لجان الدفعات

BIOCHEMISTRY

MORPHINE ACADEMY

By Maryam Alhasan

Protein metabolism

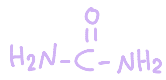
- هاد الموضوع معتمد على الamino acids ,
لانه هلا رح نصير نحكي عن الmetabolism
تبعهم ، وكل واحد لإيش رح يتحول

Proteins

عبارة عن amino acids او الproteins ال

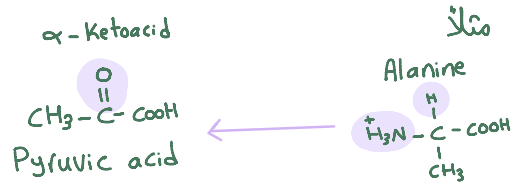
- **Nitrogen** is a characteristic component of proteins forming about ***16%*** of their weight i.e. 100 g of protein contains 16 g of nitrogen.
- Proteins are not stored in body as such
- Amino acids are degraded by deamination to ammonia and α-ketoacid

بتتحول الى



- Ammonia is used to produce urea and excreted in urine
- α-ketoacid can be metabolized to CO_2 and water, glucose, fatty acid or ketone bodies

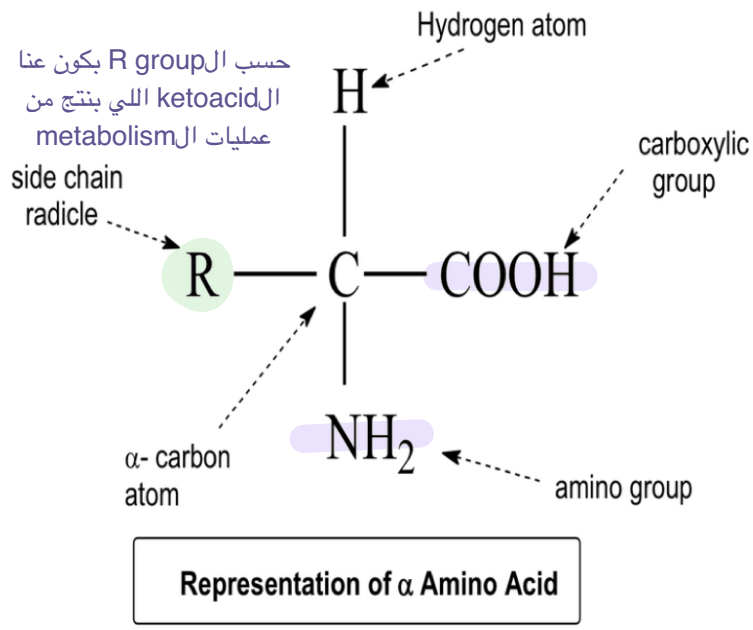
Pyruvic acid



- ما منخزن بروتينات ولكن بكسر بروتينات اللي مش محتاجها وبرجع بصنع بدالها لما اكل
- عنا اشي اسمه amino acid pool يعني اذا احتجت protein بروح بطول من هاي الpool وبصنع الproteins, فالفكرة ما عندي مخزن للproteins
- الalpha ketoacid اللي هو الpyruvic acid بصيرله further metabolism ، ممكن اصنع منه glucose وممكن اكمل احوله لacetyl CoA وبعدين ادخله Krebs cycle واكمل عملية metabolism اله
- الammonia مندخلها urea cycle بتروح للliver ، طبعا ابدا مش ممكن اطلع الammonia لبرا الخلايا وامشيها بالدم as ammonia وتروح عالliver زي ما هي ليش؟ لانه الammonia طبيعتها basic رح تغيرلي الph وتخربطلي الpathways فلازم احولها لneutral ، واخر اشي لما اوديها عالliver برجعها ammonia وبدخلها urea cycle والurea cycle بحولي ياها لurea واللي هي طبيعتها neutral فبصيرلها diffusion من liver cells بتضل طالعة بالدم وبتروح عالkidney وهناك بتتفلتر وبتطلع من الجسم عشكل urea
- فالproteins ممكن اصنع منهم glucose وممكن اكسرهم للحصول على طاقة ، طبعا كلشي ammonia بحتوي N بالجسم بتصنع من amino acids, يعني nucleotides اللي عنا بجيبهم من amino acids ، و catecholamines كمان من amino acids

Structure

- L-a-Amino acids are the structural or the building units of proteins
- The common amino acids have the general structure depicted in the following figure:



Representation of α Amino Acid

Polar

non Polar

مهم جدا نعرف مين polar وnon polar

Abbreviations for the 20 Amino Acids

Amino Acid	Abbreviation		Amino Acid	Abbreviation	
	Three letter	One letter		Three letter	One letter
Alanine	***Ala***	**A**	Leucine	***Leu***	**L**
Arginine (Basic)	***Arg***	**R**	Lysine (Basic)	***Lys***	**K**
Asparagine	***Asn***	**N**	Methionine	***Met***	**M**
Aspartic acid (Acidic)	***Asp***	**D**	Phenylalanine	***Phe***	**F**
Cysteine	***Cys***	**C**	Proline	***Pro***	**P**
Glycine	***Gly***	**G**	Serine	***Ser***	**S**
Glutamine	***Gln***	**Q**	Threonine	***Thr***	**T**
Glutamic acid (Acidic)	***Glu***	**E**	Tryptophan	***Trp***	**W**
Histidine (Basic)	***His***	**H**	Tyrosine	***Tyr***	**Y**
Isoleucine	***Ile***	**I**	Valine	***Val***	**V**

Metabolic Classification of Amino Acids

	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Aromatic
Phenylalanine
Histidine
Tryptophan

Branched chain
Isoleucine
leucine
Valine

يعني لازم احصلهم من الdiet بقدرش اصنعهم داخل الجسم

- الketogenic معناها انه بطلع acetyl CoA او acetoacetyl CoA , يعني قادر على تصنيع fatty acids او تحصيل طاقة ، يعني ممكن acetyl CoA ادخلها krebs cycle واطلع منها طاقة ، او ممكن نحولها لfatty acid ، او ممكن نحولها لketone bodies يعني ketogenic , بس ابدا ما بقدر اصنع منه glucose

- الglucogenic ، مثلا الalanin تحول لpyruvic acid واللي هو بقدر اصنع منهglucose , لoxaloacetate وبعدين بطلع glucose
  الasparagine وasparatate بحولهم لoxaloacetate
- الباقي كلهم في جزء بقدر احوله لalpha ketoglutarate وجزء بتحول لpyruvate وجزء بتحول لoxaloacetate , كلهم التلات للkrebs cycle وبوصل فيهم لoxaloacetate اللي هي الخطوة التانية منgluconeogenesis, معناته بقدر اصنع منهم glucose

- الglucogenic و ketogenic ، هدول بطلعلولي فعليا واحد هيك وواحد هيك ، يعني مثلا في واحد منهم بطلع succinyl CoA وواحد acetyl CoA , الsuccinyl CoA بkrebs cycle بقدر احوله لoxaloacetate

Amino acid metabolism

- Amino acid pool: بالوزن المثالي
  - There is about 12 kg of protein in 70 kg man
  - 75% of aa are used in synthesis of new tissue proteins
  - The remainder is used as precursor for synthesis of many substances

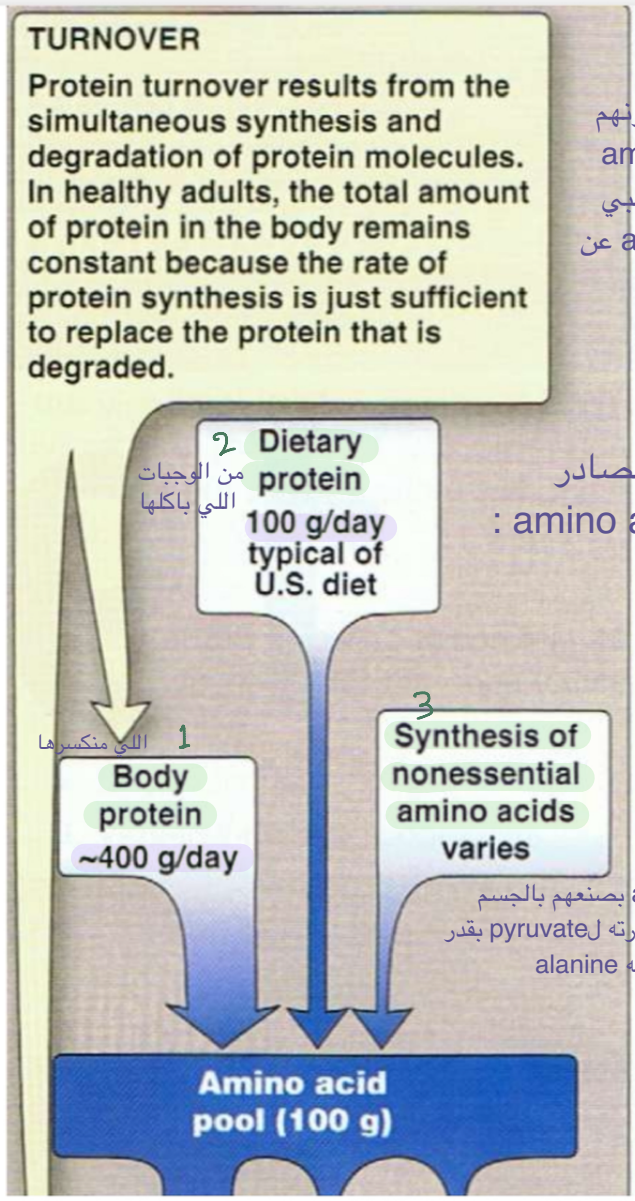
ال25% اللي ضلوا بدخلو بتصنيع مواد اخرى هلا منحكي عنهم
purines, pyridines , neurotransmitters وكتير مركبات

- Protein turnover:
  - Proteins are constantly degraded and synthesized which is regulated by the concentration of protein in the cell
  - 300-400 g of proteins are hydrolyzed and resynthesized/day
  - Protein turnover varies: short lived (regulatory and misfolded proteins), long-lived (most of tissue proteins) and structurally stable (collagen)

