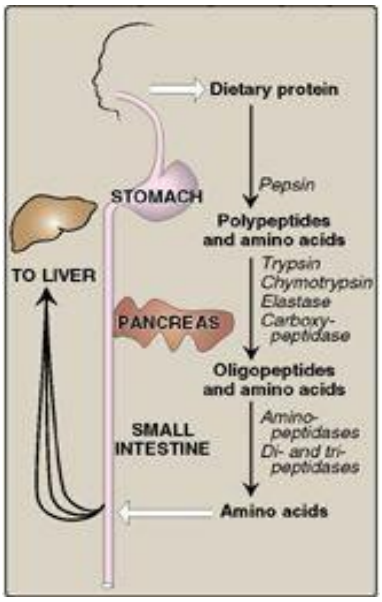
. Hydrochloric acid:

as it first enters the stomach it is subjected to HCL which is secreted by the parietal cells of the stomach and part of the gastric secretion , functions to kill some bacteria and to denature proteins, thereby making them more susceptible to subsequent hydrolysis by proteases.

. Pepsin:

This acid-stable endopeptidase is secreted by the chief cells of the stomach as an inactive zymogen (or proenzyme), pepsinogen.In general, zymogens contain extra amino acids in their sequences that prevent them from being

catalytically active. Removal of these amino acids permits the proper folding required for an active enzyme. Pepsinogen is activated to pepsin, either by hydrochloric acid or autocatalytically by pepsin molecules that have already been activated. Pepsin releases peptides and a few free amino acids from dietary proteins.



-proteolytic enzymes have some specifity towards which peptide bond to cleave .for example ,pepsin cleaves more peptide bond where the carbonyl is donated by aromatic or acidic amino acid ,it is more active towards it .The protien will be partially degraded then it is going to move to the duodenum and it is still acidic .The acidity of the protein will induce the secretion of intestinal hormone secretin which induces the production of the watery solution of bicarbonate from pancreas .The function of bicarbonate is to neutralize the acidic protein to allow the pancriatic enzymes in the intestine to work on it .

-The release and activation of the pancreatic zymogens is mediated by the secretion of cholecystokinin(CKK) and secretin, two polypeptide hormones of the digestive tract.

- cholecystokinin works on three target tissues 1) the pancrease in order to release its digestive enzymes 2) gall bladder to release the bile acids 3) smooth muscle cells of the stomach , causing them to relax in order to slow

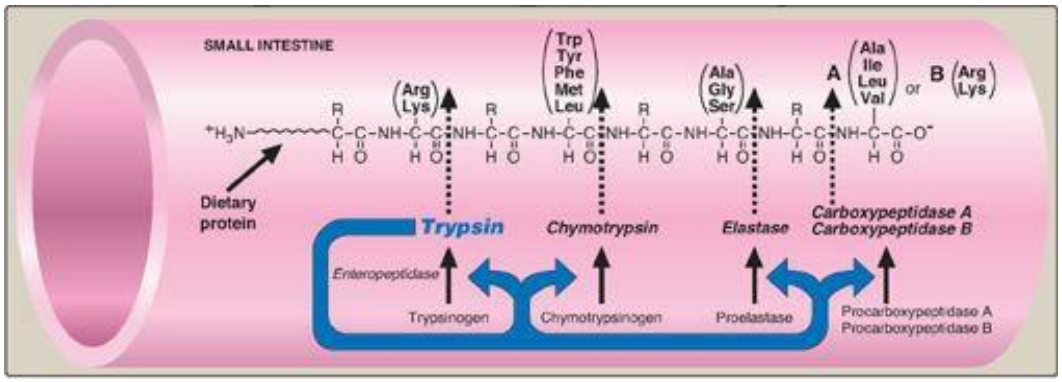
down gastric motility (gradual emptying) , in order for complete digestion to happen.

-The zymogens can work on more than one site on the protein ,it can work on the middle of it which is called endo ,and it can work on the terminals which is called exo .

Activation of zymogens:

Enteropeptidase (formerly called enterokinase), an enzyme synthesized by and present on the luminal surface of intestinal mucosal cells of the brush border membrane, converts the pancreatic zymogen trypsinogen to trypsin by removal of a hexapeptide from the N-terminus of trypsinogen. Trypsin subsequently converts other trypsinogen molecules to trypsin by cleaving a limited number of specific peptide bonds in the zymogen. Enteropeptidase, thus, unleashes a cascade of proteolytic activity because trypsin is the common activator of all the pancreatic zymogens.

