BIOCHEMISTRY

VEIN BATCH

Lecture : 16

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Amino acid metabolism lecture 2 of 3

Nitrogen metabolism and urea cycle

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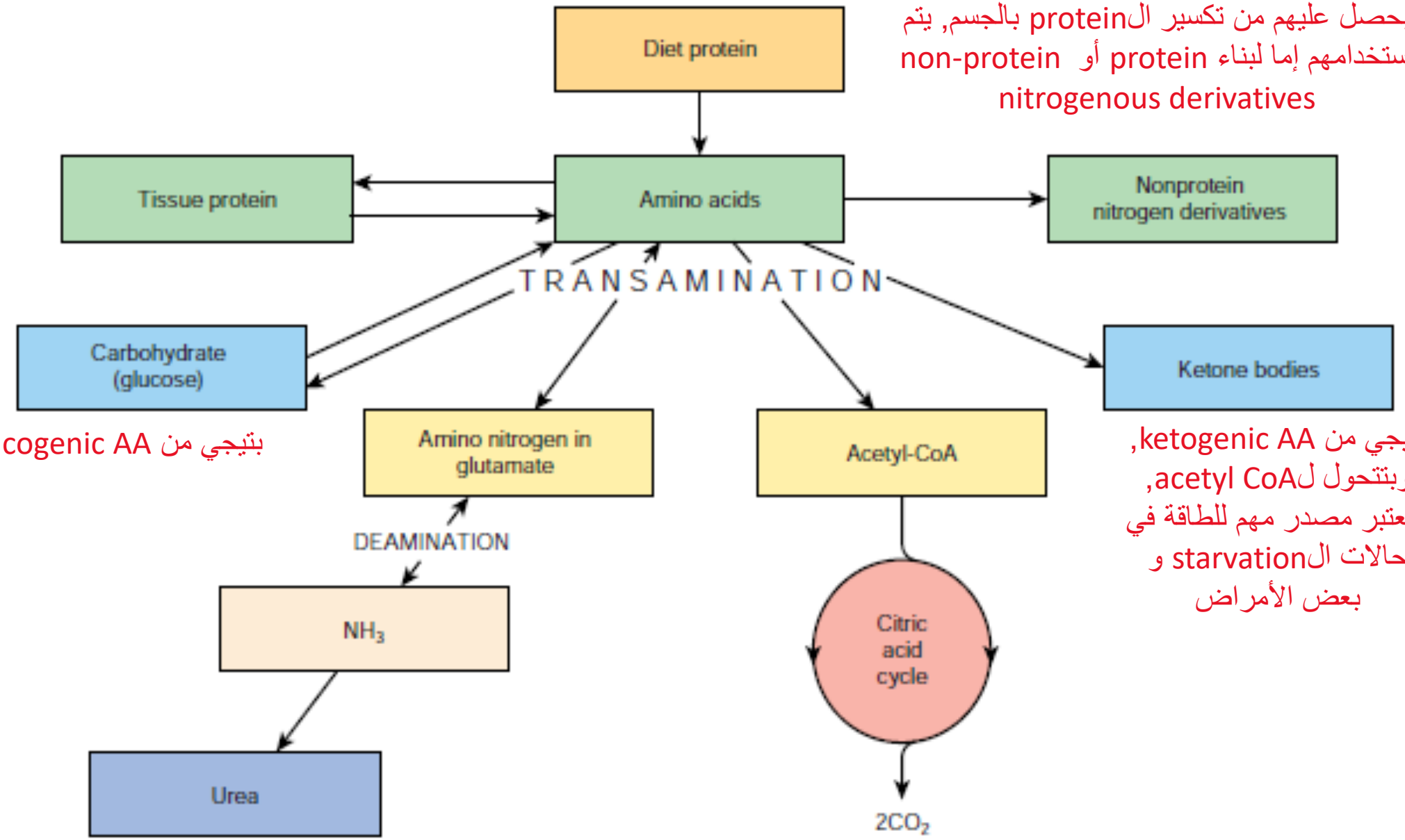
Amino acids metabolism	1.Synthesis of non-essential amino acids 2.Catabolism of amino acids 3. Nitrogen metabolism and urea cycle 4. Heme synthesis from glycine and succinyl-CoA

ال AA اللي بنحصل عليهم من ال diet, واللي بحصل عليهم من تكسير ال protein بالجسم, يتم استخدامهم إما لبناء protein أو non-protein nitrogenous derivatives



بتيجي من glucogenic AA

بتيجي من ketogenic AA, وبتتحول لـ acetyl CoA, وتعتبر مصدر مهم للطاقة في حالات ال starvation و بعض الأمراض

اللهم افتح لنا أبواب حكمتك، وانشر علينا رحمتك، وامنن علينا بالحفظ والفهم

Nitrogen metabolism

- An adult consuming 100g of protein/d excretes 16.5g nitrogen/d; 95% in urine and 5% in faeces (v small amounts in sweat & other routes) (زي الnails)

ذكرنا سابقا إنه 16% من الprotein عبارة عن nitrogen, يعني لو شخص تناول 100g من الprotein هاض يعني إنه فيهم 16.5g من الN

- **Nitrogen balance:** quantitative difference between nitrogen intake & output

- **Positive nitrogen balance:** intake > output هاض بصير لما تكون كمية الN اللي بنوخذها أكبر من الكمية اللي بتم إخراجها
  - Growth, muscular training, pregnancy, recovery from negative nitrogen balance

وممكن نشوفه في حالات الrecovery من بعض الأمراض, زي شخص كان جسمه في catabolic state نتيجة starvation وكان يفقد وزنه وكتلته العضلية ثم بدأ يتعافى, أو ممكن في حالة التعافي من الmetastatic cancer, حيث التعافي يعني إنه المريض is gaining weight and muscle mass, ما يعني إنه عنده positive N balance

- **Negative nitrogen balance:** output > intake
  - Inadequate protein diet, loss of protein, increased protein catabolism

- **Nitrogen equilibrium** → output = intake
  - Normal healthy adult on an adequate diet

في الحالة الطبيعية لما ما يكون عند الشخص أي أمراض ونظام أكلهم متوازن فالN بكون في حالة equilibrium

Ammonia

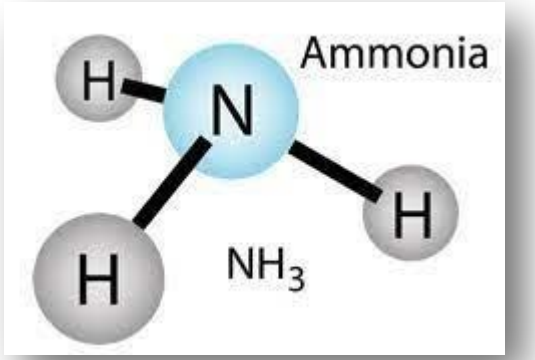
- Universal participant in amino acid synthesis and catabolism (deamination)

ammoniaال مهمة جدا في بناء وتكسير ال amino acids

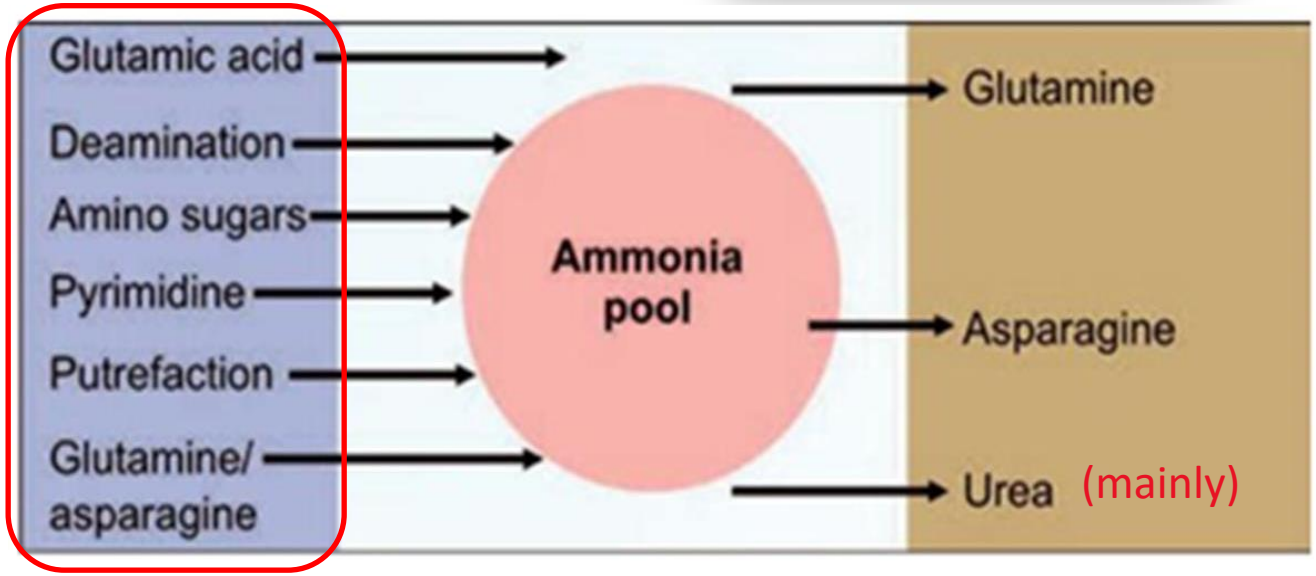
- Accumulation in abnormal concentrations → **toxic effects**

لو نسبة الammonia زادت عن حدها وصارت تتراكم رح تأدي لحدوث toxic effects, عشان هيك لازم الجسم دايما يتخلص منها بعد انتاجها