منكسر يوميا ومنرجع نبنيهم لما مناكل

Half life الهم

البروتينات اللي بدي اكسرها هي عادة الregulatory proteins ، مثلا hormone او enzyme ، مثلا insulin hormone لما اكون بمرحلة جوع ما بحتاجه برجع بصنعه لما اكل ، اي هرمون ما بحتاجه بكسره وبستعمله كمصدر للطاقة ، او عشان اصنع منه glucose بوقت الجوع ولما منرجع مرا تانية نوكل منرجع نبني ال300-400g من proteins



من الوجبات اللي باكلها

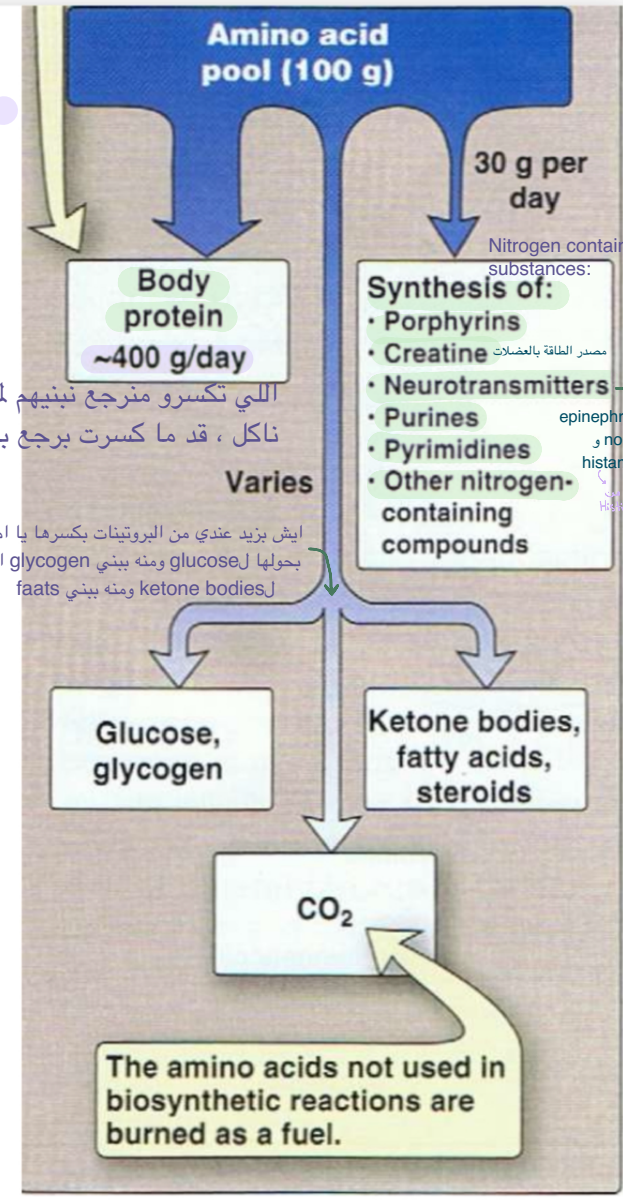
اللي منكسرها

مجموعة من aa بصنعهم بالجسم مثلا glucose كسرته لpyruvate بقدر اصنع منه alanine

٣ مصادر للamino acids :

هون دخلتهم للaa pool

حكينا الproteins ما بقدر اخزنهم لكن بحطهم بamino acid pool منقدر نستعملها لما نحتاج ، ونعبي فيها لما يزيد عندي amino acids عن الحد



Nitrogen containing substances:

مصدر الطاقة بالعضلات

مثل dopamine و epinephrine و norepinephrine و serotonin و histamine

اللي تكسرو منرجع نبنيهم لما ناكل ، قد ما كسرت برجع ببني

ايش بزيد عندي من البروتينات بكسرها يا اما بحولها لglucose ومنه ببني glycogen او لketone bodies ومنه ببني faats

بدي اطلعهم

كل ما زاد كمية الprotein اللي مناكلها بتزيد كمية الurea والعبئ عالكلى بصير اكبر

Nitrogen Balance

- **Positive Nitrogen Balance means N2 intake is more than N2 output:**

- This exists when intake of N2 exceeds the output. It occurs whenever new tissues are being built up for example:

1- During growth (growing children).
2- Pregnancy.
3- Muscular training.
4- Convulsions from different diseases.

Nitrogen Balance

B. Negative Nitrogen Balance: N_2 Output is more than N2 intake:

- It occurs in cases of :

1- Decreased protein intake: e.g. starvation, malnutrition and G.I.T. diseases.

2- Increased Loss of proteins: e.g. in chronic hemorrhage, albuminuria and Lactation on an inadequate protein diet.

3- Increased of protein catabolism: e.g. fever, hyperthyroidism, diabetes mellitus, Cushing syndrome, advanced cancer and post-surgical.

- Prolonged periods of negative nitrogen balance are dangerous and may lead to death.

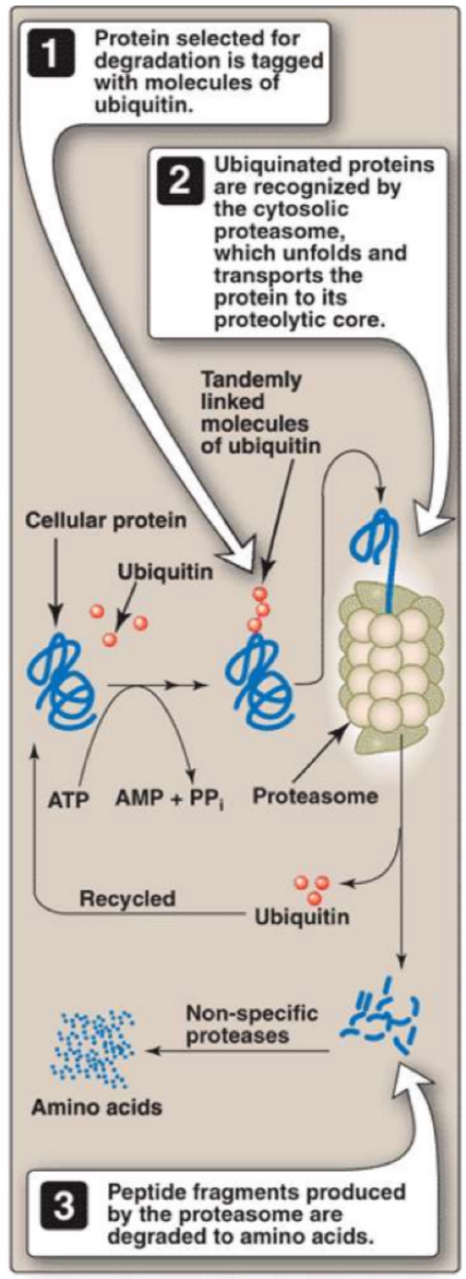
Protein metabolism

- Protein degradation occurs by:
  - energy dependent ubiquitin-protesome mechanism (endogenous proteins)
  - non-energy dependent lysosomes (extracellular protein)
- Oxidized or ubiquitin tagged proteins are preferentially degraded
- Certain aa sequences:
  - Serine (S)at N-terminal: long t1/2 (>20 hr)
  - Aspartate (D) at N-terminal: short t1/2 (3 min)
  - Proteins rich in the sequence (PEST) are rapidly degraded

Proline, Glutamic acid, Serine, Threonine

تصير إله half life

كيف نعرف الhalf life للproteins ؟
من الN terminal الموجودة عليه



- هاي ممكن تدلنا انه البروتين هو regulatory protein ولا اشي stable protein

- في جزء حكينا عنه ، متذكرين الglycoproteins والproteins اللي بتكون عسطح الخلايا ، هدول حكينا عنهم كيف بصيرلهم degradation اوmetabolism , بصيرلهم endocytosis بتبلعهم الخلية وبتربطهم مع lysosomes والlysosomal enzymes بتتكفل بالعملية وبتكسرلي ياهم

- في عنا النوعية التانية اللي جوا الخلايا ، في عنا اشي اسمه protesome شو بتعمل ؟ اول شي الprotein اللي لازم اكسره بتعمله labeling, اول اشي يا اما oxidation يا اما labeling بالubiqutin اللي هي molecules صغيرة ، ubiquitinisation للبروتين دليل انه بدنا نكسره
- هلا مجرد ما الubiquitin ارتبط فيه بدخل للprotesome , فبنفصل عنه الubiquitin والبروتين بطلع على شكل oligopeptides ، وبعد هيك الoligopeptide بـproteases موجودة عندي بالخلية جوا او بالblood ممكن تكسرلي ياه لamino acids

- اذا البروتين عندي شو ما كان مصدره دخل as it is to the blood ، هاد antigenic ، الجسم بعمل immune system وبطلع antibodies
- فالproteins in general are antigenic ، الglycoproteins antigenic اكتر ، يعني بروتين صغير antigenic شوي ، لو اكبرantigenic اكتر ، اذا glycoprotein بكون antigenic اكتر
فالantigenicity بتتفاوت من واحد للتاني
- عشان هيك لازم نكسر البروتينات نحولها لamino acids نمتصها عشكلamino acids ما بقدر ادخل بروتينات غريبة لداخل الجسم

Digestion of proteins

- protein is antigenic i.e. able to stimulate an immunologic response. The digestion of protein destroys its antigenecity. So, proteins must be digested into amino acids:

1) In the stomach : اول ما مناكل بروح لل

يعني الdimention structure 3 اللي كانت بتفتح بكسر كل الروابط الموجودة بخلي بس peptide bond

A- gastric acid: denature the protein

B- Pepsin: is the major proteolytic enzyme in the stomach :

- Pepsin is produced and secreted by the chief cells of the stomach as the inactive zymogen, pepsinogen, which activated by HCl produced by parietal cells of stomach.
- Pepsin catalyzes the cleavage of proteins into smaller polypeptides.

2) in small intestine: large polypeptides are further cleaved to oligopeptides and amino acids by a group of pancreatic proteases.

Each of these enzymes has a different specificity (trypsin cleaves only at C-terminal of arginine or lysine).

