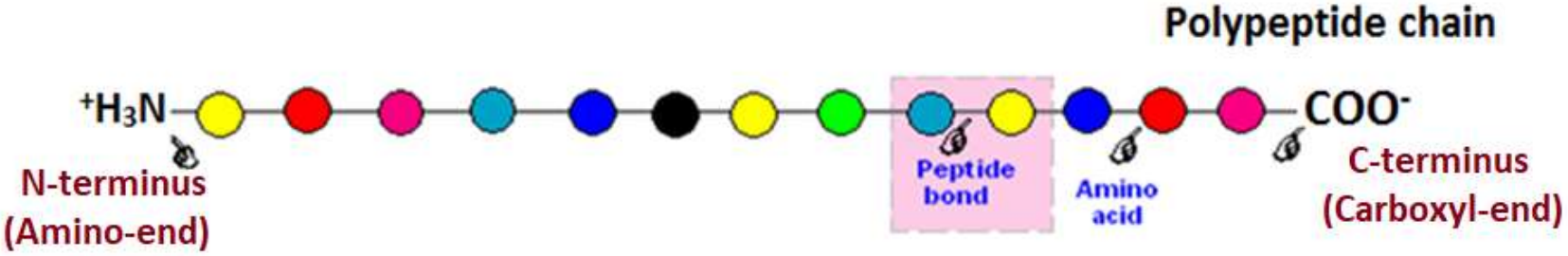
Amino acid Metabolism

Revision

Proteins are polymers of 100 – 1000s of amino acids linked by covalent peptide bonds

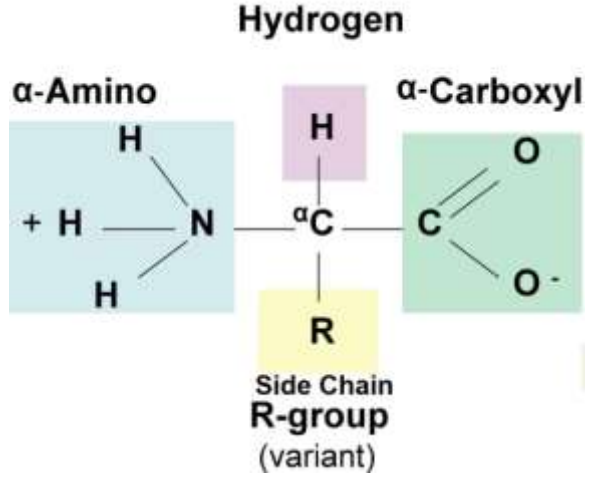


- About 500 type of amino acid in nature
- 21 amino acids incorporated to the polypeptide chain during the synthesis (20 of them are coded by the genetic material "the common amino acids")
- The 21th is ***Selenocysteine*** is not coded by the genetic material but can be incorporated during the synthesis of some proteins under specific conditions

<u>The general structure of amino acids</u>

they all have central ***α-carbon*** attached to it:

- H-atom
- α-amino group
- α-carboxyl group
- Side chain (R-group)



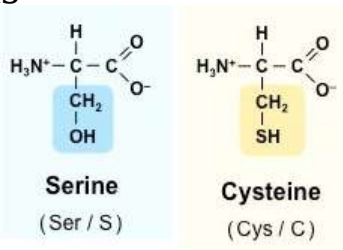
- R-group differ from one amino acid to another
- All amino acids used to build our protein are in the ***L-configuration***

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

According to the side chain; amino acids are classified into 4 groups

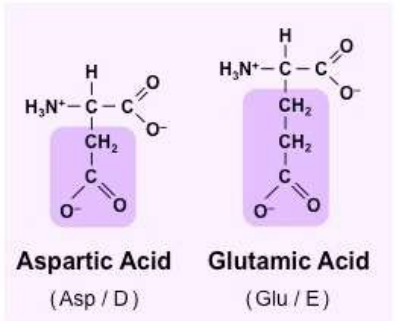
1. Nonpolar Amino acids (R→ Non-polar)
2. Polar uncharged Amino acids (R→ polar, not charged)
3. Acidic Amino acids (R→ acidic, -ve charge)
4. Basic Amino acids (R→ Basic, +ve charge)

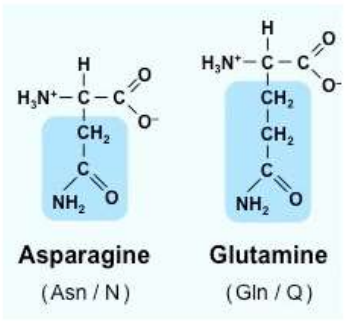
- Val, Leu and Ile are called ***Branched*** amino acids
- Trp, Phe, Tyr are ***aromatic*** amino acids
- Ser (OH) and Cys (SH)

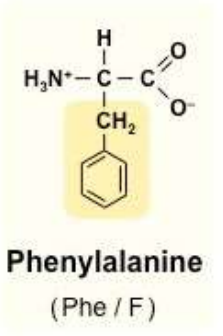


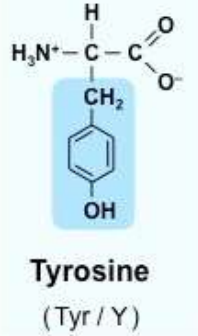
- Cysteine is synthesized from Methionine and both **contain S**
- Tyrosine is synthesized from Phenylalanine by Hydroxylation

- Add amine to Asp → Asn
- Add amine to Glu → Gln









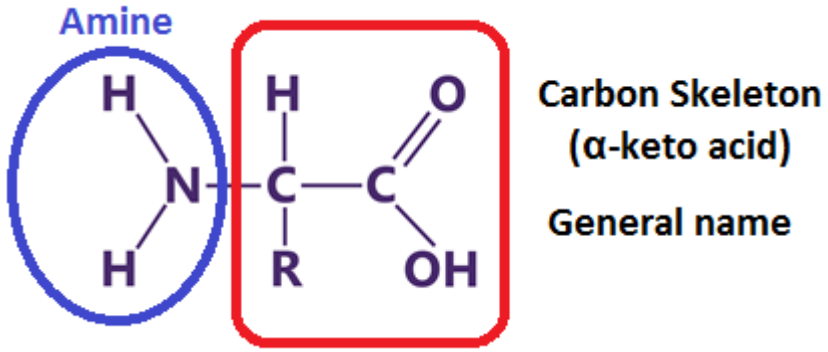
- There are many non-protein amino acids (not found in proteins) such as Ornithine, Citrulline, and Sarcosine