- Ammonia must be eliminated as soon as it is formed



sourcesال مهمة



Sources and fate of ammonia

Fate of the ammonia removed

أحيانا قبل ما يتم التخلص من الammonia الجسم ممكن يستخدمها لfunctions معينة بحتاجها , زي synthesis of non-essential AA الـ, أو لتصنيع nitrogenous compounds الـ

Ammonia

Synthetic/ Anabolic pathway

Synthesis of nonessential AA

Synthesis of nitrogenous compounds as: purines, pyrimidines, and amino sugars

Excretory/ Catabolic pathway

Liver

الliver هو الorgan الأهم بالنسبة لل ammonia excretion, حيث قبل ما يصير الexcretion رح يتم تحويل الammonia إلى urea بداخله, بعدين الurea بتروح عالkidney عشان تنزل في الurine

Other tissues

Kidney
Small quantities under normal conditions, increased in acidosis

لكن في كميات من الammonia بتنزل زي ما هي في الurine, وهاي الكميات بتزيد بشكل كبير في حالات الacidosis, والهدف هون إنه الkidney بتستعمل الammonia عشان تتخلص من الH أو الacids وتنزلهم في الurine

•Fate of products of deamination:

(A)Fate of the ammonia removed

(A)Fate of the carbon skeleton

اللهم إني أسالك التوفيق والنجاح, في الدنيا والآخرة

Ammonia transport from tissues to liver/ kidney

- Inside the cells of almost all tissues, the trans-amination of amino acids produce glutamic acid

و زي ما قلنا الtransamination بحدث بكل الخلايا, وبعطينا glutamate

- **First line of Defense (Trapping of ammonia):** Being highly toxic, ammonia should be eliminated or detoxified, as and when it is formed
  - Even very minute quantity of ammonia may produce toxicity in central nervous system

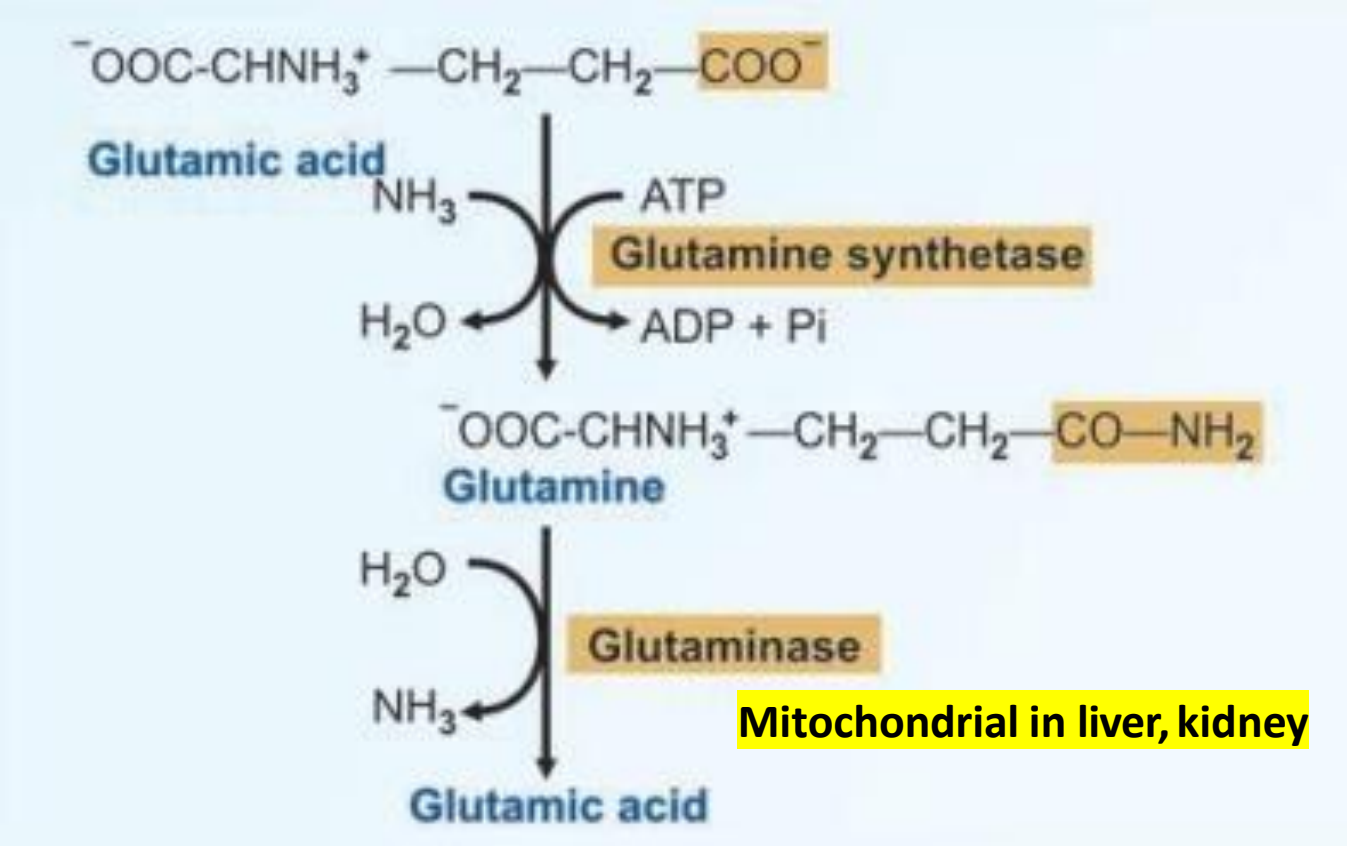
وكميات قليلة منها ممكن تسبب toxicity , خاصة للcentral nervous system والbrain

- Intracellular ammonia is immediately trapped by glutamic acid to form **glutamine**, especially in brain cells
  - The glutamine is then transported to liver, where the reaction is reversed by the enzyme **glutaminase**

الglutamic acid أصلا بحتوي على NH3, وبعد ما عمل trapping صار يحتوي على 2N (الثانية بتكون على شكل NH2) وصار اسمه glutamine, وهاض الحكي بصير في كل الخلايا, لكن specially في الbrain, لإنه لو ما صارله trapping في الbrain رح يأدي لضرر كبير, بعد هيك بتم نقل الglutamine للliver عشان يتم فصل الNH3 عنه ويتم التخلص منها في الurine

- Aspartic acid may also undergo similar reaction to form **asparagine**

Ammonia trapping as glutamine



Glutamate is critical to intracellular AA metabolism

Glutamate synthetase: mitochondrial enzyme, high concentration in brain, liver & kidney

وعملية تكوين الglutamine تتم عن طريق ال glutamine synthetase (اللي من اسمه بنعرف إنه بستهلك ATP), وهو موجود بشكل رئيسي في الmitochondria in brain/ liver/ kidney.
وبعد هيك بتم نقله للliver عشان يتم فصله لglutamic acid و NH3 عن طريق الglutaminase

*الstructures وتفاصيل الreactions مش مطلوبة, لكن المهم نعرف الenzymes و وين بتم استهلاك ATP, وإنه نضل متتبعين تنقلات الammonia خلال الprocess

Catabolic and excretory pathways:

- Being highly toxic to tissues, the ammonia produced **in excess of the requirements for anabolic purposes** is rapidly disposed of

ammoniaال بتدخل في بعض الanabolic processes, لكن لو كمية الammonia كانت زائدة عن حاجتنا رح يصيرلها disposition مباشرة

- The method of disposal depends upon the tissue in which deamination occurs

A- In the liver:

The liver is the main site of deamination of amino acids

(طبعا بتوصل الliver على شكل glutamine)

- Most of the ammonia released (via glutaminase) is converted to urea
- The urea formed goes via the blood to the kidneys to be excreted in urine

B- In the kidneys:

The ammonia resulting from the deamination of AA in the kidneys is directly excreted in urine

This accounts for about 40% of the urinary ammonia

الآن بشكل عام الexcretion للammonia بالجسم الأغلبية العظمى منه بتم عن طريق الurea, والammonia اللي بالkidney بتشكل كمية قليلة من إجمالي الammonia اللي رح تطلع من الجسم, و الammonia اللي بالkidney بتيجي من مصدرين, المصدر الأول هو عن طريق الdeamination للAA في الkidney نفسها, حيث بتم التخلص من الamino group اللي بهضول الAA, وبتطلع الammonia بالkidney زي ما هي, وهاض المصدر بعطينا 40% من الurinary ammonia, واللي زي ما حكينا بتشكل نسبة ضئيلة من الactual ammonia that is excreted in the form of urea

C- In extrarenal tissues:

The ammonia resulting from the deamination of AA in extrarenal tissues, particularly the brain, is converted to glutamine

يا حيّ يا قيوم برحمتك أستغيث, أصلح لي شأني كله, ولا تَكِلْني إلى نفسي طرفة عين

المصدر الثاني للammonia في الkidney بيجي عن طريق الglutamine, حيث بعد ما يتم نقله للkidney رح يتم تكسيره لglutamic acid و ammonia, اللي رح تنزل زي ما هي في الkidney, وهاض بشكل 60% من الurinary ammonia. ف صفّى عنا بالkidney عدة شغلات, عنّا urea (اللي جاية من ammonia, وهي الmain route of excretion of ammonia), وعنّا برضه ammonia, اللي جاية من مصدرين (تكسير الAA اللي في الkidney / تكسير الglutamine)

- Glutamine goes, via the blood, to the kidneys where it becomes hydrolyzed by **glutaminase** into **glutamic acid** and **ammonia**
  - The ammonia is excreted in urine, accounting for about 60% of urinary ammonia
  - This amount increases in acidosis (forms salts with metabolic acids) → counteracting acidosis

- Glutamic acid acts as the link between amino groups of amino acids and ammonia
- The concentration of glutamic acid in blood is 10 times more than other amino acids