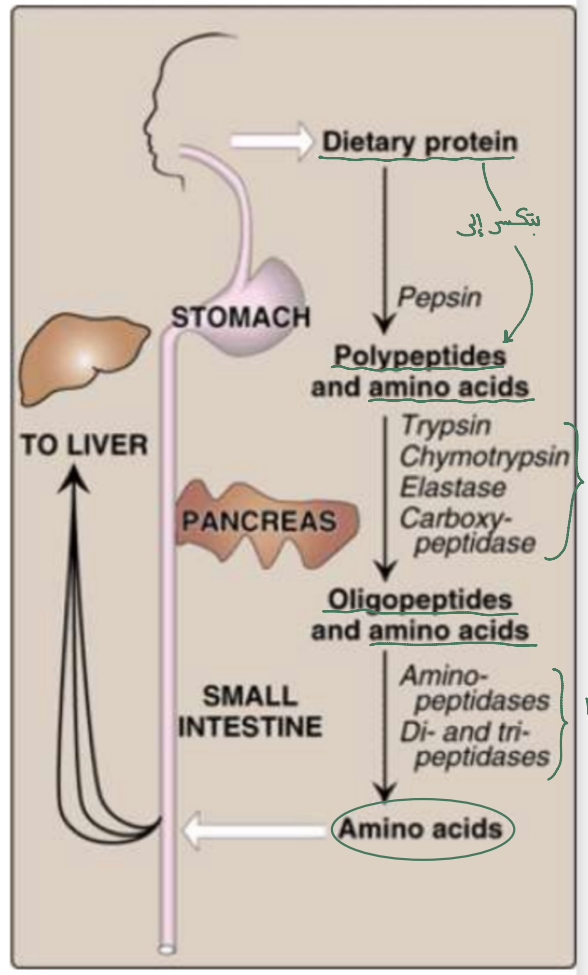
Activation of zymogens: Enteropeptidase converts the pancreatic trypsinogen to trypsin which starts a cascade of proteolytic activity, because trypsin is the activator of all the pancreatic zymogens

- لازم يصيرلهم activation ، فاللي بصير عنا ، بالsmall intestine في عندي مجموعة من الاشياء ، اول اشي عنا enteropeptidases ، انزيمات proteases بتنفرز من الenterocytes الي همه خلايا الامعاء نفسها ، بتعمل activation للtrypsinogen بتحول لtrypsin , الtrypsin بتكمل ، كل باقي الenzymes هو اللي بعملها activation

Digestion of proteins

Abnormalities in protein digestion:

- In individuals with a deficiency in pancreatic secretion (chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas), the digestion and absorption of fat and protein is incomplete.
- This results in the abnormal appearance of lipids (Steatorrhea) and undigested protein in the feces.



Digestion of oligopeptides by enzymes of the small intestine

- The luminal surface of the intestine contains **aminopeptidase** (an exopeptidase that repeatedly cleaves the N-terminal residue of oligopeptides to produce free amino acids and smaller peptides.

- عندي N terminal وعندي C terminal ، مش في بالبروتين جهة NH2 وجهة carboxylic ،
الcarboxypeptidase بتكسر حبة حبة من جهة الcarboxyl , وال aminopeptidase بتكسر وحدة وحدة من جهة الamino group NH2
فإذا كان عندي ضايل ٤ مربوطين مع بعض الNH2 ممكن يكسرلي ياهم

- اخر اشي بضل عندي يا اما free amino acids يا اما dipeptides , هاي ممكن من خلال transporters تاع aa الcarriers اللي هي بتنقل actively يعني active transport بدها ATP ممكن تدخل enterocytes عشكل free amino acids او dipeptides ,
بالportal vein لما بفوت للدم ما بصير يكون dipeptide فبسكرها جوا الenterocytes وبدخلها free amino acids

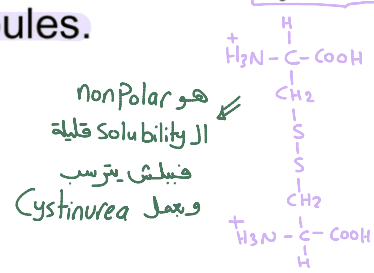
- لو صار عنا اي abnormality بالprotein digestion, زي يكون عنا pancreatic secretion ما عم توصل intestine يا اما شايلينله البنكرياس يا اما عنده chronic pancreatitis , او متذكرين الcystic fibrosis لما قلنا كل الsecretions تبع هاد الشخص بتكون defected اصلا وكل الducts بتكون مسكرة بسبب viscous secretion فما في عندي enzymes تروح للintestine ، هاي الحلات كلها فش بروتين بصيرله digestion معاهم الlipase وpancreatic alpha amylase ، فبكونو موجود مع pancreatic enzymes, بالتالي لا protein ولا fat ولا carbohydrate بصيرله digestion وكلهم بروحو للfeces , ممكن يعملو steatorrhea اللي هي زي diarrhea

Absorption of amino acids and dipeptides

- Free amino acids and dipeptides are taken up by the intestinal epithelial cells.
- the dipeptides are hydrolyzed in the cytosol to amino acids before being released into the portal system (only free amino acids are found in the portal vein)
- The absorption of amino acid is active process that needs energy (ATP).

Transport of aa to the cells

- Amino acids are transported to the cells by active transport systems, driven by the hydrolysis of ATP
- At least seven different transport systems are known that have overlapping specificities for different amino acids.
- For example, one transport system is responsible for reabsorption of the amino acids cystine, ornithine, arginine, and lysine in kidney tubules.



Basic
عليهم شحنة +
وداسين رضلوا رايحين للـ Urine
وما في مشكلة

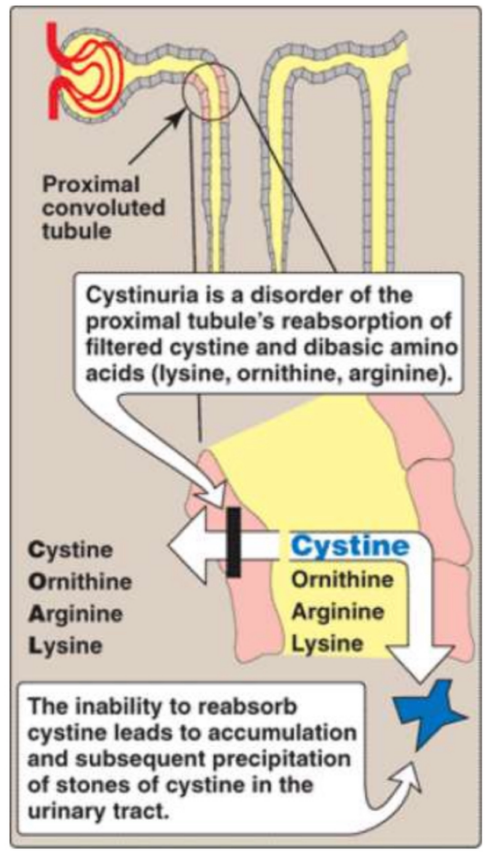
كل 3 او 4 من الـamino acids الهم transport, انا عندي amino acids 20 ، فعندي بحدود transporter system 7, مسؤولين عن نقل aa لداخل الخلية

خلصنا نقلناهم جوا الخلايا هلا بدنا نكمل عملية metabolism ، في عنا transporter ممكن يصير فيها خلل اللي هي الموجودة بالـkidney , مش احنا بالـkidney منفلتر كلشي بعدين proximal tubules بتعمل reabsorption لكل nutrients من ضمنها aa , هلا هاي الـtransport عنا , cystine ornithine, arginine ,lysine اللي بالـkidney هدول الـreabsorption الهم بتم من خلال one type of transporter
اذا كانت هاي الـtransporter defected ، معناته هدول الاربعة رح يتفلترو وما رح يقدرو يرجعو

Cystinuria

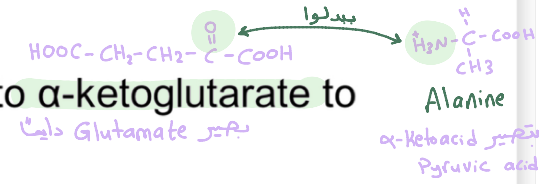
- In the inherited disorder **cystinuria**, this carrier system is defective, resulting in the appearance of all four amino acids in the urine.
- Cystinuria is the most common genetic error of amino acid transport.
- The disease expresses itself clinically by the precipitation of cystine to form kidney stones (calculi) that may block the urinary tract.
- Oral hydration is important in treatment for this disorder

الحل يشرب مي كتير عشان يضل دايب الcystine



Removal of nitrogen from aa

- Removing the α-amino group is essential for producing energy from any amino acid
- transamination and oxidative deamination reactions which provide ammonia and aspartate, the two sources of urea nitrogen
- The first step is transfer their α-amino group to α-ketoglutarate to produce an α-ketoacid and glutamate.
- Glutamate produced by transamination can be oxidatively deaminated or used as an amino group donor in the synthesis of nonessential amino acids.