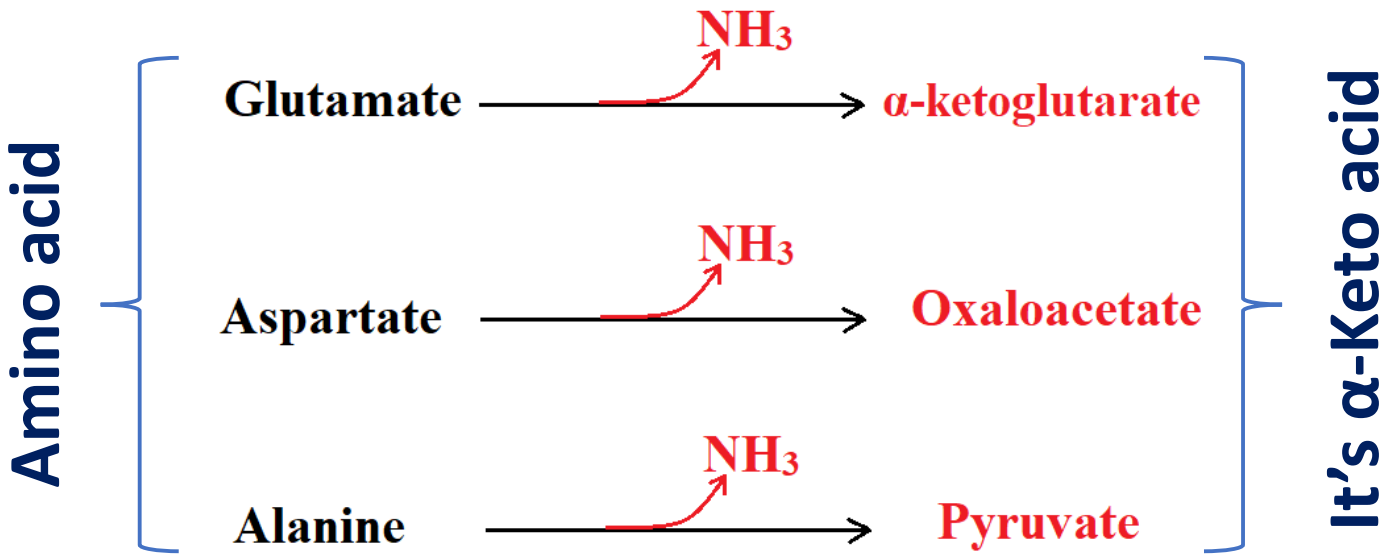
Amino acids is used to build our proteins and to synthesize Nitrogen-containing compounds such as Heme, Nucleotides, Neurotransmitters, Carnitine, Choline, vitamins, non-protein amino acids…..
Unlike carbohydrate and fat; amino acids cannot be stored in the body so any excess amino acids in diet will be degraded

Amino acids Catabolism

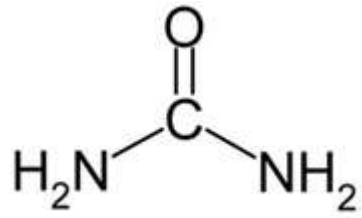
During catabolism; we deal with the amino acid as 2 parts:

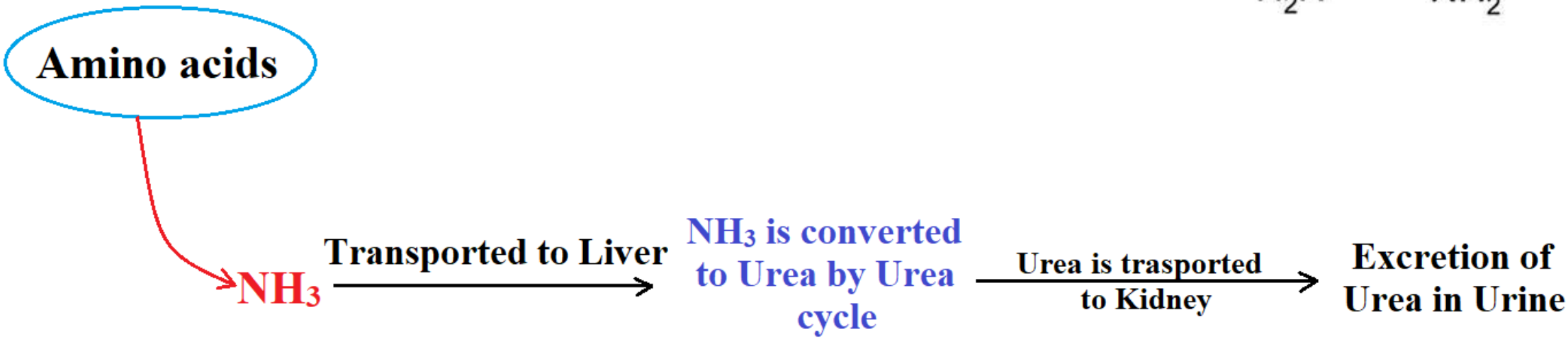
- α-amino group
- The rest called the Carbon skeleton or ***α-keto acid***





- During amino acid catabolism the α-amino group is released as ammonia (NH_3) = Ammonium (NH_4^+)
- Ammonia is CNS toxic, so ammonia is converted to less toxic compound called **Urea** by Urea cycle
- Urea is Excreted in Urine
- Urea cycle occur mainly in **Liver cells**, very low level in kidney and Brain