وتواجده بهاي النسبة المرتفعة برجع لأهميته في الurea-ammonia cycle

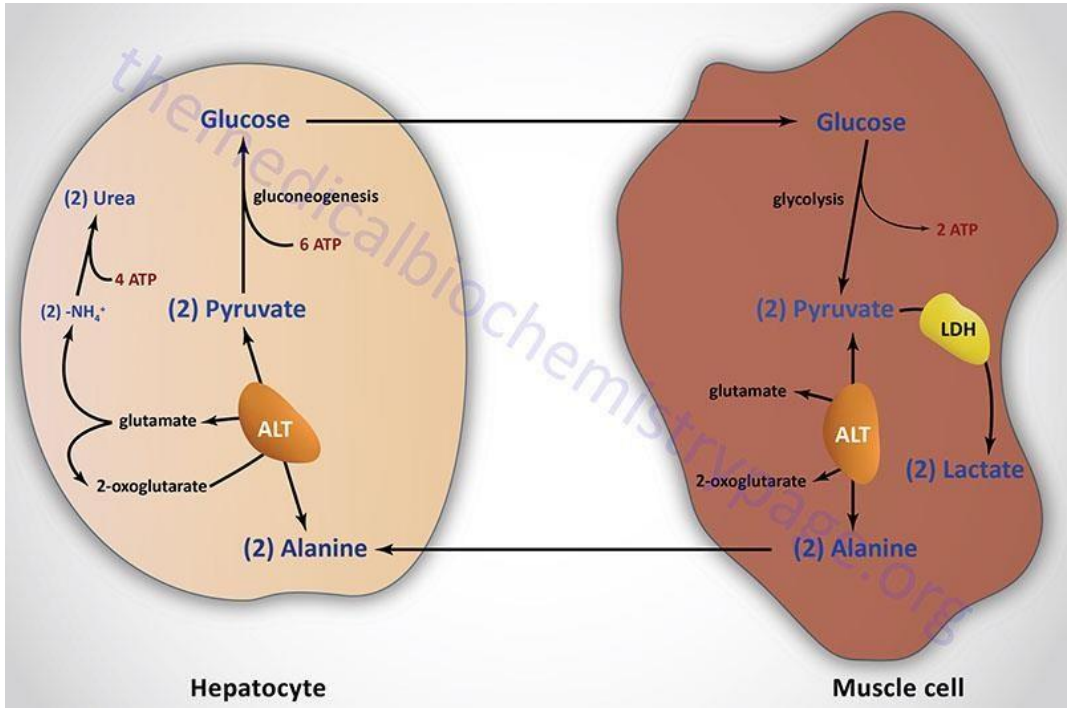
Glutamine is the transport forms of ammonia from brain and intestine to liver; while alanine is the transport form from muscle

نقطة مهمة جدا

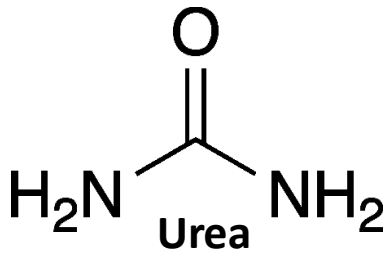
الglutamine هو الناقل للammonia من الbrain/ intestine.
الalanine هو الناقل للammonia من الmuscles

Glucose-Alanine cycle

- Alanine is transported from muscle to liver, transaminated → pyruvate → glucose
- Glucose can enter glycolytic pathway to form pyruvate which is transaminated → alanine
- Glucose-alanine cycle is of primary importance in conditions of starvation
- **Importance**
  - Transfer if 3C of pyruvate to the liver to give glucose
  - Transfer of NH3 in non-toxic form from muscle to liver to be converted to urea
  - Related to Cori cycle



Urea cycle



- Urea is the main way of excretion of ammonia resulting from the deamination of AA

- Ammonia is highly toxic to the CNS; it is converted to non toxic urea in the **liver only**
  - Urea is water soluble easily excreted by the kidneys in urine. Urea is the main end product of protein (amino acids) metabolism

protein metabolismل end productال هي ureaال

- Plasma urea is 15-45 (20-40) mg/dl, it is formed in the liver and transported in blood to the kidney to be excreted in urine (urinary urea is 15-45 (20-40) g/day)

اللي مهم نعرفه, إنه الureaال يتم تكوينها بالliver, ما يعني إنه لو يصير مشكلة بالliver (liver failure) رح يرتفع مستوى الammonia,
ولو صار مشكلة بالkidney (kidney failure) رح تأدي لزيادة الurea بالدم, وممكن برضه يأدي لزيادة الammonia

- Urea **cycle** is known as **Krebs–Henseleit** cycle (5 reactions, 1-2 in mitochondria; 3-5 in cytosol)

تمت تسميتها هيك لإنه تم اكتشافها من قِبَل نفس العالِم اللي اكتشف الTCA cycle

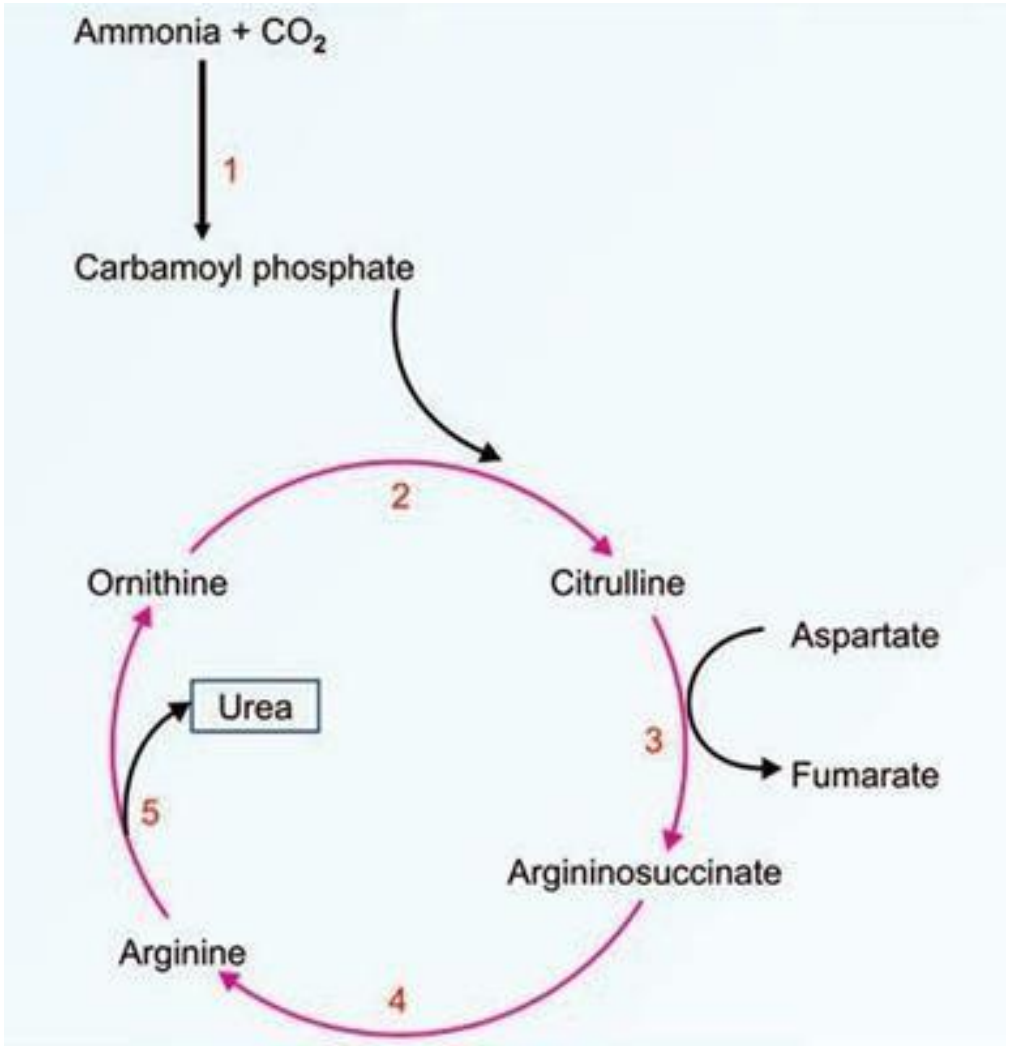
- As ornithine is the first member of the reaction, it is also called as **Ornithine cycle**

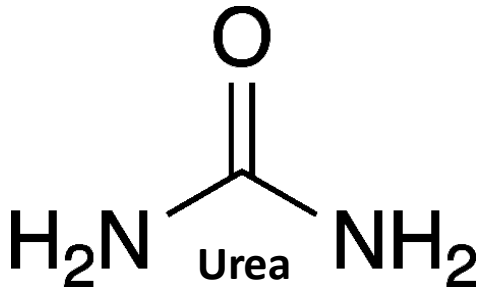
دور الornithine هون شبيه ب دور الoxaloacetate في الTCA cycle, حيث يمكن اعتباره catalyst, عشان هيك ممكن نسميها ornithine cycle

- The two nitrogen atoms of urea are derived from two different sources:
  - one from ammonia; and
  - the other directly from the alpha amino group of aspartic acid

نقطة مهمة

Urea cycle





الammonia بتعطينا carbamoyl phosphate,
اللي رح يدخل بcycle, وسبب تسميتها بcycle إنه
التفاعلات فيها بتشكل حلقة مستمرة, والornithine
دوره فيها إنه هو المركب اللي بتفاعل مع
الcarbamoyl phosphate ببداية الcycle,
وبرجع بصيرله regeneration بنهاية الcycle,
وخلال الcycle بدخل الaspartate وبطلع على
شكل fumarate, وبما إنه الfumarate بدخل
بالTCA cycle, فهاض يعني إنه رح يكون في
linkage بين الcycles 2

Urea cycle, summary. Note that aspartate enters and fumarate leaves at different steps