- خلص دخلنا كلشي على الخلايا ، بدنا نبدا عملية الmetabolism للaa
- اسم العملية tranamination باستثناء ، الthreonine وlysine اسمه oxidative deamination
- الtransamination ، كلهم بتفاعلوا مع alpha ketoglutarate , اللي بصير عنا انه الamino group بتنتقل و carbonyl بتنتقل (ببدلوا)

Transamination

- The transfer of amino groups from one carbon skeleton to another is catalyzed by a family of enzymes called **aminotransferases**.
- These enzymes are found in the cytosol of cells throughout the body (especially the liver, kidney, intestine, and muscle).
- All amino acids (except lysine and threonine) participate in transamination at some point in their catabolism.
- Lysine and threonine lose their α-amino groups by deamination

اكتر اشي

مثلا : alanine aminotransferase
Aspartate aminotransferase
وهيك يعني منحط الsubstrate تبعه ومنكمل aminotransferase

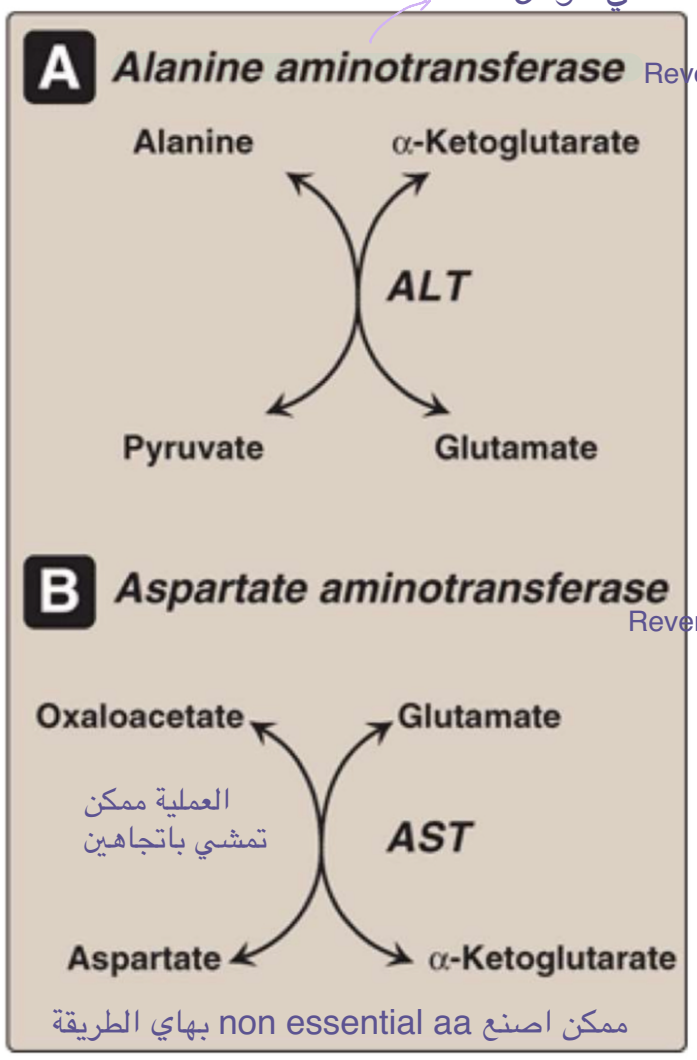
Aminotransferases Reversible

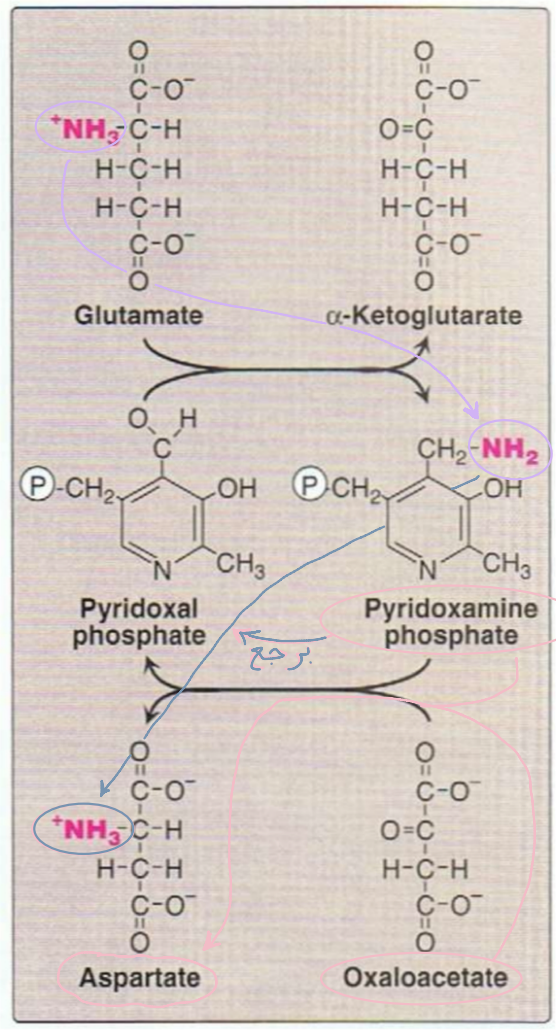
- Each aminotransferase is specific for one or, at most, a few amino group donors and named after that enzyme
- Alanine aminotransferase (ALT): enzyme catalyzes (reversibly) the transfer of the amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate.
- Aspartate aminotransferase (AST) is During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle
- All aminotransferases require the coenzyme pyridoxal phosphate

الALT بعني في damage بخلايا الكبد الhepatocytes خلى ALT يطلع لبرا للدم هو المفروض يكون جوا

الخطوة اللي وراها ، الglutamate باخده بوديه للliver وهناك عنا glutamate dehydrogenase , الفكرة كلها بدي الammonia اللي كانت عالaa ، فبنقلها ، ولسا ما بنقل glutamate للدم لازم بالاول احوله لglutamine كمان مرة NH3 رح ترتبط وتتحول لglutamine بعد هيك بنقلها as glutamine بوديها عالliver وهناك ببلش اكسر الammonia وبتحول glutamine لglutamate ، وglutamate لammonia و alpha ketoglutarate كمان مرة

اللي هو الALT





Diagnostic value of plasma aminotransferases

- Aminotransferases are normally intracellular enzymes, (low levels in the plasma)

اذا لقيتهم برا يعني عندي damage

ممكن يكون السبب hepatic او non hepatic

- The presence of elevated plasma levels of aminotransferases indicates damage to cells rich in these enzymes. Two aminotransferases (AST and ALT) are of particular diagnostic value when they are found in the plasma.

ال ALT و AST التنين مرتفعين

a. hepatic disease: Plasma AST and ALT are elevated in nearly all liver diseases, specially in extensive cell necrosis (severe viral hepatitis, toxic injury, and prolonged circulatory collapse).

Elevated serum bilirubin results from hepatocellular damage that decreases the hepatic conjugation and excretion of bilirubin

بيجي من metabolism لل heme

ال AST مرتفع mainly

b. Nonhepatic disease: Aminotransferases may be elevated in nonhepatic disease (myocardial infarction and muscle disorders) but those can be clinically distinguished.

ال AST مش distinguishable لل liver بس بتعطيني indication انه في مشكلة بالجسم

- مقدارالارتفاع ومين اللي مرتفع هو الي بحددلي شو المشكلة ووين مكانها
- ال ALT هو liver specific فارتفاعه بكون بس بحالات ال liver

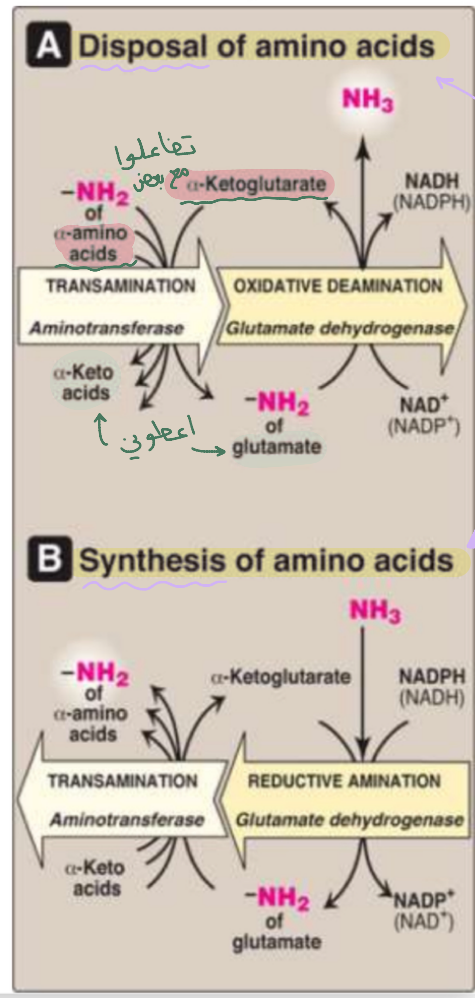
Glutamate dehydrogenase
(the oxidative deamination of amino acids)

- It is the transfer amino groups from glutamate, oxidative deamination, by glutamate dehydrogenase results in the liberation of the amino group as free ammonia.
- occur primarily in the liver and kidney.

في mainly موجود glutamate dehydrogenase enzymeال

- Glutamate is unique in that it is the only amino acid that undergoes rapid oxidative deamination

- Glutamate dehydrogenase can use either NAD or NADP as a coenzyme. NAD is used primarily in oxidative deamination and NADPH is used in reductive amination



منستخدم enzymeال

لحد الآن انا نقلت الamino group من الamino acid للalpha ketoglutarate وكونت glutamate الglutamate هاد بوديه عالliver , في عندي شغلتين ممكن نسويهم , ممكن الglutamate ارجع مع NAD+ وglutamate dehydrogenase اعمله oxidative deamination واحوله لalpha ketoglutarate ، اللي هو بتفاعل مع amino acids وحولي ياه لglutamate زائد ketoacid , هاي بتصير بالخلايا وممكن كمان بالliver

الglutamate dehydrogenase enzyme وهو very important enzyme ، بعمل oxidative deamination بكسر لammonia وalpha ketoglutarate مرة تانية ، بما انه في اشي صارله oxidation ، في اشي بالمقابل لازم يصيرله reduction ، الNAD+ بتحول لNADH
هلا هاد الenzyme هو reversible, فممكن الamino group مع الalpha ketoglutarate يرتبطو مع بعض وبعد هيك اسمها glutamate dehydrogenase enzyme برضو بال reductive amination , وبما انها عملية reduction بالمقابل في اشي لازم يصيرله oxidation اللي هو NADPH (متذكرين لما كنا نحكي عن ratio قلنا مين كميته اكبر ، الNADPH اكتر من NADP+ , والNAD+ اكتر من NADH) معناته عملية الoxidation بتفضل تستعمل NAD+ , وعمليات الreduction بتستعمل NADPH

لا تنسوا عن glutamate dehydrogenase و الaminotranferase التنين بشتغلوا bidirectional بالاتجاهين

Glutamate dehydrogenase

- The direction of the reaction depends on the relative concentrations of glutamate, α-ketoglutarate. and ammonia, and the ratio of oxidized to reduced coenzymes.
- After ingestion of a meal containing protein, glutamate levels in the liver are elevated and enhance amino acid degradation and the formation of ammonia
- The reaction can also be used to synthesize amino acids from the corresponding α-ketoacids
- ATP and GTP are allosteric inhibitors of glutamate dehydrogenase, whereas ADP and GDP are activators of the enzyme.