Some Terms you should know

Transamination: transfer of amine group from one substance to another

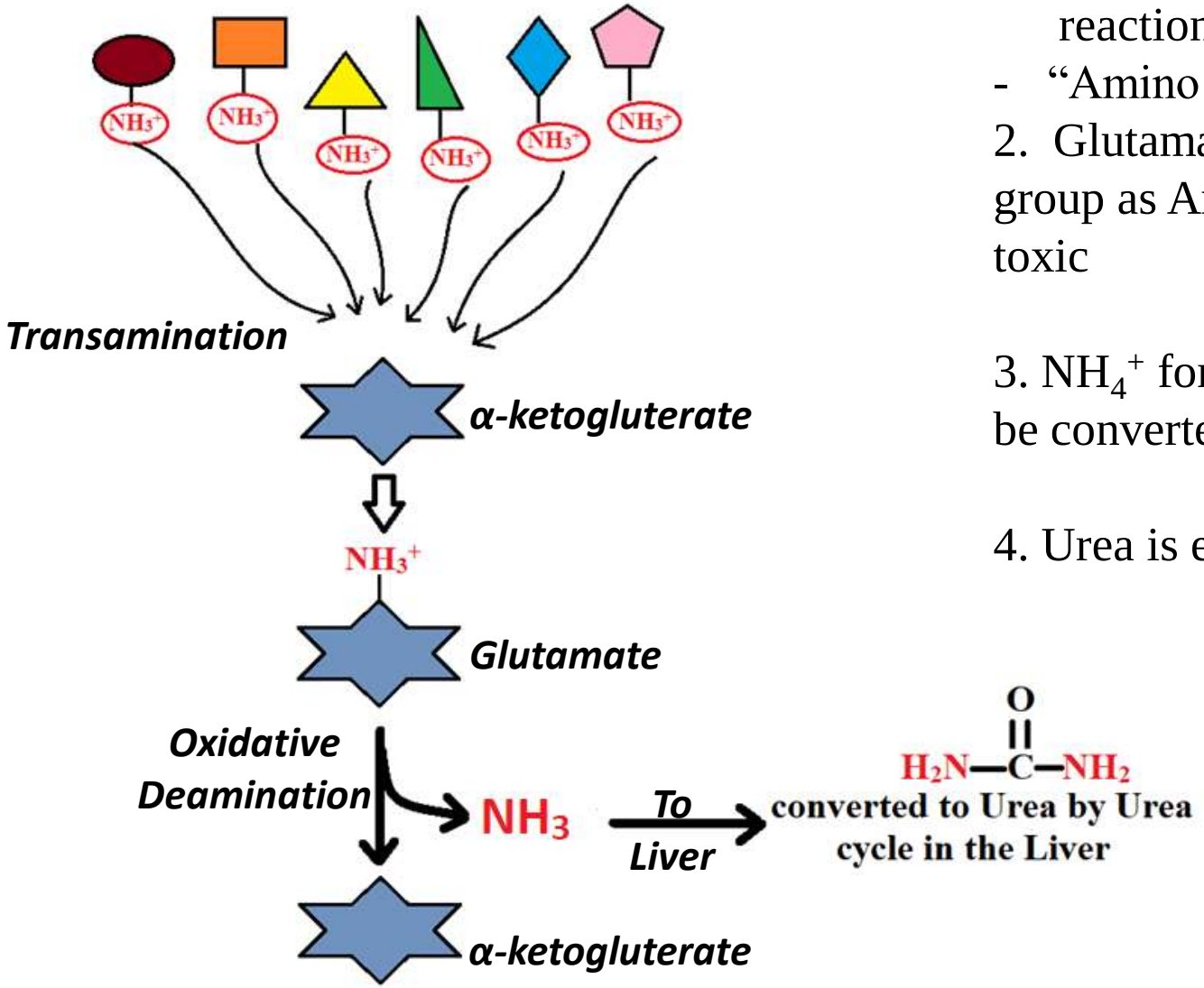
Deamination: Release of amine group as NH_3

Amination: addition of NH_3 to an Organic compound

How to release the α-amino group of amino acids?

There are many ways:

1. Transamination reaction (major)



1. The amino group of amino acids is transferred to a common acceptor which is α-ketogluterate forming Glutamate in a reaction called ***Transamination***

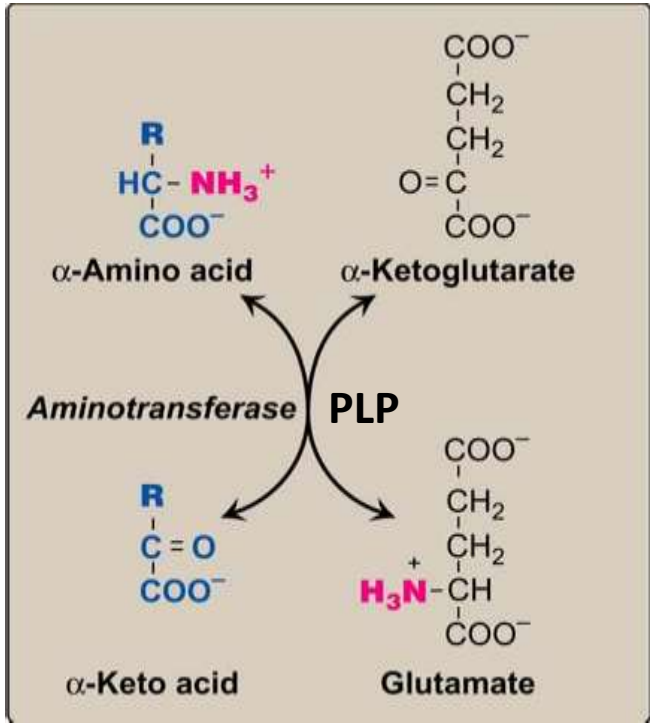
- "Amino groups are funneled in Glutamate"

2. Glutamate is ***Oxidatively deaminated***; releasing the amino group as Ammonium NH_4^+ (Ammonia NH_3) which is CNS toxic

3. NH_4^+ formed outside liver is transported to the liver cells to be converted to less toxic compound called ***Urea*** by Urea cycle

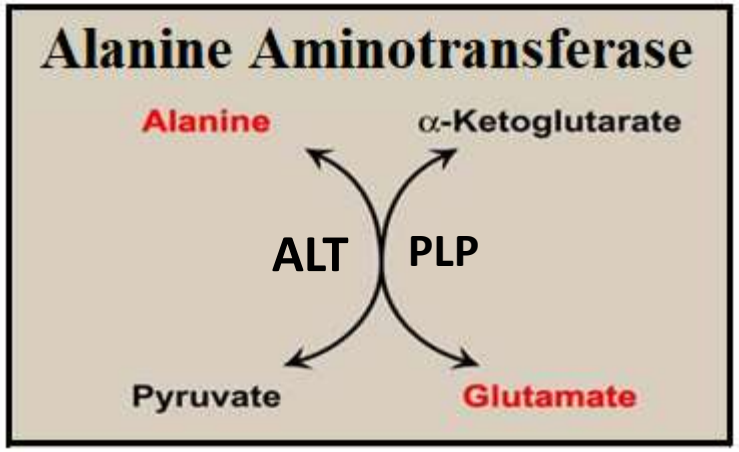
4. Urea is eliminated in the Urine

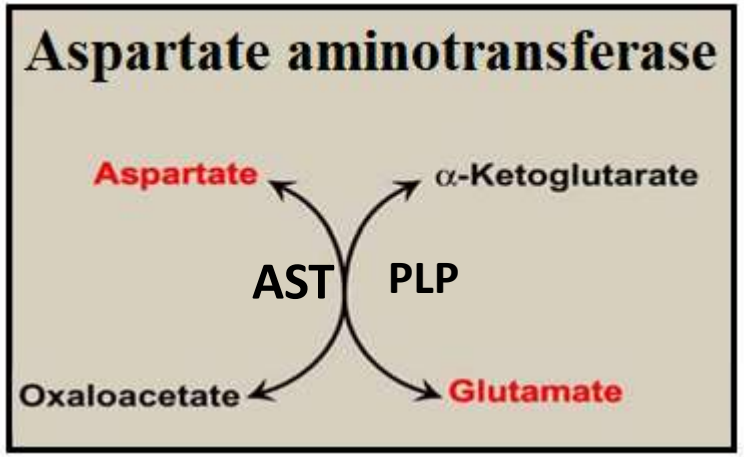
- Transamination is catalyzed by Enzymes called ***Aminotransferases*** also called in the past ***Transaminases***
- They are specific, each amino acid has it's own Amino-transferase **except Lysine and Threonine**
- These enzymes require Coenzyme called **Pyridoxal Phosphate (PLP**), the active form of Vit B6 (Pyridoxine)