اللهم إنك عفوّ تحب العفو فاعفُ عنا

Step 1. Formation of Carbamoyl Phosphate

*Which is a high energy compound

- One molecule of ammonia condenses with CO2 in the presence of **two molecules of ATP** → form carbamoyl phosphate

والCO2 هاي المسؤولة عن أول reaction بتيجينا من الTCA cycle

وتحويل 2 ATPs لـ2 ADPs يعني إنه تم نزع 2 P groups, لكن اللي خرج عنا هو فقط 1 Pi, والسبب إنه الثانية بدخل في تركيب الcarbamoyl P

- The reaction is catalysed by the mitochondrial enzyme **carbamoyl phosphate synthetase-I (CPS-I)**

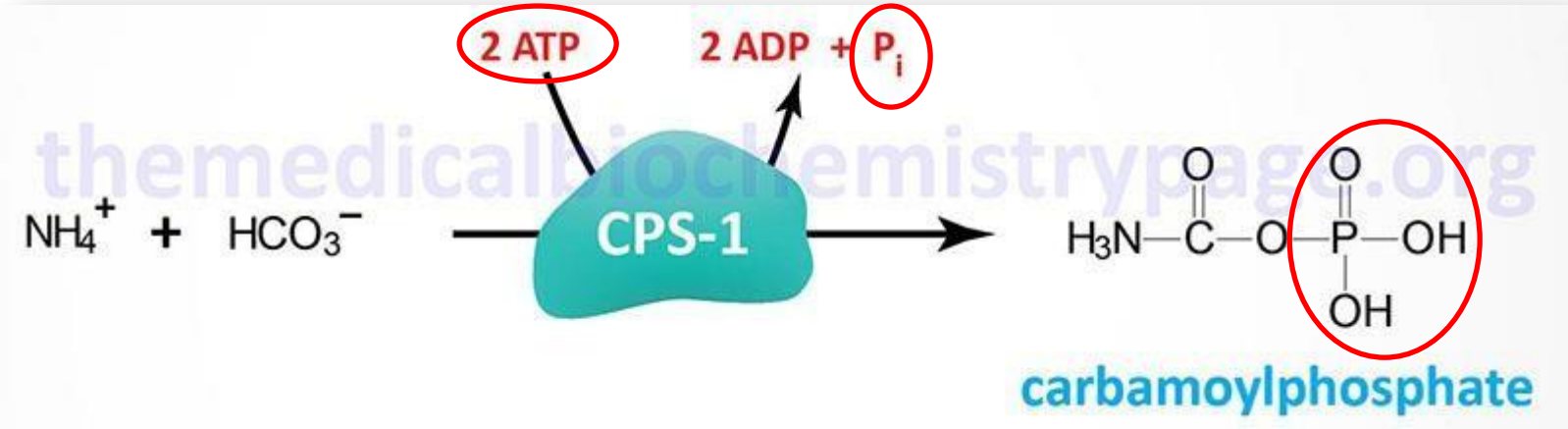
*CPS-1 is activated by N-acetylglutamate

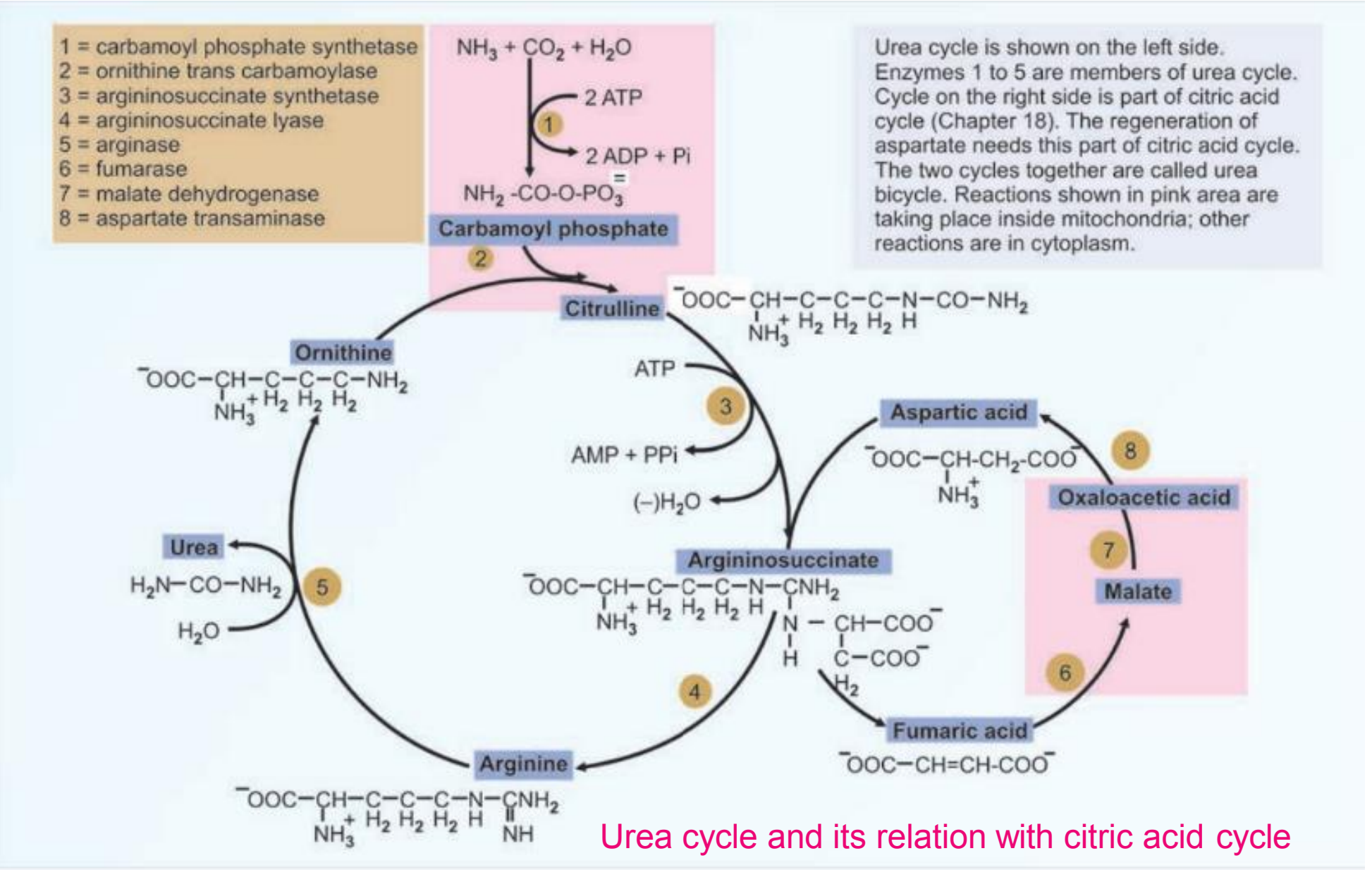
- An entirely different cytoplasmic enzyme, carbamoyl phosphate synthetase-II, (CPS-II) is involved in pyrimidine nucleotide synthesis

نقطة مهمة جدا

الCPS-1 مختلف كليا عن الCPS-2, من حيث مكان وجوده و الreactions اللي بدخل فيها,
حيث الCPS-2 موجود في الcytoplasm وبدخل في تصنيع الpyrimidine nucleotide

- **CPS-I reaction is the rate-limiting step in urea formation (**It is irreversible and allosterically regulated)





Urea cycle and its relation with citric acid cycle

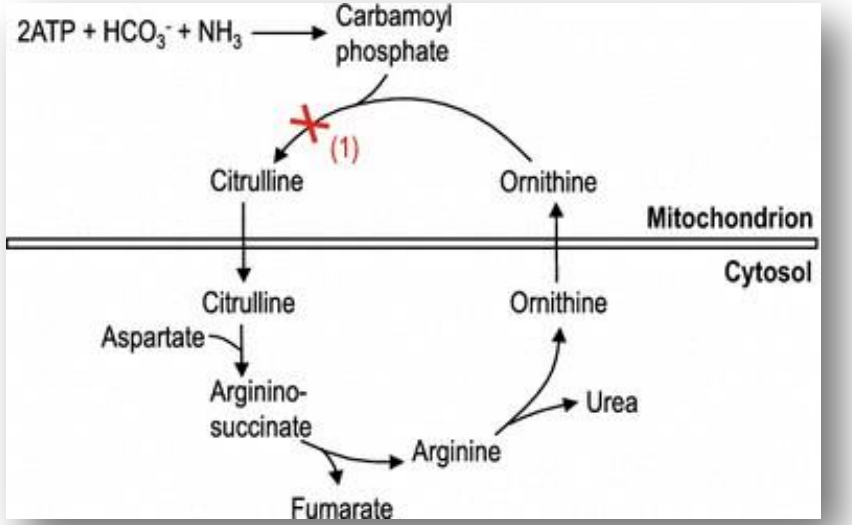
الreactions اللي عليها مربع باللون الزهري تحدث في الmitochondria, أما باقي reactions الف تحدث في الcytoplasm

والcycle الصغيرة اللي على اليمين هي جزء من الTCA cycle اللي في بينه وبين الurea cycle linkage , ولإنه بالمحصلة الreaction بكون أشبه بـ2 cycles صار البعض يطلق عليه اسم urea bicycle, والارتباط بينهم بكون عن طريق ال aspartate والfumarate