الاشياء اللي بتخليه يعمل desposal للaa ولا synthesis, حسب مين الsubstrate الموجودة ، يعني متوفر ketoglutarate اكتر ولا glutamate, بناءً عليه بتحفز الpathway

اذا الواحد ماكل معناته الglutamate عالي بالliver فالaa degradation رح تتحفزورح يزيد formation of ammonia ، والammonia بتدخل urea cycle بالliver وبتتحول لurea

والعكس لما يكون بحاجة لaa مش موجودة بالdiet ، بروح لعملية synthesis

لما يكون دخل على جسمنا D aa مش L

D-Amino acid oxidase

- D-Amino acids are present in the diet, and are efficiently metabolized by the liver using D-Amino acid oxidase (FAD-dependent enzyme) that catalyzes the oxidative deamination of these amino acid isomers.

بعطيني pyruvic acid ما بهمني مصدره

- The resulting α-ketoacids can enter the general pathways of amino acid metabolism, and be reaminated to L-isomers, or catabalized for energy.

اللي منوخده oral الtransporters تبعتها بتميز D من L ؟ اه بتميز مهي proteins الtransporters وبتمشيلي L موD

اخدت injection antibiotic الantibiotic مصدره بكتيري ممكن يكون فيه D aa ، مرات بصير معنا bacterial infection بطلع معي D aa

الenzymes بس بتشتغل L , يعني لما برجع pyruvic acid برجع لL aa (يعني لما بصنع بصنع بس L)

الglucose بD

Transport of ammonia from tissues to the liver

There are two mechanisms:

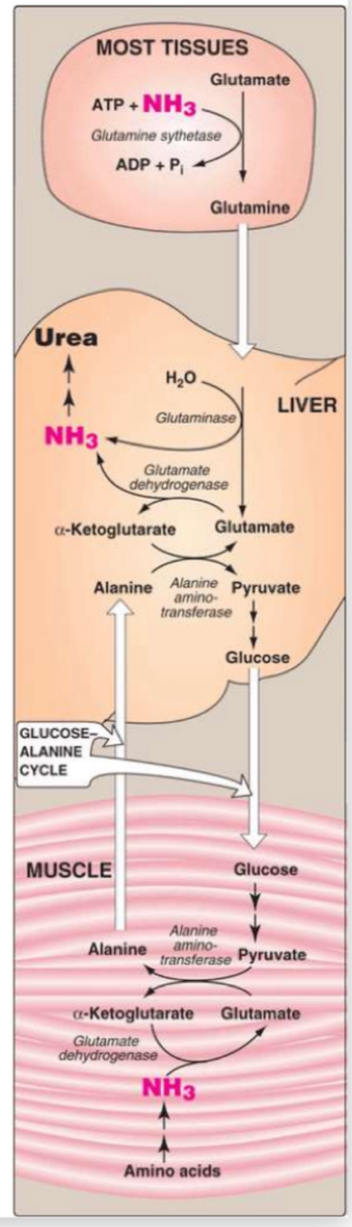
- ❑ found in most tissues, uses glutamine synthetase to combine ammonia with glutamate to form glutamine (a nontoxic transport form of ammonia)

The glutamine is transported in the blood to the liver where is cleaved by glutaminase to produce glutamate and free ammonia

- ❑ used primarily by muscle, involves transamination of pyruvate (the end-product of aerobic glycolysis) to form alanine

Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination (pyruvate is used in gluconeogenesis). This pathway called the **glucose-alanine cycle**.

بتكون بين الmuscle و liver



- احنا عملنا disposal للaa حولتها كلها لglutamate, هلا بنقلها ، تخيل انه كمية هائلة من glutamate طالعة من الbrain او organs كبيرة وmuscles ، ورايحة عالliver ، شو حتعمل بPh الدم ؟ رح تمتصها يعني كل وجبة بروتين بده ينزل ph بدمي ؟ لا ، فاللي بصير انه جسمي بطلعش glutamate عالدم زي ما هو لازم احوله لاشي neutral

- فاللي بصير عنا in most tissues الglutamate برتبط بammonia وبحتاج ATP وglutamine synthase enzyme ، فبتحول لglutamine

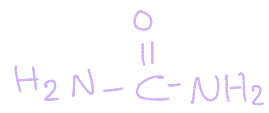
- الalanine وaspartate و glutamate و glutamine كلهم بقدر اصنعهم

- الglutamine طبيعته polar uncharged يعني neutral, يعني الamide neutral ، فبوديه عالliver وهناك عنا glutaminase enzyme بكسر لglutamate وammonia ، والglutamate بالglutamate dehydrogenase اللي حكينا عنه قبل شوي كمان مرة بنكسر لalpa ketoglutarate و ammonia, والammonia اللي طلعت منهم بوديها على الurea cycle

- بالmuscles , عندي شوي طريقة مختلفة ، عنا عمليات الmetabolism الaa بتحولي ياه لammonia, الammonia بتفاعل مع alpha ketoglutarate وبعطينا glutamate , الglutamate بتفاعل مع الpyruvate والalanine tranferase بحولي ياه لalanine
- الalanine طبيعته nonpolar وصغير فبنتقل بالدم وبروح للliver وبالliver برجع بتحول لpyruvate وبصنع منه glucose ، الglucose برجع للmuscles وبرجع مرا تانية pyruvate بعدين alanine اللي بروح للliver وهيك الcycle بتضل شغالة

- الalanin بالalpha ketoglutarate بتحول لpyruvate ، و الglutamate بصيرله disposal لammonia وalpha ketoglutarate مرة تانية فبتضلها العملية شغالة

UREA



الاشكال اللي بنقل فيها الammonia
Glutamine
Alanine
Urea

UREA CYCLE

بقدر انقلها بالدم Neutral

- Urea is the major disposal form of amino groups derived from amino acids (90% of the nitrogen-containing components of urine).

- One nitrogen of the urea molecule is supplied by free NH3, and the other nitrogen by aspartate, the carbon and oxygen of urea are derived from CO2.

الurea cycle بس موجودة في

- Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

- Reactions of the cycle:

rate limiting اهم واحد و

1. Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I which requires 2 ATP. N-acetylglutamate is required as allosteric activator.

عبارة عن الglutamate اللي جاي من الdiet زائد acetyl CoA
بربطهم التنين مع بعض وبعملهم acetylation وبزيد
الconcentration للمركب

UREA CYCLE

ما الهم codon ما بدخلوا بتصنيع البروتينات ، بدخلوا بالurea cycle

2. Formation of citrulline: Ornithine and citrulline are basic amino acids that participate in the urea cycle (But not into cellular proteins, no codons). citrulline is transported to the cytosol.

3. Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea, which is driven by the cleavage of ATP to AMP and pyrophosphate (PPi).

4. Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea. Fumarate can reenter the TCA cycle

5. Cleavage of arginine to ornithine and urea by **arginase**
occurs almost exclusively in the liver, whereas other tissues (kidney), can synthesize arginine by these reactions

الانزيمات تاعتها باستثناء arginase enzyme اللي هو exclusively in liver , الباقي كله في liver and kidney

اللي بالkidney مسؤولين عن تصنيع الarginine بس ، بينما بالliver بكمل cycle بطلع urea

UREA CYCLE

6. Fate of urea: Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.

عندي هون normal flora urease producer

A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO_2 and NH_3 by bacterial urease. This ammonia is partly lost in the feces and is partly reabsorbed into the blood.

ال urea بتنكسر الى

كميات ال urea اللي منطلعها مش كتير كبيرة عشان هيك كميات ال ammonia اللي نتجت مش كبيرة ، بترجع للدم وبتروح ل kidney وهناك ممكن تشتغل as buffer , واذا مش بحاجة الها بصيرلها execration

In patients with kidney failure, plasma urea levels are elevated (hyperammonemia), promoting a greater transfer of urea from blood into the gut.

وبتزيد بالدم

فصار كتير من urea يتكسر وال NH_3 رح ترجع مرة تانية عالدم وترفعلي ph

اول اشي بتضرر من تغير ph هو brain

طريقة للعلاج

Oral administration of neomycin reduces the number of intestinal bacteria responsible for this NH_3 production.

ال neomycin ما اله امتصاص ، بشتغل locally بال gi , بروح آكل ال normal اللي بتطلع urease , فتجنبت احول ال urea ل ammonia flora

Overall stoichiometry of the urea cycle

$$\text{Aspartate} + NH_3 + CO_2 + 3ATP \longrightarrow \text{Urea} + \text{fumarate} + 2ADP + AMP + 2\ Pi + PPi + 3\ H_2O$$

- the synthesis of urea is irreversible, with a large, negative ΔG.