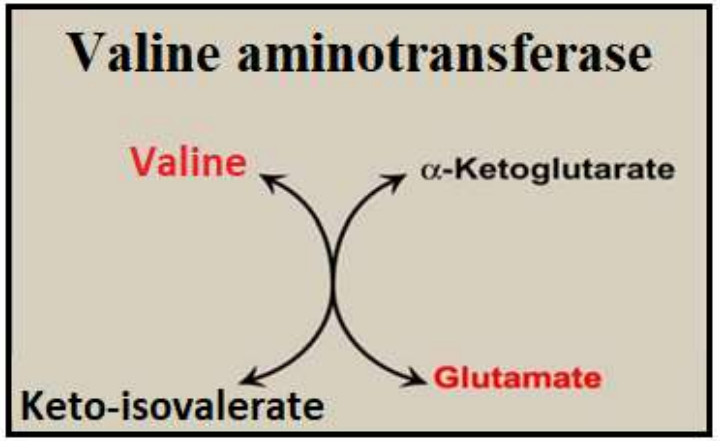


The main acceptor for these transaminases is **α-ketoglutarate** forming **Glutamate**
So the α-amino groups of amino acids are funneled/ Sinked to Glutamate
* The most important Aminotransferases that you should memorize are:

- ***Alanine Aminotransferase (ALT)*** also called Pyruvate –Glutamate Transaminase
- ***Aspartate Aminotransferase (AST)*** also called Oxaloacetate –Glutamate Transaminase



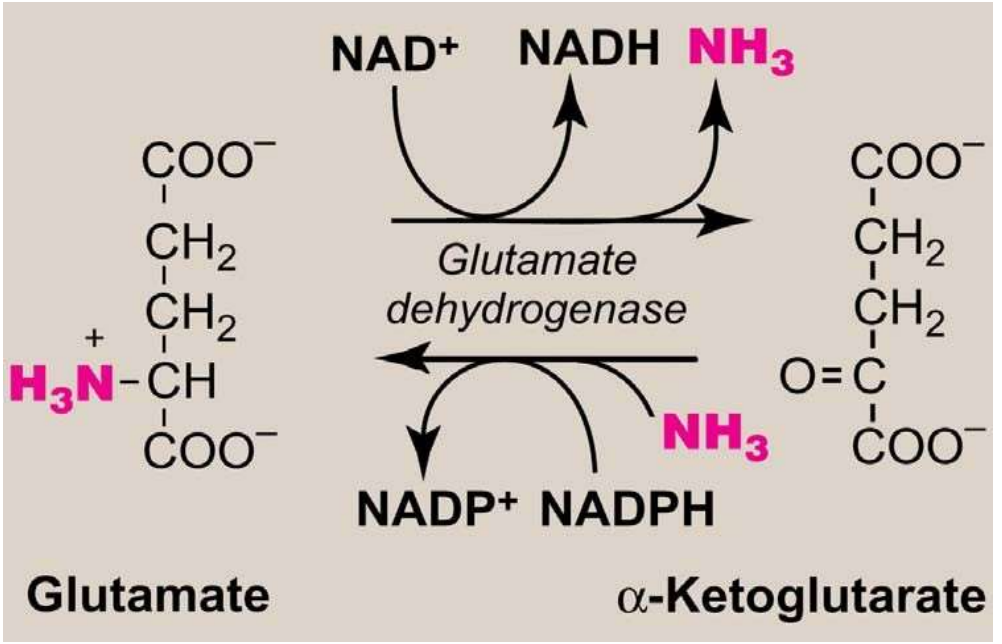




these Enzymes are reversible; the direction of the reaction depends whether you want to synthesize or degrade amino acids

Now,
The Next step is **Oxidative Deamination** of Glutamate catalyzed by **Glutamate dehydrogenase (GDH)** results in the liberation of the amino group as **free ammonia (NH_3)** and α-ketoglutarate

This Enzyme is reversible, and the direction depends whether you want to degrade or synthesize amino acids



During amino acids disposal: تكسير
Oxidative Deamination of Glutamate releasing NH_3 and α-Ketoglutarate
In this direction NAD^+ is reduced to NADH

During amino acid synthesis:
Reductive Amination binding Free NH_3 to α-Ketoglutarate forming Glutamate (ammonia Fixation)
In this direction NADPH is oxidized to $NADP^+$

Ammonia Fixation: binding free ammonia (NH_3) to an organic compound

Direction of Glutamate dehydrogenase depends on: the relative concentrations of glutamate/ α-ketoglutarate, and the of $NADH/NAD^+$ and $NADPH/NADP^+$.