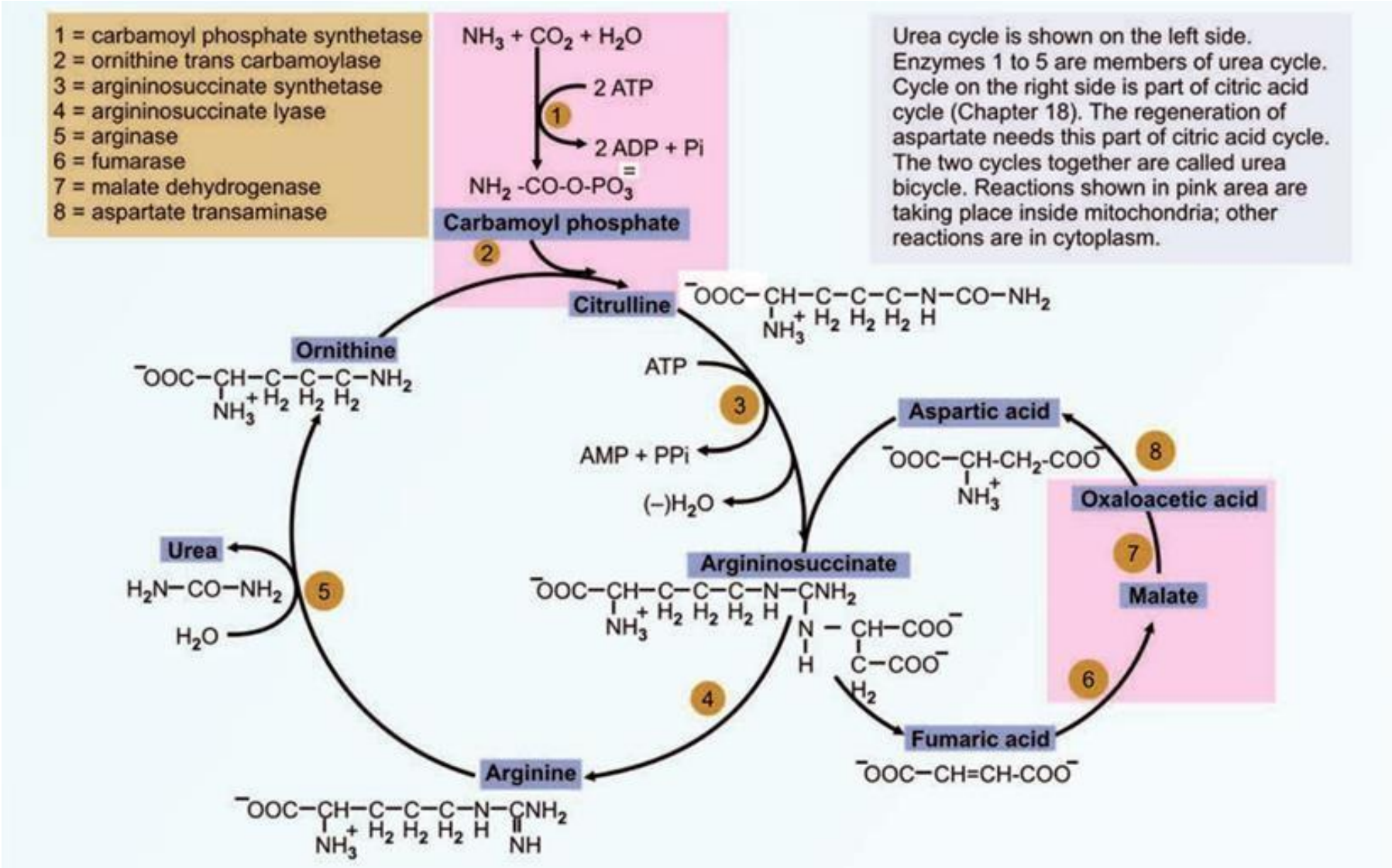
*للتذكير, الornithine هو أحد أهم الamino acids في الجسم, لكنه مش من ضمن الAA 20 اللي بدخلوا في structure of proteinsال

Step 2. Formation of Citrulline

- The second reaction is also **mitochondrial**
- The carbamoyl group is transferred to the NH_2 group of ornithine by **ornithine transcarbamoylase** (OTC) (Ornithine is considered as a catalyst)
- Citrulline leaves the mitochondria and further reactions are taking place in cytoplasm



بهاي الstep بتكون الcitrulline,
واللي رح يخرج من الmitochondria بعد تكوينه, لإنه باقي الsteps بتصير في الcytosol



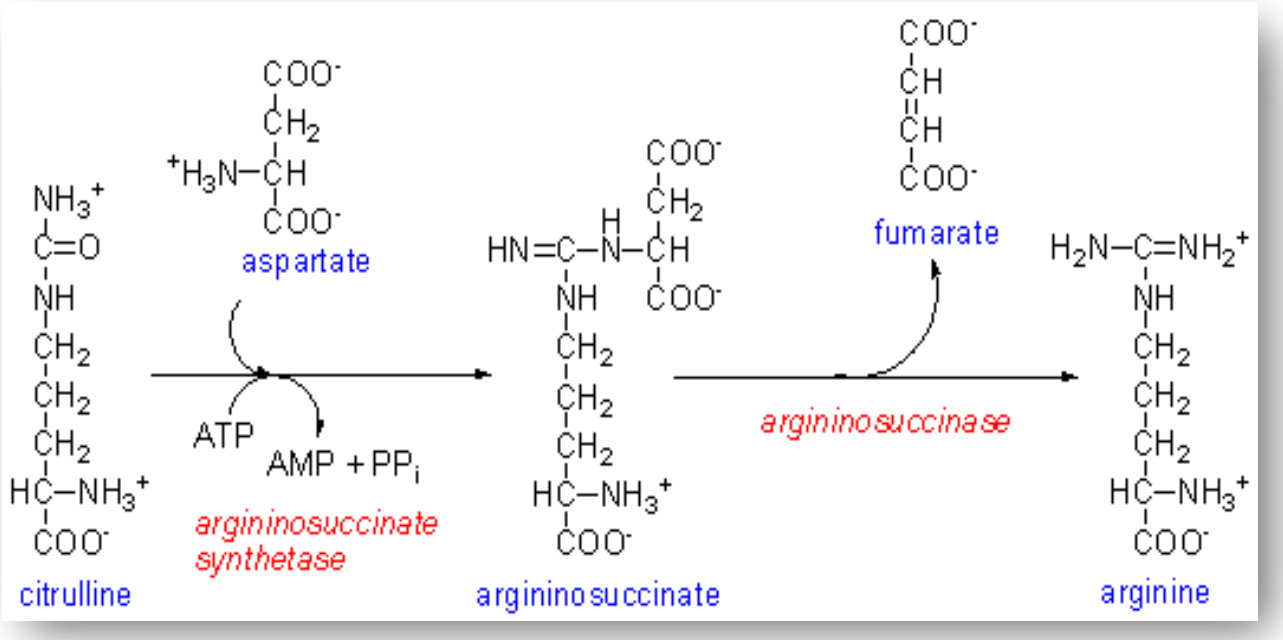
Urea cycle and its relation with citric acid cycle

Step 3. Formation of Argininosuccinate

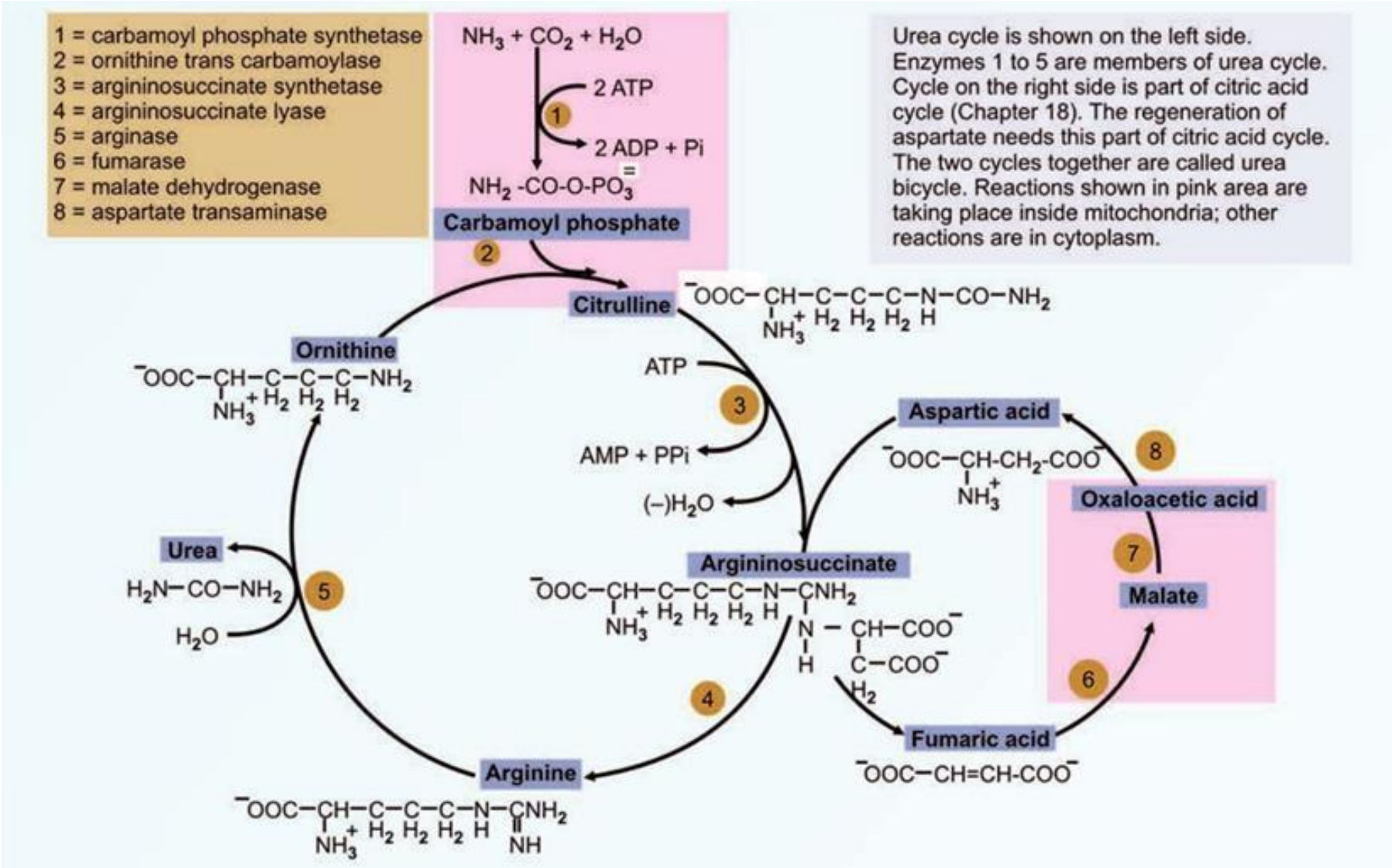
One molecule of aspartic acid adds to citrulline forming a carbon to nitrogen bond which provides the 2nd nitrogen atom of urea