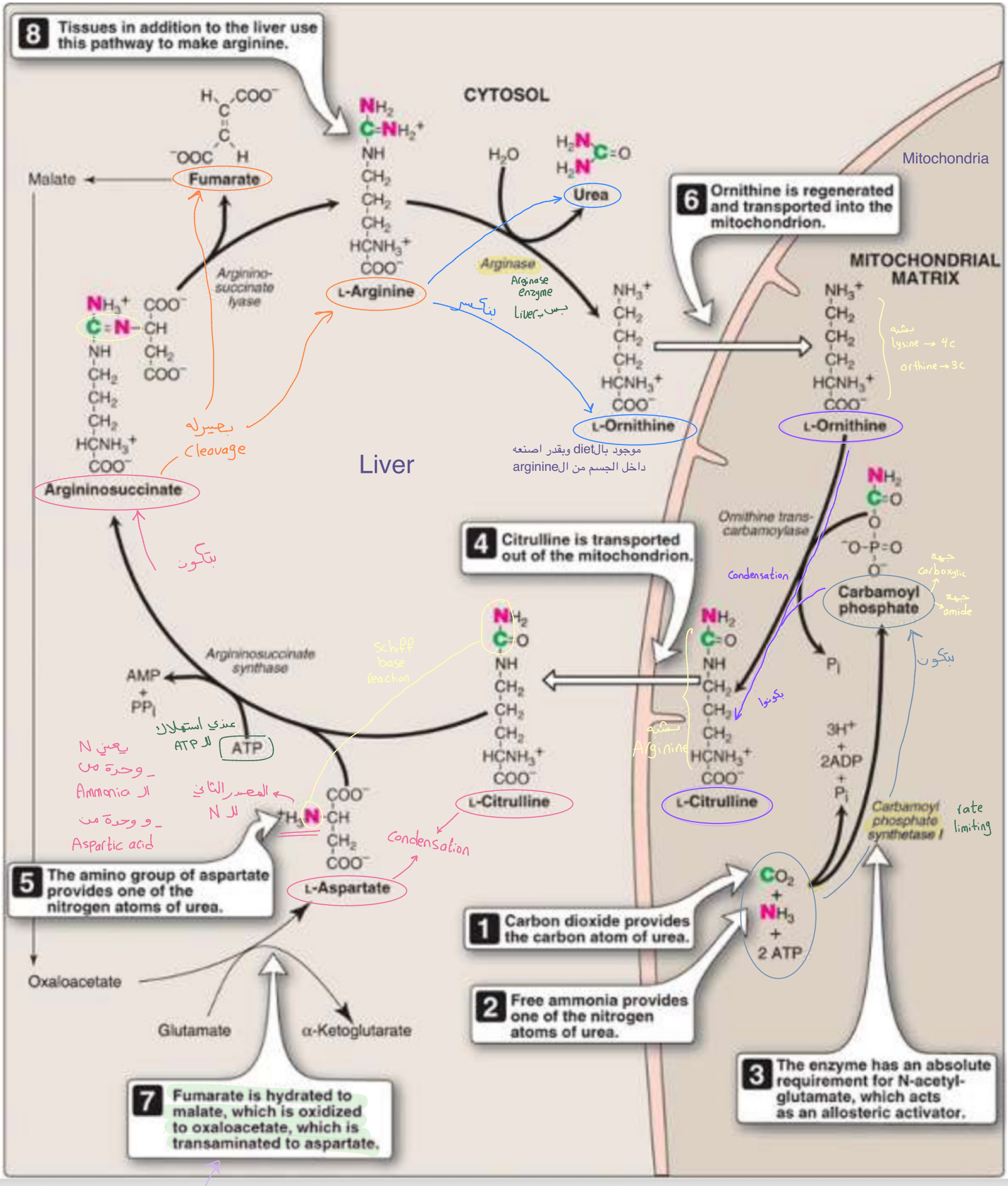
Spontaneous

Regulation of the urea cycle

- N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I (the rate-limiting step in the urea cycle) (synthesized from acetyl CoA and glutamate using arginine as an activator).
- the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis.

↑glutamate

- This leads to an increased rate of urea synthesis.



من وين بجيب aspartate ؟

مهم نعرف مين الenzymes اللي exclusively in liver ، منهم الarginase enzyme (ممكن يجي سؤال عليهم)

Metabolism of ammonia

السبب انه جزء منها بروح الintestine والnormal flora بتحولي ياه لammonia

- Slight increase in the concentration of urea in blood leads to hyperammonemia which is toxic to the CNS

مصادر للammonia

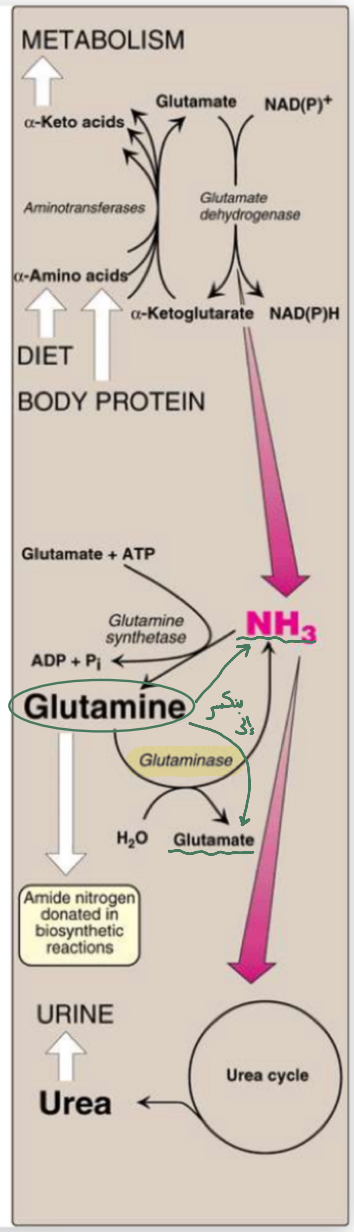
- Sources of ammonia:
  - From amino acids: mainly in liver by the aminotransferase and glutamate dehydrogenase reactions Transamination deamination منعمله
  - From glutamine: The kidneys form ammonia from glutamine by the action of renal glutaminase. Ammonia is also obtained from the hydrolysis of glutamine by intestinal glutaminase.
  - From bacterial action in the intestine: Ammonia is formed from urea by the action of bacterial urease in the lumen of the intestine.

normal flora اللي هو
بتكسره لammonia

  - From amines: Amines obtained from the diet, and monoamines that serve as hormones or neurotransmitters

oxidative بصيرلهم amine group عندهم
ammonia فهمه مصدر ل deamination

  - From the catabolism of purines and pyrimidines



Transport of ammonia in circulation

Neutral

- As **urea**: the most disposal form of ammonia which moves from liver to the kidney

Neutral

- As **Glutamine**: From tissue to liver
  - Occurs primarily in the muscle and liver and nervous system.
  - Circulating glutamine is removed by the kidneys and deaminated by glutaminase.

Neutral
alanine عنا muscle برضو بال
From muscles to liver

Hyperammonemia

- when the liver function is compromised, due either to genetic defects of the urea cycle, or liver disease, blood levels can rise above 1000 µmol/L.
- hyperammonemia is a medical emergency, because ammonia has a direct neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision).

مشكلة
kidney بال

- At high concentrations, ammonia can cause coma and death.

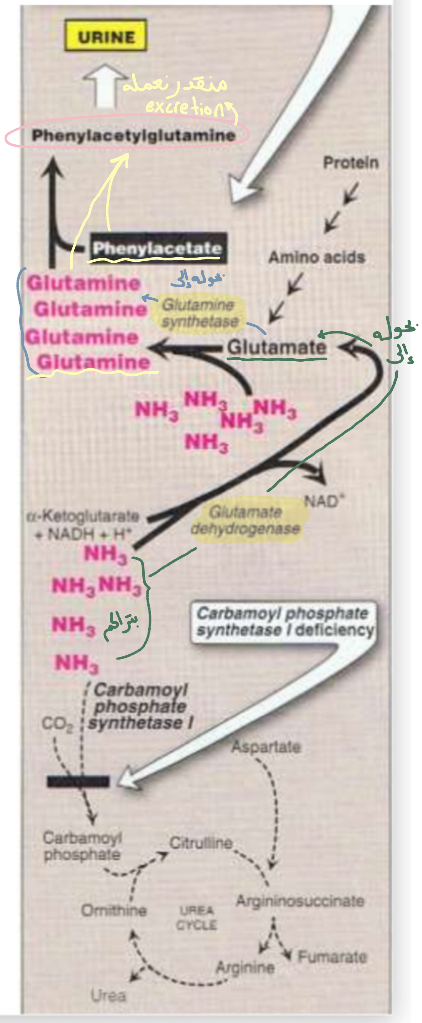
كان شغال الامور تمام عنده ، فجأة مثلا اذا كان بتعاطى كحول ، صار عنده liver cirrhosis يعني خلايا الliver كلها damaged فما بقدرو يعملو urea cycle فالammonia حتبلش تتراكم

Hyperammonemia

- **Acquired hyperammonemia**: It may be due to viral hepatitis, ischemia, or hepatotoxins. Cirrhosis of the liver caused by alcoholism, hepatitis, or biliary obstruction may result in formation of collateral circulation around the liver.

عنده مشكلة بالurea cycle, حكينا عنا 5 enzymes فيها ، فلو واحد defected معناته الurea cycle كلها وقفت وببلش يتراكم ammonia

- **Hereditary hyperammonemia**: Genetic deficiencies of each of the five enzymes of the urea cycle had an overall prevalence estimated to be 1 in 30,000 live births.
  - Ornithine transcarbamoylase deficiency, which is X-linked, is the most common of these disorders, affecting males predominantly (بصير بالmale اكتر)
  - All of the other urea cycle disorders follow an autosomal recessive inheritance pattern. The failure to synthesize urea leads to hyperammonemia during the first weeks following birth leading to mental retardation
  - Treatment includes:
    - limiting protein in the diet
    - administering compounds that bind covalently to amino acids, producing nitrogen-containing molecules that are excreted in the urine (phenylbutyrate given orally is converted to phenylacetate)



بدنا نعرف نرسم الstructures عشان نعرف الmetabolism كيف نحول

Catabolism of the carbon skeleton
Amino acids that form oxaloacetate

- Asparagine is hydrolyzed by asparaginase, liberating ammonia and aspartate

بتحولوا الى oxaloacetate

- Aspartate loses its amino group by transamination to form oxaloacetate

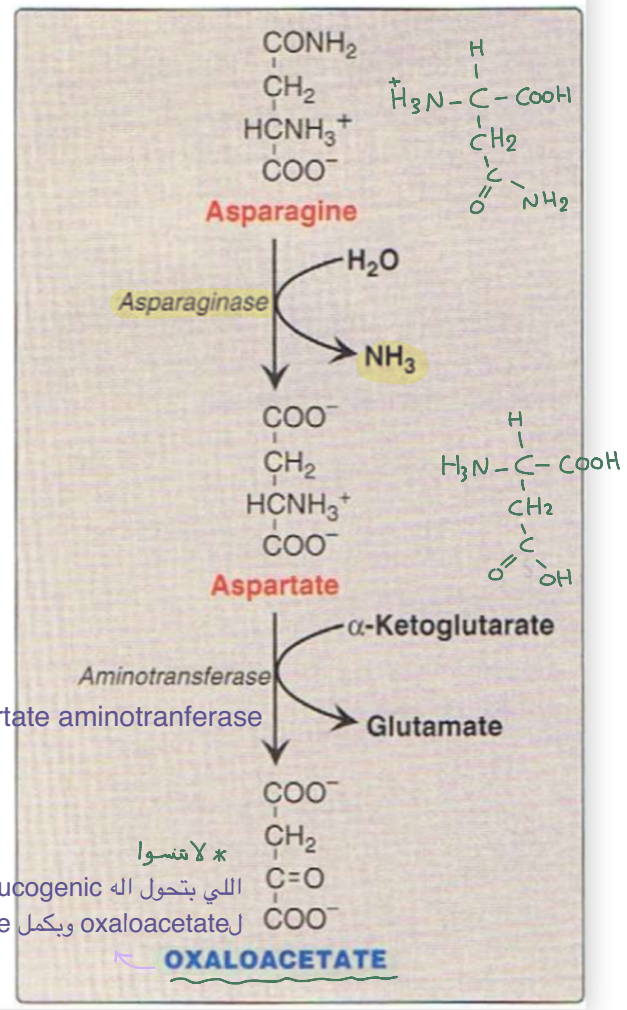
بقدر اصنعه من asparagine او not essential فهو oxaloacetate

- Some rapidly dividing leukemic cells are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells.