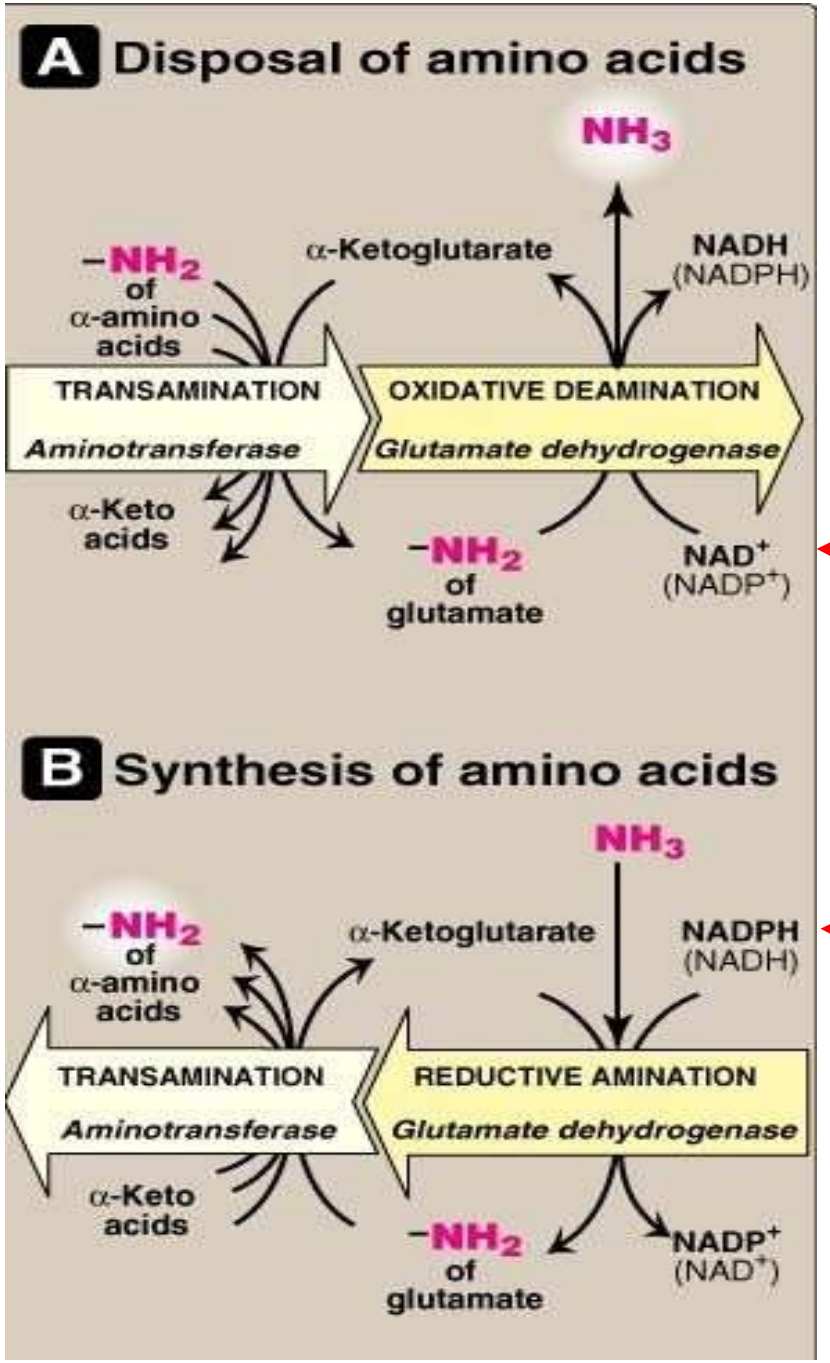
النسبة بين

Disposal:

1. Transamination from amino acids to α-ketoglutarate forming Glutamate
2. Oxidative deamination of glutamate to release NH_3 that is converted to Urea for excretion

Synthesis:

1. Reductive amination of α-ketoglutarate forming Glutamate
2. Transamination from Glutamate to specific α-ketoacids forming specific amino acids



← Main coenzyme

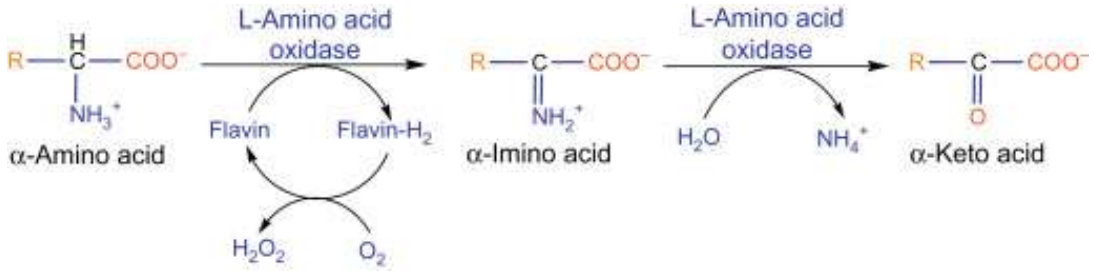
← Main coenzyme

Other methods to release the α-amino group from amino acids?

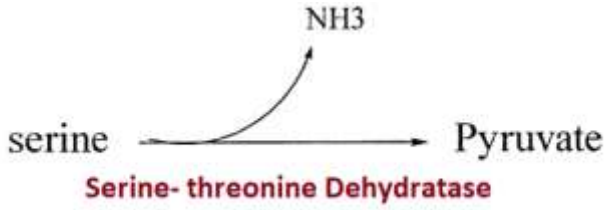
2. Oxidative deamination of the amino acids by ***L-amino acid Oxidase*** (all amino acids except Serine and Threonine)

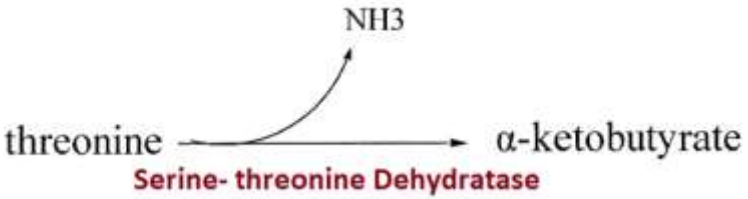
L-amino acid oxidase is Flavin (FAD) containing Enzyme
Work in 2 step:

1. Oxidation of the L-amino acid forming α-Imino-acid (FAD is reduced to $FADH_2$) the 2H are transferred to O_2 forming H_2O_2
2. Deamination of the α-Imino-acid releasing NH_4^+ and the α-keto-acid



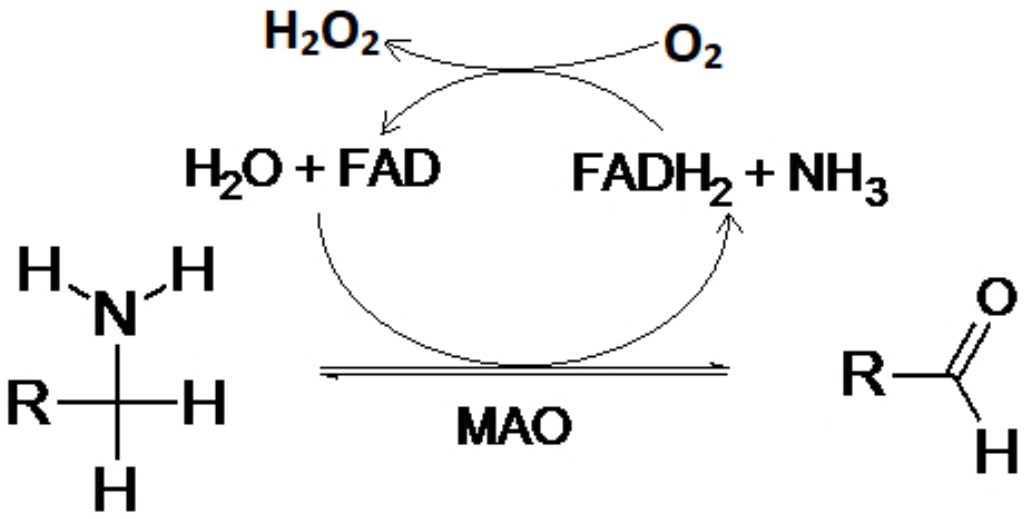
3. non-oxidative Deamination by ***pyridoxal-dependant Dehydratases*** which release the α-amino group of Serine, Threonine and Cysteine





4. monoamine oxidase (MAO): present in the liver, catalyzes the release amino group of wide variety of physiologically important amines such as epinephrine, norepinephrine, dopamine, and serotonin.