- **Argininosuccinate synthetase** catalyzes the reaction
- This needs hydrolysis of ATP to AMP level, so "**two relatively high energy phosphate bonds**" are utilized
- The PPi is an inhibitor of this step

بهاي الstep بظهر الaspartate وبتفاعل مع الcitrulline
عشان يعطينا Argininosuccinate, ومن اسم الenzyme اللي
بحفز التفاعل فهو بحتاج ATP, وبعطينا AMP, ما يعني إنه كسرنا
2 high energy bonds (الأولى high energy, والثانية
relatively high energy), بالإضافة لخروج pyrophosphate



اللهم إني أسألك الهدى والتقى والعفاف والغنى



Urea cycle and its relation with citric acid cycle

Step 4. Formation of Arginine

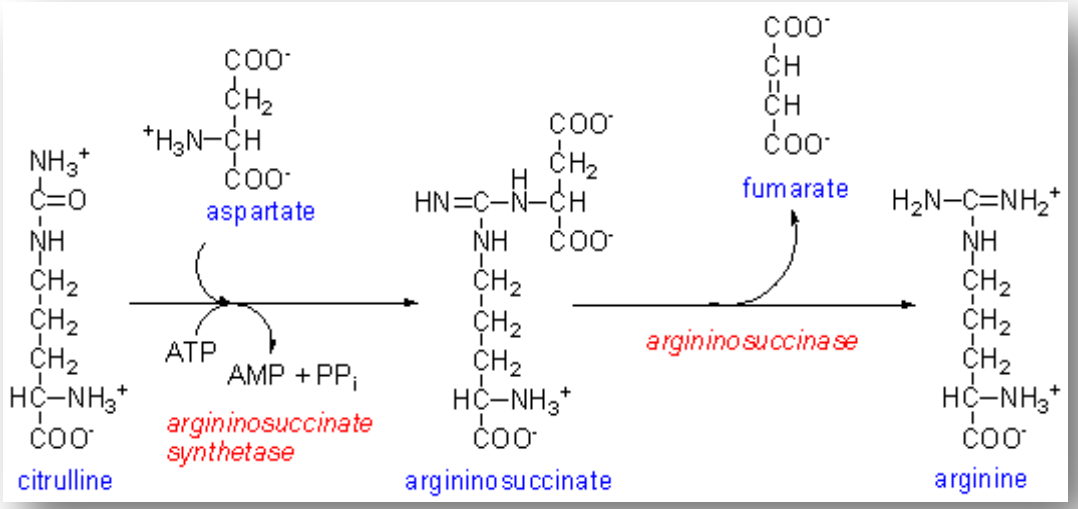
- Argininosuccinate is cleaved by **Argininosuccinate lyase** (argininosuccinase) to arginine and fumarate

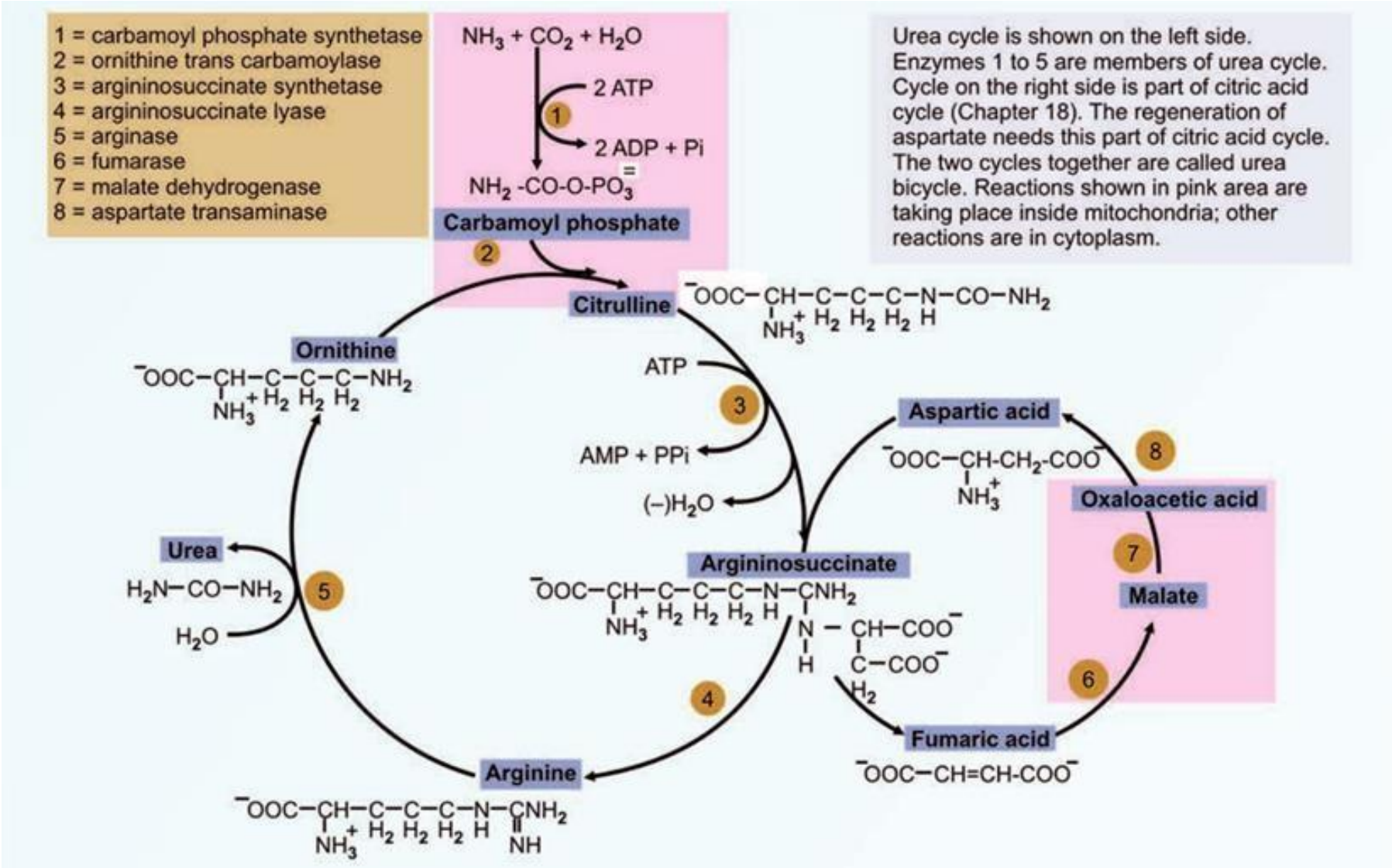
بالرغم من إنه الfumarate ممكن يعمل inhibition, لكن بما إنه الfumarate أصلا مكانه في الmitochondria عشان يدخل في الTCA cycle, ف رح compartmentalization بحيث يتم نقله للmitochondria, وبالتالي زيادته رح يبطل إلها تأثير على الreaction لإنه مش رح يضل بالcytosol

- The enzyme is inhibited by fumarate
  - But this is avoided by the cytoplasmic localization of the enzyme
- The fumarate formed may be funneled into TCA cycle to be converted to malate and then to oxaloacetate to be transaminated to aspartate

وبالحقيقة بالنهاية رح نستفيد منه, لإنه رح يعمل regeneration للaspartic acid, اللي بدخل بstep 3

- Thus the urea cycle is linked to TCA cycle through fumarate
- The 3rd and 4th steps taken together may be summarized as:
  - Citrulline + aspartate → Arginine + fumarate