الحاجة للasparagine في حالات leukemia بتكون عالية

- Asparaginase can be administered systemically to treat leukemic patients.

بكسر asparagine بحوله لaspartate
فنقصت كمية الasparagine اللي كانت متوفرة للخلايا السرطانية بالتالي بتموت الخلايا السرطانية ، كان الasparagine non essential وصار essential لانه بطل موجود



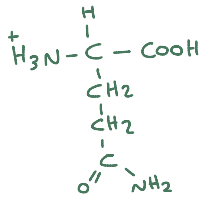
* لانسوا اللي بتحول اله glucogenic لانه pyruvate لoxaloacetate وبكمل glucose

Amino acids that form α-ketoglutarate

بتحولوا الى

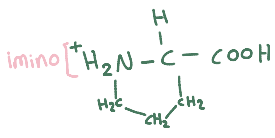
هاد كمان Glucogenic لانه موجود
krebs cycle بـ glucose وبعطيني

Glutamine



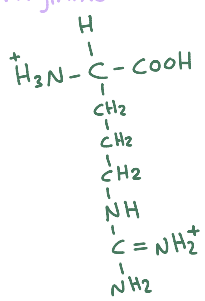
1. **Glutamine** is converted to glutamate and ammonia by the enzyme glutaminase. Glutamate is converted to α-ketoglutarate by transamination, or through oxidative deamination by glutamate dehydrogenase.

Proline



2. **Proline** is oxidized to glutamate. Glutamate is transaminated or oxidatively deaminated to form α-ketoglutarate.

Arginine



3. **Arginine** is cleaved by arginase to produce ornithine (occurs primarily in the liver). Ornithine is subsequently converted to α-ketoglutarate.

5

ornthine
رح نحو من aa اللي بتتحول
α-ketoglutarate لـ

Amino acids that form α-ketoglutarate

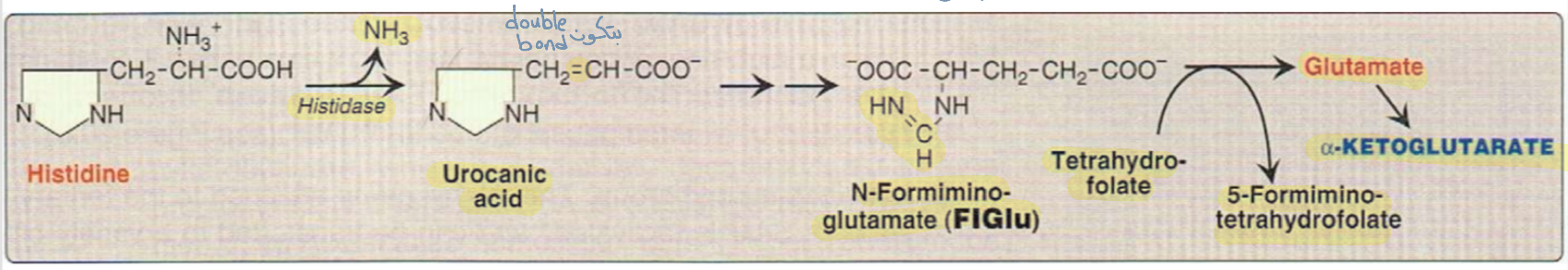
4. **Histidine** is oxidatively deaminated by histidase to urocanic acid. which subsequently forms N-formiminoglutamate (FIGlu). FIGlu donates its formimino group to tetrahydrofolate, leaving glutamate.

هاي العملية بتحتاج folic acid

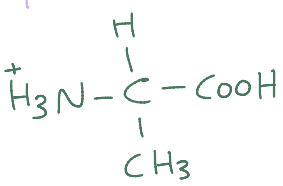
- Individuals deficient in folic acid excrete increased amounts of FIGlu in the urine (after ingestion of a large dose of histidine). The FIGlu excretion test has been used in diagnosing a deficiency of folic acid.

tetrahydro folate معناته ما عندي
folic acid بال deficiency يعني

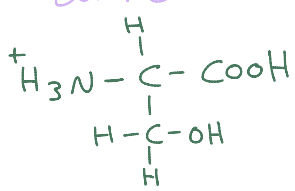
Formino group → -CH=NH



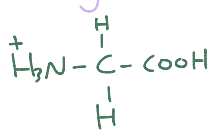
Alanine



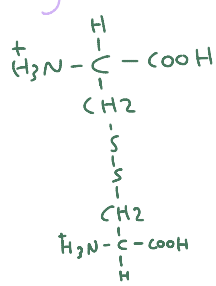
Serine



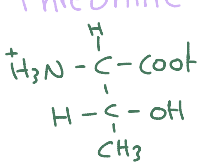
Glycine



Cystine



Threonine

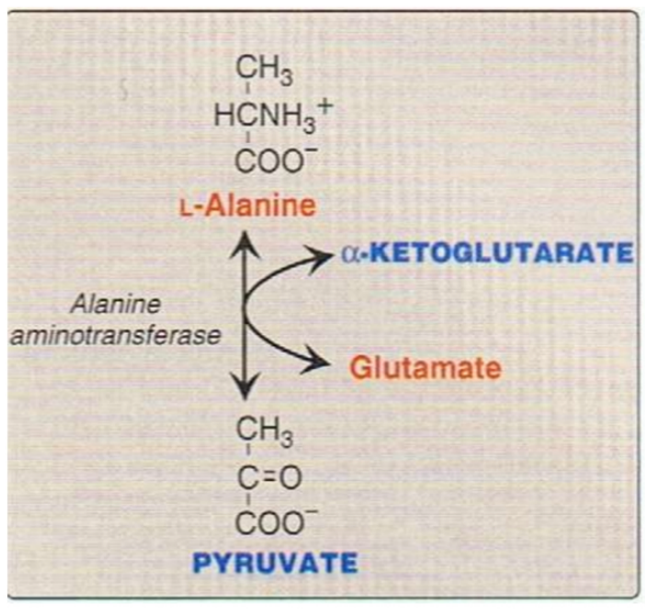


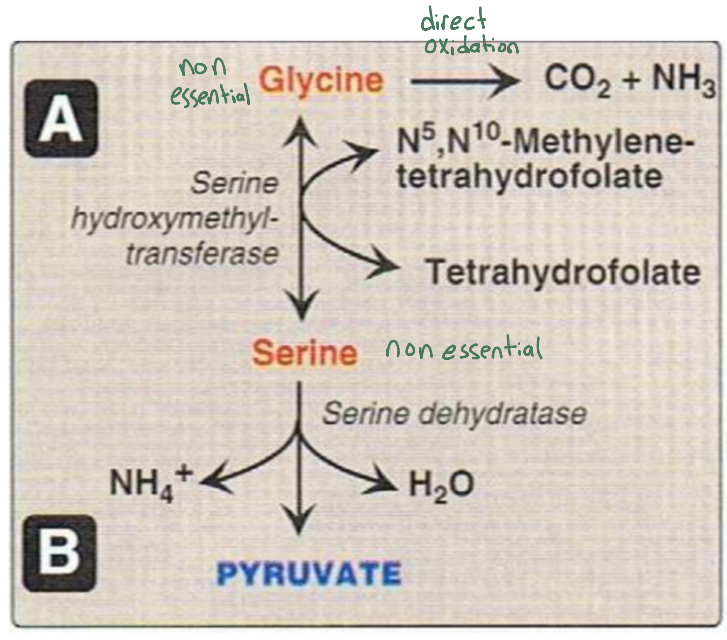
Amino acids that form pyruvate

1. **Alanine** loses its amino group by transamination to form pyruvate
2. **Serine** can be converted to glycine and N5,N10-methylenetetrahydrofolate. Serine can also be converted to pyruvate by serine dehydratase.
3. **Glycine** can either be converted to serine by addition of a methylene group from N5,N10-methylenetetrahydrofolic acid, or oxidized to CO_2 and NH_4^+
4. **Cystine** is reduced to cysteine, using NADH + H as a reductant. Cysteine undergoes desulfuration to yield pyruvate.
5. **Threonine** is converted to pyruvate or to α-ketobutyrate, which forms succinyl CoA.