1. Oxidation (FAD is reduced to $FADH_2$) the 2H are transferred to O_2 forming H_2O_2
2. Deamination releasing NH_3



Excess nitrogen (Ammonia) is CNS toxic and must be eliminated from the body

- Birds eliminate N as Uric acid
- Fish eliminate N as is in the form of ammonia
- Mammals (including human) eliminate excess N as Urea

Now Ammonia produced in the Extrahepatic tissue must be transported to liver cells to be converted to Urea, how body your body cells transport ammonia to Liver or Kidney ***safely***?

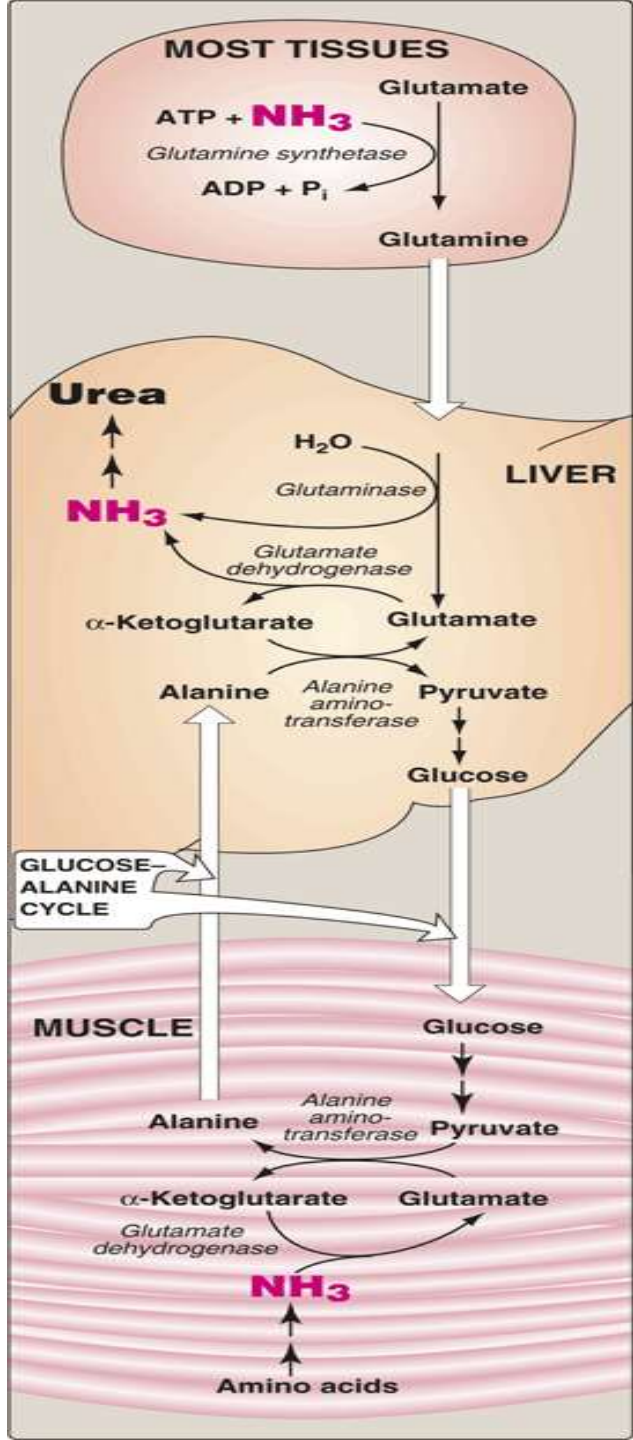
Transport of ammonia to the liver or kidney

NH_3 is transported from peripheral tissues to liver or kidney for conversion to urea.
Two mechanisms for ammonia transport **Safely**:

1. ***By glutamine synthetase*** that combines NH_3 with Glu to form Gln
- The process called ***Ammonia Fixation***, Found in most tissues
- Requires energy
- The resulting glutamine is transported in the blood to the liver to be cleaved by **glutaminase** to produce glutamate and free ammonia.
- Then glutamate is oxidatively deaminated by GDH to second NH_3 and α-ketoglutarate

2. By transamination of pyruvate to form alanine by ALT
- Primarily in muscles
- Alanine is transported by the blood to the liver to be converted to pyruvate by transamination.
- Then glutamate is oxidatively deaminated by GDH to NH_3 and α-ketoglutarate
- Pyruvate can be used in gluconeogenesis (glucose-alanine cycle)

- ***Muscles use both pathway***
- ***The most abundant amino acid in the blood is Glutamine***