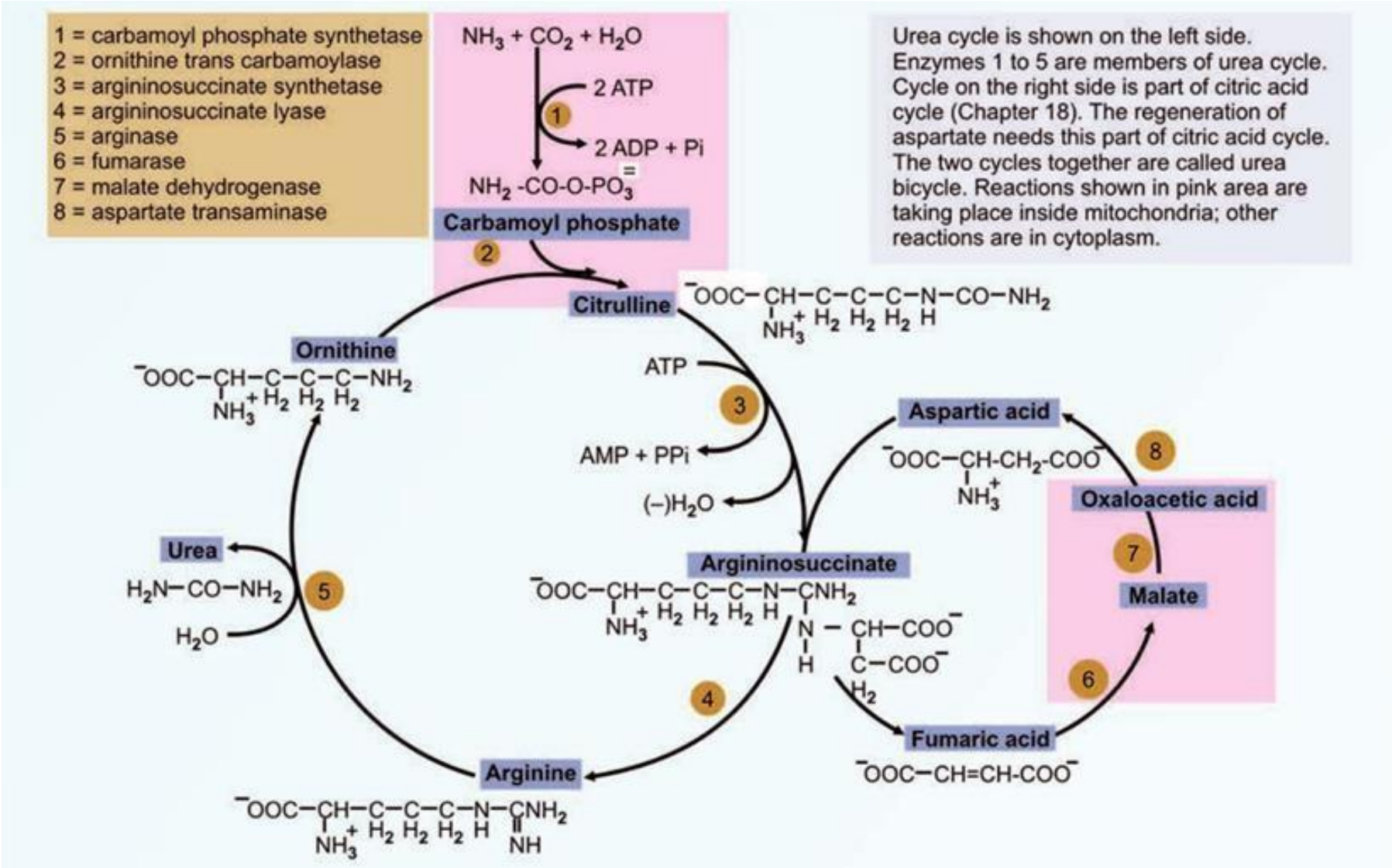


Urea cycle and its relation with citric acid cycle

Step 5. Formation of Urea

- The final reaction of the cycle is the hydrolysis of arginine to urea + ornithine by **arginase**
    - The ornithine returns to the mitochondria to react with another molecule of carbamoyl phosphate so that the cycle will proceed
    - Thus, ornithine may be considered as a catalyst which enters the reaction and is regenerated

سبحان الله وبحمده, عدد خلقه, و زِنة عرشه, ومداد كلماته



Urea cycle and its relation with citric acid cycle

Energetics of Urea Cycle

- The overall reaction may be summarized as:

NH_3 + CO_2 + Aspartate → Urea + fumarate

- ال NH3 بيجي من ال deamination
- ال CO2 وال aspartate بيجوا من ال TCA cycle

- During these reactions, 2 ATPs are used in the 1st reaction

- Another ATP is converted to AMP + PPi in the 3rd step, which is equivalent to 2 ATPs

- The urea cycle consumes **4 high energy phosphate bonds** (ما ننسى إنه وحدة من هضول ال4 هي relatively high)

- However, fumarate formed in the 4th step may be converted to malate
  - Malate when oxidised to oxaloacetate produces 1 NADH equivalent to 2.5 ATP (new system)

- So **net energy expenditure is only 1.5 high energy phosphates**
  - The urea cycle and TCA cycle are interlinked, and so, it is called as "**urea bicycle**"

*لو نلاحظ ف بالنهاية ال TCA cycle بتلعب دور بال metabolism لكل اشي تقريبا, حيث بتدخل بال CHO/ lipid/ protein metabolism

Relationship between urea cycle and tricarboxylic acid cycle (Kerbs cycle):

- Fumarate produced in urea cycle can be oxidized in Kerbs cycle to oxaloacetate which by transamination give aspartate needed for urea synthesis

- Co2 needed in urea formation is derived mainly from TCA cycle

- ATP needed in urea formation is derived from TCA cycle

Regulation of urea cycle:

- **Corse control → Effect of feeding and fasting:** the enzymes of urea cycle are:
  - increased by high protein diet
  - decreased by low protein diet

الenzymes لل urea cycle بتم تحفيزها بتناول الprotein,
وبتم تقليل عملها بتقليل تناول الprotein

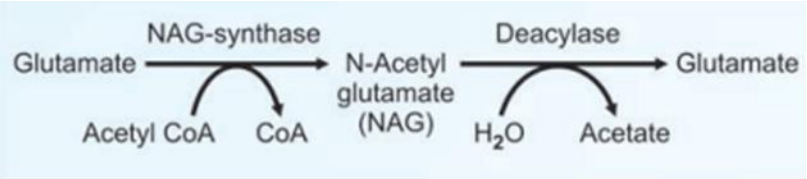
- **Fine control →** N-acetylglutamate acts as activator for carbamoyl phosphate synthetase I (CPS I) which is inactive in its absence

ارتفاع كمية الAA رح تأدي لزيادة تكوين الN-acetylglutamate, واللي بدوره رح يحفز الurea cycle

Compartmentalization

- The urea cycle enzymes are located in such a way that the 1st two enzymes are in the mitochondrial matrix
  - The inhibitory effect of fumarate on its own formation is minimized because Argininosuccinate lyase is in the cytoplasm, while fumarase is in mitochondria

↑↑ AA → ↑↑transdeamination → ↑↑ glutamate which combines with acetyl coA forming N-acety glutamate



NAG synthesis and breakdown

Diagnostic importance of plasma urea determination:

- Plasma urea is one of the kidney function tests

- Plasma urea is increased in kidney diseases like renal failure (uremia)

- In liver failure: liver cells cannot convert ammonia to urea so there will be:

(زيادة الammonia)
- **hyperammonemia** (ammonia intoxication); and
- **urea is decreased**

اللهم إني أعوذ بك من الهم والحزن, وأعوذ بك من العجز والكسل

Disorders of Urea Cycle

- Deficiency of any of the urea cycle enzymes would result in **hyperammonemia**

بشكل عام رح تأدي لارتفاع الammonia في الدم

- When the block is in one of the earlier steps, the condition is more severe, since ammonia itself accumulates
- Deficiencies of later enzymes result in the accumulation of other intermediates which are less toxic and hence symptoms are less

لو صار الblockage في واحد من الenzymes بالsteps المتأخرة فالضرر نوعا ما أقل,
والسبب إنه الammonia مش قاعد بصيرلها accumulation زي ما هي , بل رح تكون بلشت ترتبط بمركبات أخرى وتتفاعل معها, لكن لو
الblockage صار بالsteps الأولى الammonia رح تضل زي ما هي بهيئة NH3 وتتراكم

- As a general description, disorders of urea cycle are characterized by **hyperammonemia, encephalopathy**

وممكن تعمللنا مشاكل بالbrain لإنها highly toxic إله

- Clinical symptoms include vomiting, irritability, lethargy and severe mental retardation (if untreated)
- Infants appear normal at birth, but within days progressive lethargy sets in
- Treatment is more or less similar in the different types of disorders

وبشكل عام, العلاج للdisorders المختلفة بكون similar نوعا
ما, وهو عن طريق تقليل الproteins في الغذاء, واستخدام
ادوية تساعد على التخلص من الammonia وتطلعها بالurine

- Low protein diet with sufficient arginine and energy by frequent feeding can minimize brain damage since ammonia levels do not increase very high

Disorders of Urea Cycle

Type I and II hyperammonemia are more severe than the other types

enzyme deficiencies وسببهم ,Congenital disorders هضول

المطلوب من الجدول : الdiseases كاملة, مع معرفة الmost severe/ mild diseases, و الmost common disease,
معرفة الenzymes اللي صار المرض بسبب نقصها, وبالنسبة للfeatures فالمطلوب هو اللي عليه highlight بالأصفر فقط

Diseases	Enzyme deficit	Features
Hyperammonemia type I The most severe	CPS-I	Very high NH_3 levels in blood. Autosomal recessive. Mental retardation. Incidence is 1 in 100,000.
Hyperammonemia type II The 2nd severe **Commonest**	(OTC) Ornithine transcarbamoylase	Ammonia level high in blood. Increased glutamine in blood, CSF and urine. Orotic aciduria due to channelling of carbamoyl phosphate into Pyrimidine synthesis. X-linked.
Hyperornithinemia	Defective ornithine transporter protein	Failure to import ornithine from cytoplasm to mitochondria. Defect in ORNT1 gene. Hyperornithinemia, hyperammonemia and homocitrullinuria is seen (HHH syndrome). Decreased urea in blood. Autosomal recessive condition.
Citrullinemia	Argininosuccinate synthetase	Autosomal recessive. inheritance. High blood levels of ammonia and citrulline. Citrullinuria (1-2 g/day).
Argininosuccinic aciduria	Argininosuccinate lyase	Argininosuccinate in blood and urine. Friable brittle tufted hair (Trichorrhexis nodosa). Incidence 3/200,000
Hyperargininemia **Mild**	Arginase	Arginine increased in blood and CSF. Instead of arginine, cysteine and lysine are lost in urine. Incidence 1 in 100,000

Congenital urea cycle disorders

Reduced severity as intermediates accumulate (less toxic)

Disorders of Urea Cycle

- **Brain is very sensitive to ammonia, ↑ ammonia leads to:**
  - Ammonia will combine with α−ketoglutaric acid forming glutamate and glutamine →
    - ↓ energy production by Krebs cycle in brain leading to brain damage
  - ↑ levels of glutamine → ↑ osmotic pressure in the astrocytes → which become swollen
  - **+ other mechanisms**

ال mechanisms مهمة

خطورة ارتفاع نسبة الammonia للbrain بتصير عن طريق 5 mechanisms :

1- رح تأدي للformation of glutamine, اللي رح يزيد من الosmotic pressure في الbrain cells, ما يؤدي لحدوث brain edema, واللي يعتبر من أسباب الencephalopathy.