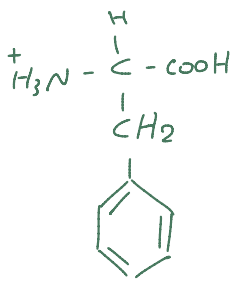
! glutarate ليس

Amino acids that form pyruvate

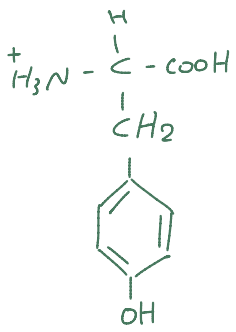




Phenylalanine



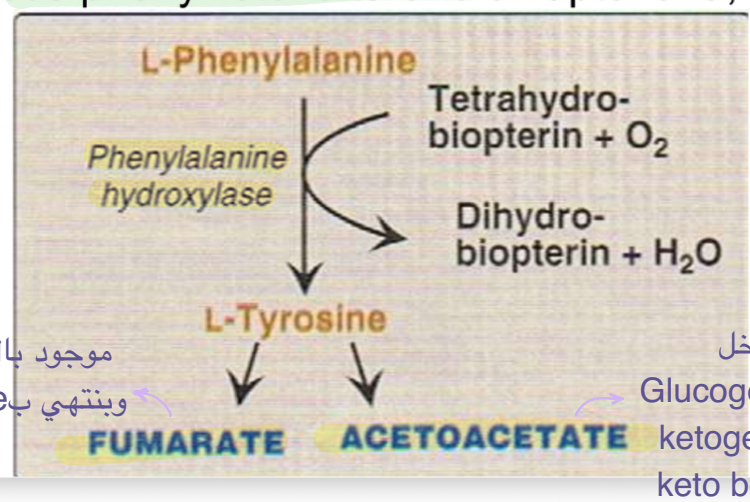
Tyrosine



Amino acids that form fumarate

1. **Phenylalanine and tyrosine:** Hydroxylation of phenylalanine leads to the formation of tyrosine, which is catalyzed by phenylalanine hydroxylase. Thus, the metabolism of phenylalanine and tyrosine merge, leading ultimately to the formation of fumarate and acetoacetate. Phenylalanine and tyrosine are, therefore, both glucogenic and ketogenic.
2. Inherited deficiencies in the enzymes of phenylalanine and tyrosine metabolism lead to the diseases phenylketonuria and alkaptonuria, and the condition of albinism.

بصير لون urin اسود

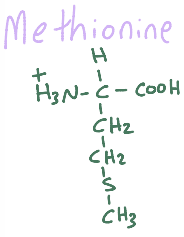


موجود بال krebs cycle
وبنتهي ب oxaloacetate

ما اله دخل
بال Glucogenic
هو ketogenic
هو keto body

Amino acids that form succinyl CoA

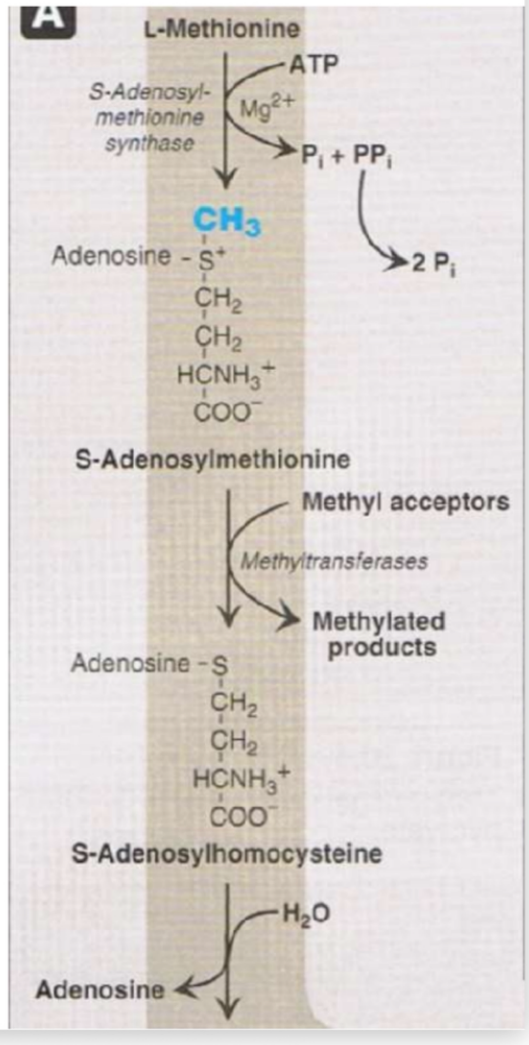
Methionine



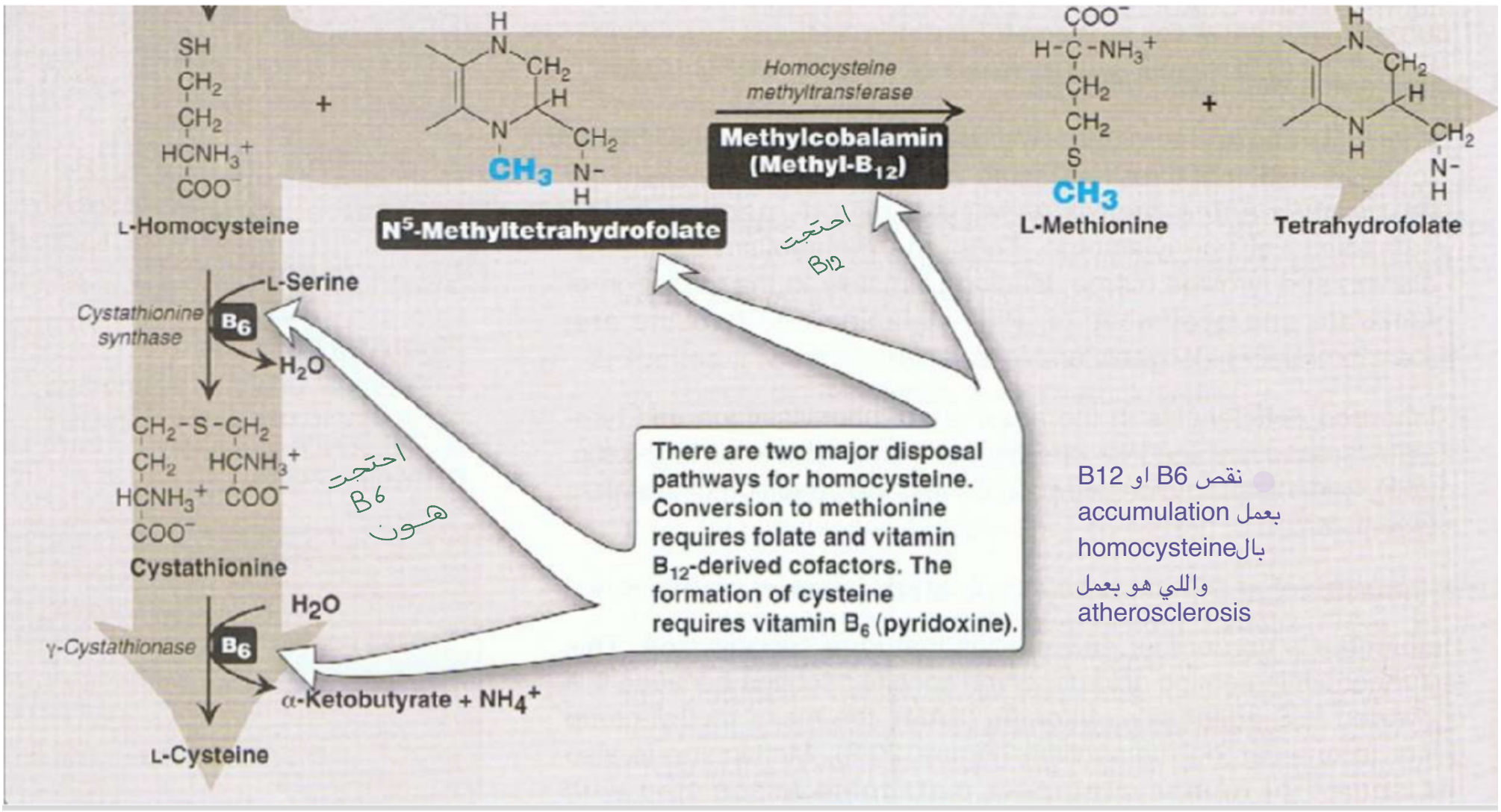
عبارة عن ال methyl doner بالجسم

- **Methionine:** Methionine is one of four amino acids that form succinyl CoA. This sulfur-containing amino acid deserves special attention because it is converted to S-adenosylmethionine (SAM), the major methyl-group donor in one-carbon metabolism

- Methionine is also the source of homocysteine, a metabolite associated with atherosclerotic vascular disease.



ال homocysteine بفرق عن cysteine انه one CH2



نقص B6 او B12 بعمل accumulation بال homocysteine واللي هو بعمل atherosclerosis

Amino acids that form succinyl CoA

Degradation of valine, isoleucine, and threonine also results in the production of succinyl CoA- a TCA cycle intermediate and glucogenic compound.

1. Valine and isoleucine are branched-chain amino acids that yield succinyl CoA.

2. Threonine is dehydrated to a-ketobutyrate, which is converted to propionyl CoA, the precursor of succinyl CoA

3. Threonine can also be converted to pyruvate.

Amino acids that form acetyl CoA or acetoacetyl CoA

ketogenic هدول

اذا بعطيني اشي تاني معهم معناته ممكن يكون ketogenic او Glucogenic

- Leucine, isoleucine, lysine, and Tryptophan form acetyl CoA or acetoacetyl CoA directly, without pyruvate serving as an intermediate (through the pyruvate dehydrogenase reaction.
- there are a total of six ketogenic amino acids.

ketogenic هاد بس

1. **Leucine** is exclusively ketogenic in its catabolism, forming acetyl CoA and acetoacetate. Like other branched-chain amino acids, isoleucine and valine.

Glucogenic و ketogenic هاد

2. **Isoleucine:** is both ketogenic and glucogenic, because its metabolism yields acetyl CoA and propionyl CoA. The first three steps in the metabolism of isoleucine are virtually identical to the initial steps in the degradation of the other branched-chain amino acids. valine and leucine.

Amino acids that form acetyl CoA or acetoacetyl CoA

Ketogenic

3. **Lysine**, an exclusively ketogenic amino acid, is unusual in that neither of its amino groups undergoes transamination as the first step in catabolism. Lysine is ultimately converted to acetoacetyl CoA.

Glucogenic و ketogenic

4. **Tryptophan** is both glucogenic and ketogenic because its metabolism yields alanine and acetoacetyl CoA.

طالما alanine معناته بتحول لpyruvate

بطلعلي ketone bodies او ممكن ادخله بتصنيع fatty acids او ممكن اكسره لتنينacetyl CoA وادخله krebs cycle