<u>Cleavage of dietary protein in the small intestine by pancreatic proteases</u>



*trypsin cleaves the peptide bond that its carbonyl group is donated by arginine and lysine.

*chemotrypsin usually cleaves aromatic amino acids ,and some extent of methyonine and pepsin .

*elasetase cleaves peptide bond that its carbonyl group is donated by small aminoacids like alanine ,glycine , and serine .(the smallest three amino acids)

*carboxypeptidase a can cleave where we have alanine ,valine ,leucine ,and isoleucine.

*carboxypeptidase b starts working on the c terminal where we have arginine and lysine.we can have these c terminus by the cleaving that is done by trypsin .

-The first three are serine endopeptidases (serine because it's a part of the catalytic site of the enzyme) , whereas the last two are exopeptidases. Each is produced from an inactive zym

ogen.

from this action we will have variety of products from amino acids ,dipeptides , and tripeptides.

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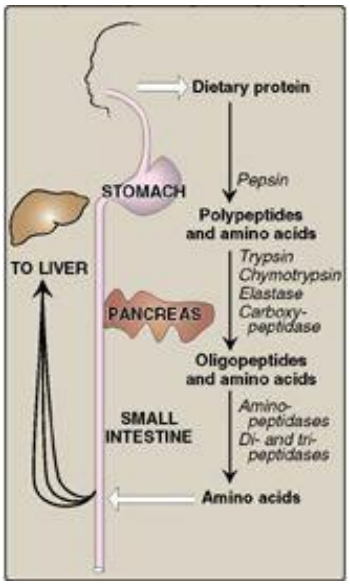
we have many stage that the degradation of protein can go through .The first stage is in the stomach ,the second one is in the pancreas ,and the third one is in the intestine because the intestinal cells can produce exopeptidase that is mostly aminopeptidase.



The products we talked about are going to be up taken by the mucosal cells.

Absorption of amino acids and small peptides :

Free amino acids are taken into the enterocytes by a sodium-linked secondary transport system of the apical membrane. Di- and tripeptides, however, are taken up by a proton-linked transport system. The peptides are hydrolyzed in the cytosol to amino acids that are released into the portal system by facilitated diffusion (through basolateral surface of these cells). Therefore, only free amino acids are found in the portal vein after a meal containing protein. These amino acids are either metabolized by the liver or released into the general circulation. (Note: Branched-chain amino acids are important examples of amino acids that are not metabolized by the liver but, instead, are sent from the liver primarily to muscle via the blood.)

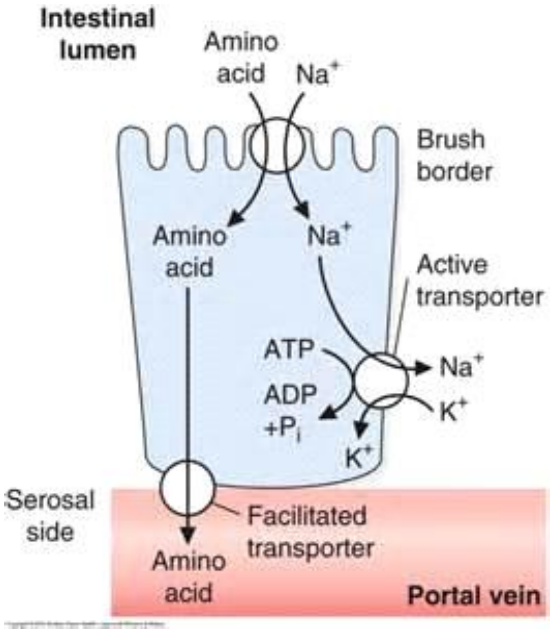
so at last we have only single amino acids in the mucosal cells .

*as carbohydrates , amino acids are also sodium dependent transport but there are some differences between them . for example ,in glucose absorption the Na dependent transport can be found in the intestinal mucosal cells ,kidney ,and tubular epithelial cells while in other cells it is transported as facilitated diffusion. In amino acids we have the Na dependent transport in all tissues.