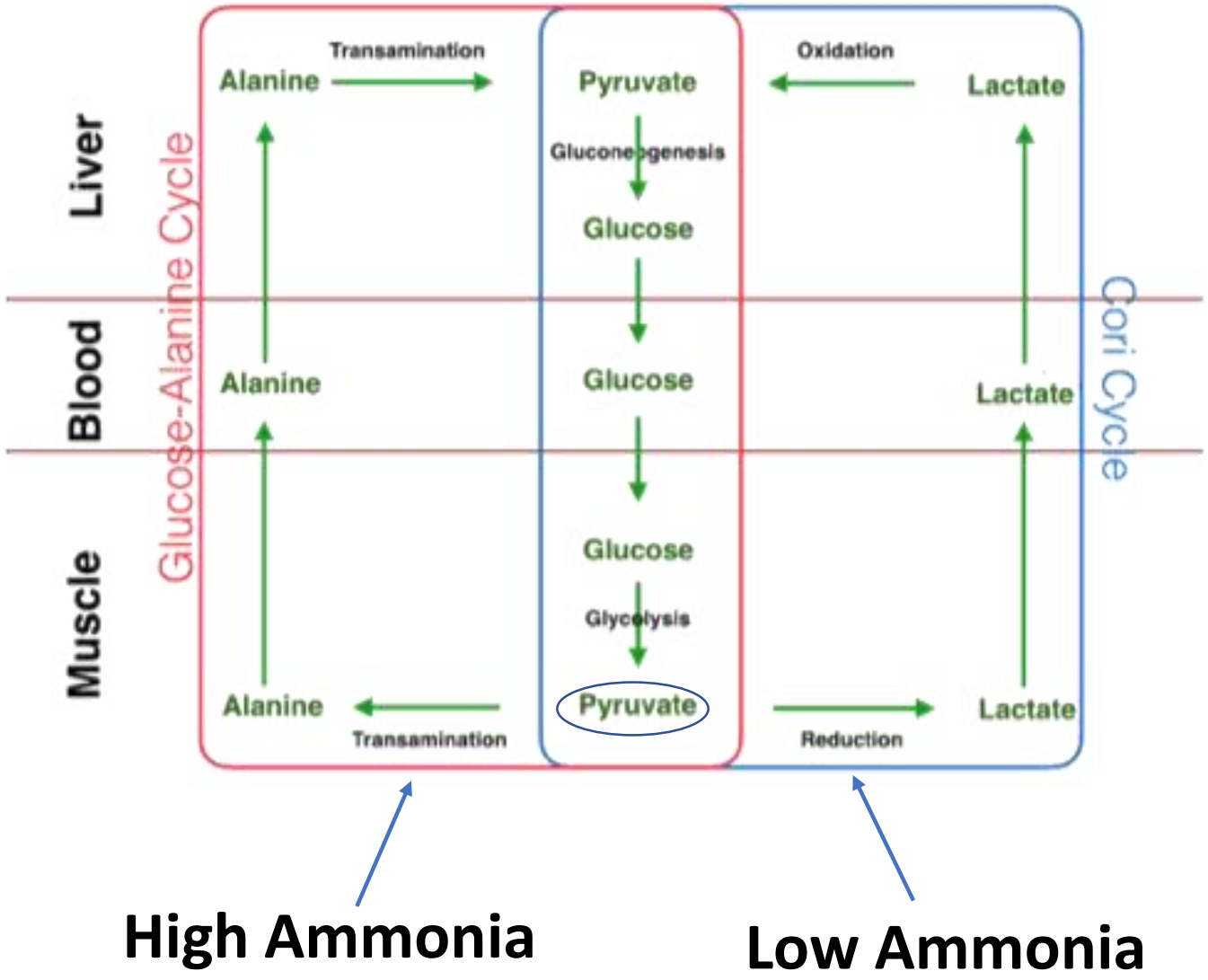
Cori cycle Vs Glucose alanine Cycle

كلاهما تحدث بين العضلات والكبد

in Cori cycle: Pyruvate in muscle is reduced to Lactate then lactate is transported to liver for glucose synthesis and then glucose is transported back to muscles

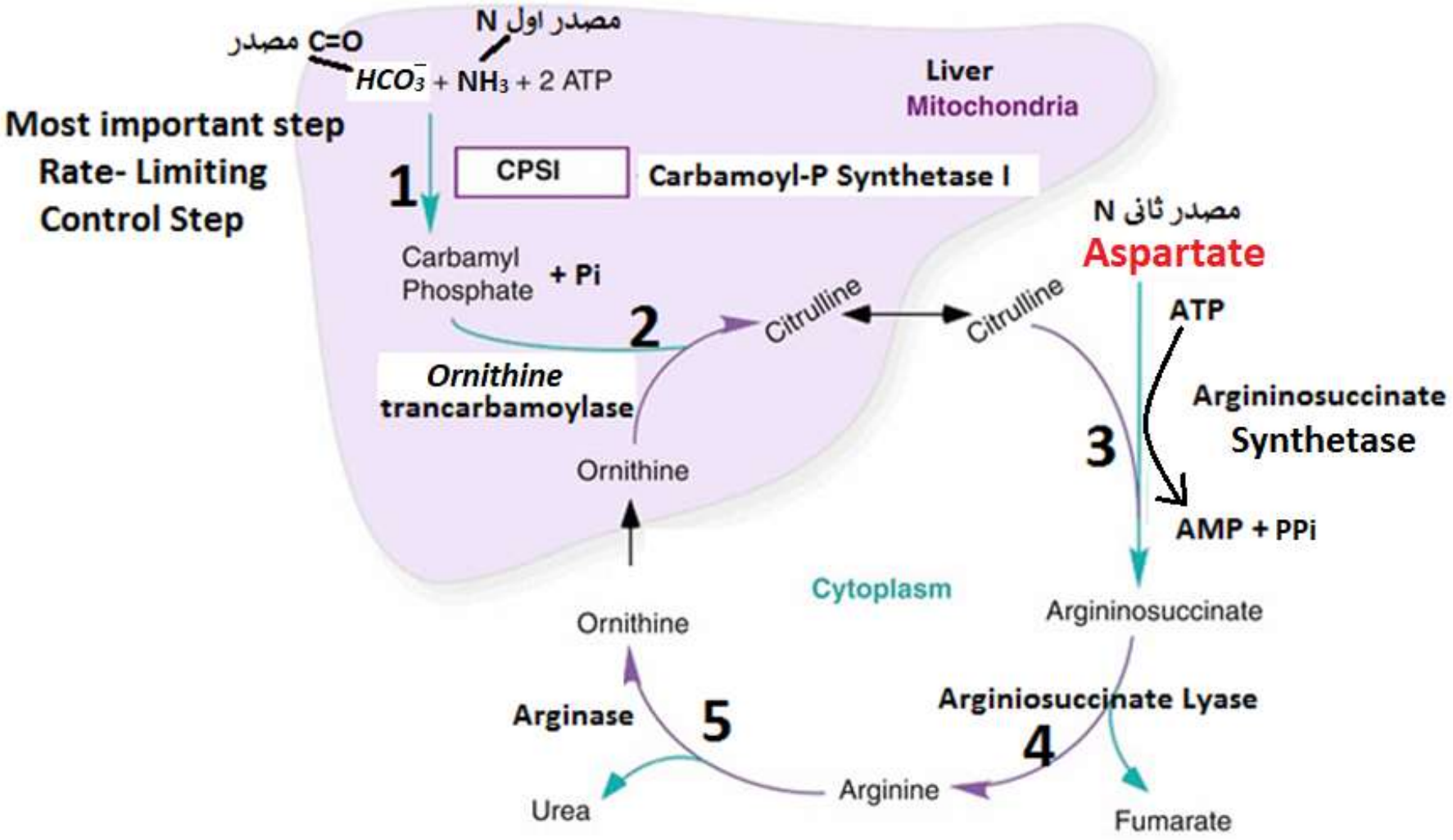
In Glucose alanine Cycle: Pyruvate in muscle is transaminated to alanine then alanine is transported to liver alanine in liver by transamination give pyruvate for glucose synthesis and then glucose is transported back to muscles

- If ammonia level in muscle is High → Glucose-Alanine cycle is preferred
- If ammonia level in muscle is Low → Cori cycle is preferred



Urea Cycle: occurs mainly in liver cell

NH_3 → to liver as *Glutamine or Alanine* → Urea Cycle → Urea → Kidney → Urine



Urea Cycle in Words:

The first 2 steps occurs in the Mitochondria, the rest of steps occurs in the cytosol