2- بالإضافة لإنه رح يقوم باستهلاك 4 ATPs في كل مرة بتصير فيها الurea cycle, و رح يصاحبه استهلاك للalpha ketoglutarate, وهاض رح يعطل الTCA cycle.

3- الammonia ممكن تأثر على الpotassium (K), اللي ممكن يأثر عالdepolarization of the cells.

4- بأثر عال GABA (gamma-aminobutyric acid) اللي هو neurotransmitter.

5- بأثر على الnitrous/ nitric oxides وغيرهم من الstress substances

- Since **Citrulline** is present in significant quantities in milk, breast milk is to be avoided in citrullinemia

Child may be put on a low protein diet and frequent small feeds are given

الcitrulline موجود بكميات كبيرة بالbreast milk, عشان هيك لما يكون في مشاكل بالenzymes تبعت الurea cycle, أو لما تكون كمية الcitrulline مرتفعة, لازم نمنع الbreast milk عن الطفل

النقاط المهمة بالسلايد هي اللي عليها highlight بالأصفر, الباقي أقل أهمية

Hepatic Coma (Acquired Hyperammonemia)

→ more common than heridetiry

(وممكن نشوفها بكثرة في مصر, بسبب كثرة الhepatitis)

- In diseases of the liver, hepatic failure can finally lead to hepatic coma and death

  الhepatic coma هو الend result لفشل الكبد (hepatic failure), وسببه زيادة في الammonia, وممكن يسبب encephalopathy

- Hyperammonemia is the characteristic feature of liver failure

- The condition is also known as hepatic encephalopathy

- Normally the ammonia and other toxic compounds produced by intestinal bacterial metabolism are transported to liver by portal circulation and detoxified by the liver
  - But when there is portal systemic shunting of blood, the toxins bypass the liver and their concentration in systemic circulation rises

- The signs and symptoms are mainly pertaining to CNS dysfunction (altered sensorium, convulsions), or manifestations of failure of liver function (ascites, jaundice, hepatomegaly, edema, hemorrhage, spider naevi)

  الأعراض بتأثر بشكل رئيسي عالCNS, وبتأدي لedema, وبالنهاية بتسبب الdeath

- The management of the condition is difficult
  - A low protein diet and intestinal disinfection (bowel clearing and antibiotics), withholding hepatotoxic drugs and maintenance of electrolyte and acid-base balance are the main lines of management

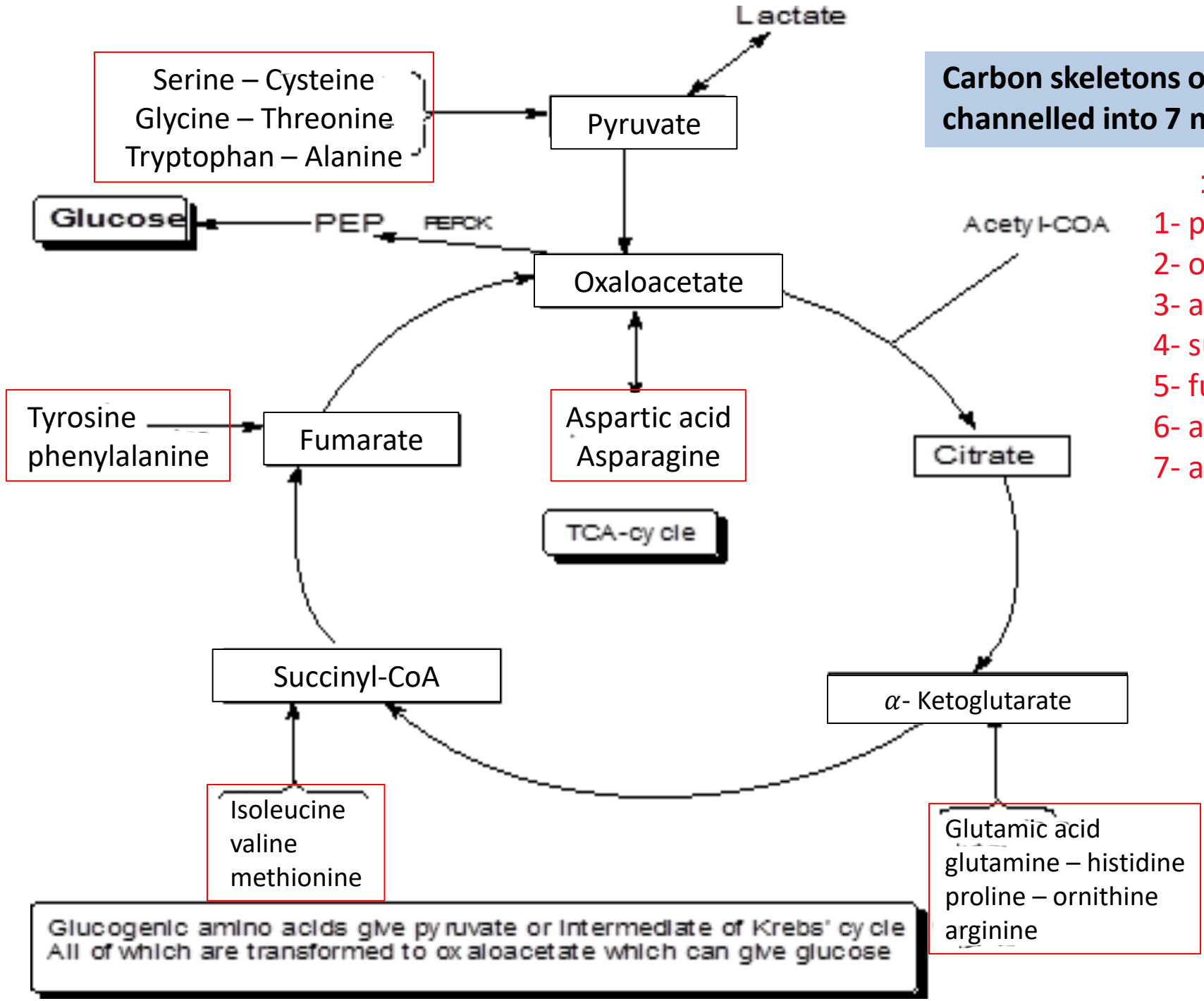
Fate of carbon skeleton of amino acids

- **Ketogenic AA:** produce acetyl coA or aceto-acetyl coA used in ketogenesis
  - Leucine
  - Lysine

- **Glucogenic and ketogenic AA:** can give both glucose & ketone bodies
  - Tyrosine
  - Phenylalanine
  - Tryptophan
  - Isoleucine

- **Glucogenic AA:** rest of AA (14)

سبحان الله وبحمده, سبحان الله العظيم



Carbon skeletons of the 20 AA are channelled into 7 molecules only

الـ7 molecules همه :

1- pyruvate
2- oxaloacetate
3- alpha ketoglutarate
4- succinyl-CoA
5- fumarate
6- acetyl CoA
7- acetoacetyl CoA

Self reading

المواضيع هاي الدكتور قال إنها self-study, وما ذكر مصدر معين لدراستها, وقال برضه إنه ما في داعي نتعمق فيها, حاولت أجمع بعض المعلومات عنها من النت, ان شاء الله تكون ضمن اللي الدكتور بده إياه (ممكن يكون عليها من سؤال لثلاث اسئلة بالامتحان)

- Understand how urinary ammonia secretion can be used to help control acid-base balance.

Renal acidification occurs primarily in the proximal tubule. Proximal tubular cells possess Na+/H+ exchangers that are responsible for the bulk of renal HCO3- reabsorption.

When blood pH falls below 7.35, the kidney responds by increasing reabsorption of bicarbonate from the urine. As blood pH rises toward 7.45, more hydrogen ions are released into the urine to return it to its normal pH of 7.

The urinary system utilizes two methods to alter blood pH. That is, excretion of hydrogen (H+) ions as dihydrogen phosphate or ammonia and production and reabsorption of bicarbonate (HCO3–) ions.

Urine is the primary route for the removal of ammonia from the body, so increased ammoniagenesis leads to decreased urinary ammonia levels and thus improved acid-base balance. Ammonia is also removed from the body through the formation of new bone via the process of osteogenesis. Thus, increased ammoniagenesis helps to correct metabolic acidemia.

- Causes of increased and decreased urinary ammonia

Increased ammonia levels are caused by : Acidosis / liver disease / Decreased blood flow to the liver / hepatic encephalopathy / Reye’s syndrome / kidney failure / Genetic diseases of the urea cycle / Hemolytic disease of the newborn.

and it's Decreased in alkalosis, Low ammonia levels can be a result of high blood pressure or consumption of certain medications.

Lecture 28/8/2022 (integration of metabolism)

(وهاض توزيع لمواضيع محاضرة 18 اللي رح يشرحها عدد من زملاءنا)

From Harper 28th edition, chapter 16:

- Pathways that process the major products of digestion → 5min
- A supply of metabolic fuels is provided in both the fed & fasting states + table 16.3 → 10 min

From Textbook of Biochemistry 7th edition, chapter 8; table 8.4

- Key enzymes under fed, fasting and starvation states (10 min) →

I will provide reference (via screenshots):

- Interconversions btwn CHO, protein and fats (10 min)