*we have different isoforms of the Na dependent transporters.(7 has been recognized so far)

*the different isoforms have overlapping specifity .(this isoform works with this group while the other works with a different group)

*we have differences between them even on a single amino acid basis such as; glutamine that has transporter present in liver but not in other tissues or has different isoforms .



Na enters the cell by virto of its high concentration outside the mucosal cells towards the inside of the cell which is low on Na and it drags with it the amino acids. Then, Na is pumped out by Na-K pump which requires energy because of that it is called ATP dependent process. Once the amino acid enters the cell it goes directly towards the portal vein (transported by facilitated transporter) .This facilitated transporter can work on both ways (moving the amino acids towards the portal vein or towards the inside of the cell "during starvation ").

types of transporters:

transporter no.1-->for basic

transporters ----->for neutral

transporters---> for proline ,and hydroxy proline

transporter no.3-->for acidic

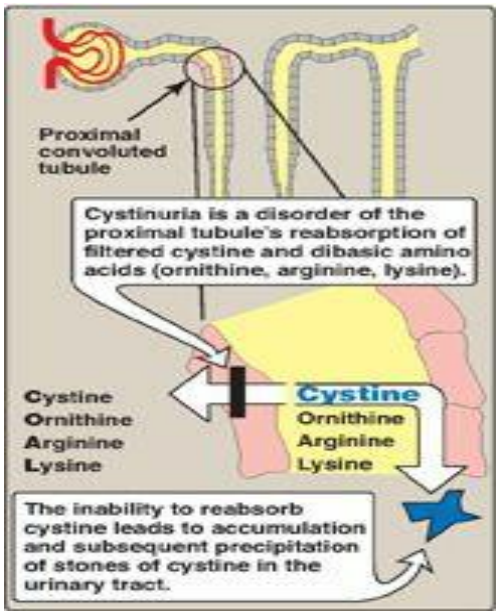
DISORDERS:

we are going to talk about one disorder which is connected to transporter no .1.it is the most prevalent disorder among the genetic disorders .ITS CALLED CYSTINURIA. it involves the intestinal and the renal epithelial .this transporter is specific for di basic amino acids (cystine ,lysine

,arginine,orthinine"aminoacid we will get to know more about it in urea metabolism").

this disorder can be detected in the reabsorption of these amino acids ,we can feel this problem in the kidney .Cystine when it is filtered in the proximal tubules it won't be reabsorbed efficiently,and cystine isn't a very soluble compound when it's present in high amounts it will form a cystine stone which can block the urinary tract .

Incidence of the disorder is 1/7000 births and it is considered relatively high .



Introduction to metabolism:

- we have to mention catabolism and anabolism .

- aminoacids are protected against oxidation when they have the amine group ,they can't be catabolized.

-the first thing we have to do in order to catabolise the amino acids is the removal of the amine group to be left as carbon skeleton .

-when we study about the catabolism of the aminoacids ,we have to study the removal of the amine group .

- the amine group can be removed from the amino acid by different mechanisms :

1-transamination : to be transformed from amino acid into ketoacid .

2- oxiditive deamination.

- the amine group that has been released is very toxic if it was converted to amonia NH_3 , it has to be transformed into a safer compound(urea) that can be transported easily through the blood into the kidney to be removed.

* the next chapter will discuss the carbon skeleton that is left after the removal of the amine group and what is going to happen to it(energy production , forming sugars,..etc) .

BACK TO THE TWO MECHANISMS:

1-transamination -> all the amino acids can undergo this process except for two (lysine ,threonine,).each one of them has its own transamination that is catalyzed by aminotransferase (named transaminase in the past).this aminotransferase needs a cofactor that is called pyridoxal phosphate(made from vitamin b6),and it is widely distributed in all the tissues .the equilibrium of the enzyme is around 1 and reach up to 10 but it is mostly one .

in this transamination we will notice that the ATP and ADP are the energy currency of the cell .ATP undergoes phosphorylation and give the phosphate to a variety of acceptors .ADP will return to being ATP.

Amino acids give their amine group to this acceptor which is α-ketoglutarate that will turn into glutamate and the amino acids will turn into ketoacid (the process can be reversed by ketoacids taking the amine group from glutamate).

-Aminotransferases are named after the specific amino group donor, because the acceptor of the amino group is almost always α-ketoglutarate .

GOOD LUCK