Step1: Bicarbonate (source of C=O) is condensed (يرتبط) with Ammonia (source of 1st N) forming Carbamoyl which is phosphorylated to carbamoyl-P, this step is catalyzed by ***Cabamoyl-P Synthestase I*** , this step consume 2 ATP

This step is the rate limiting step (Control Step) of urea cycle

Step 2: Carbamoyl is condensed with an amino acid called ***Ornithine*** releasing the phosphate group and forming larger amino acid called ***Citrulline***, this step catalyzed by ***Ornithine transcarbamoylase***

Step3: Citrulline get out of the mitochondria to the cytosol, where it condensed to Asp (source of the 2nd N) forming ***Argininosuccinate***, this step consume ATP to AMP + PPi catalyzed by ***Argininosuccunate Synthetase***

Step4: Fumarate is removed from Argininosuccinate forming ***Arginine***, this step is catalyzed by ***Argninosuccinate Lyase***

Step5: finally Arginine is hydrolyzed to ***Urea and Ornithine*** which return to Mitochondria in exchange with Citrulline by Translocase (Antiporter), this step is catalyzed by ***Arginase*** which found **mainly in the Liver cells**, that's why urea is produced mainly in the Liver

After that urea is transported to the kidneys to be eliminated with urine

Step1: feeder reaction
Steps 2,3,4, and 5 are cycle reactions

Overall stoichiometry of the urea cycle

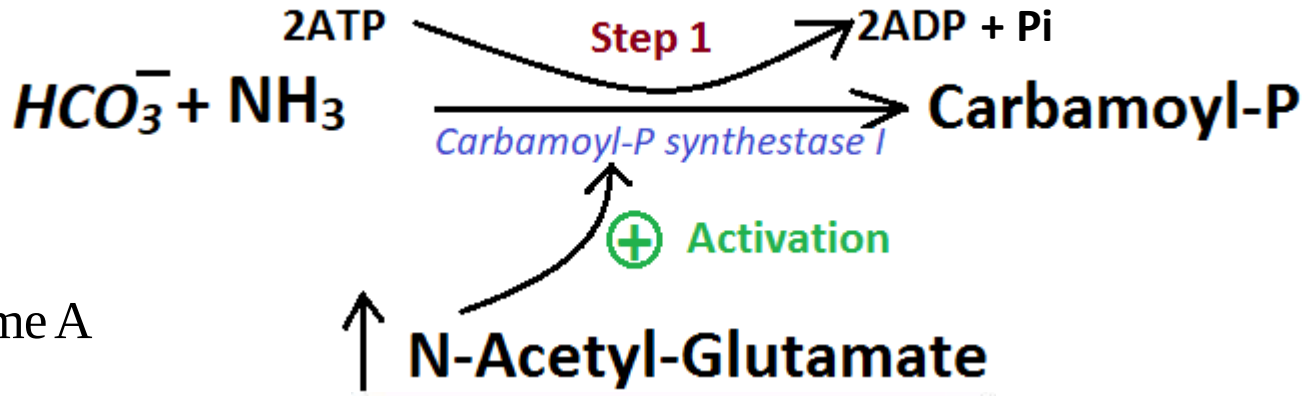
The synthesis of urea is irreversible, with a large, negative ΔG

For each urea molecule:

1. 4 ATP equivalents are consumed
2. One nitrogen of the urea molecule is supplied by free NH_3(by glutaminase or GDH)
3. The other nitrogen is supplied by aspartate.
4. The C and O of urea are derived from CO_2 = HCO3$^-$

Control of Urea Cycle

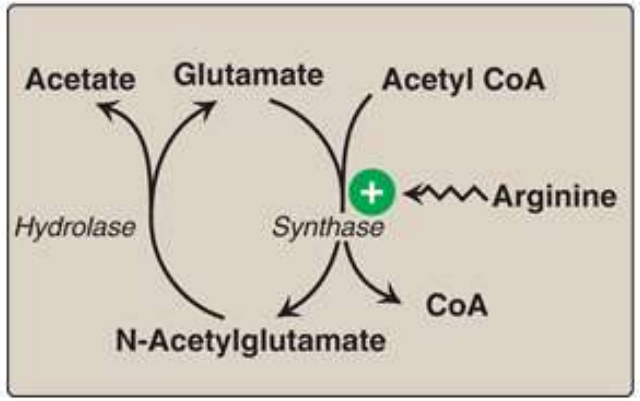
N-Acetylglutamate is an essential **activator** for **carbamoyl phosphate synthetase I (CPS I)** (the rate-limiting step in the urea cycle)



N-Acetylglutamate is synthesized from acetyl coenzyme A and glutamate by ***N-acetylglutamate synthase***

Arginine is an **activator** for N-Acetylglutamate synthesis

Note: CPS II (Carbamoyl-P synthetase II) found in cytosol and its important for Pyrimidine synthesis (Uracil, Cytosine, and Thymine)



Genetic deficiency can affect any of the 5 urea cycle enzymes leading to Hyperammonemia (high plasma ammonia level over 4 x 10^{-5}M)

Hyperammonaemia:

- CNS toxic and may cause mental retardation
- Ammonia added to α-ketoglutarate forming Glutamate, so α-ketoglutarate (TCA cycle intermediate) will be depleted

• Arginase deficiency disease (most serious) result in progressive spastic tetraplegia and mental retardation and Argininemia (high plasma Arg level)

Amino acids can be Classified into

Essential amino acids: amino acids that we (human) cannot synthesize and must obtained from Diet

PVT TIM HALL

Phenylalanin
Valine
Tryptophan
Threonine
Isoleucine
Methionine
Histidine
Arginine
Leucine
Lysine

Not necessarily the one letter abbreviation of the these amino acids

Non-essential amino acids: amino acids that we (human) can synthesize them

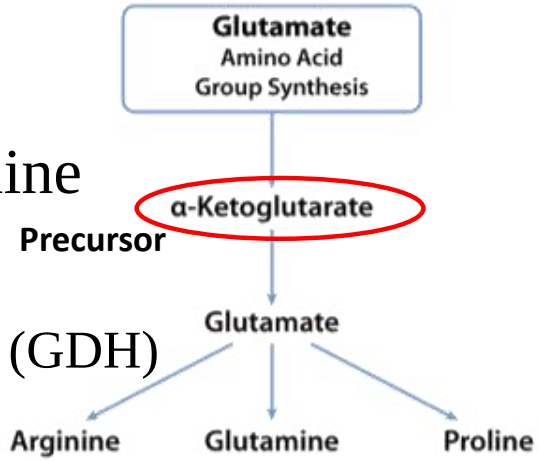
Glycine
Alanine
Proline
Serine
Cysteine
Tyrosine
Asparagine
Aspartate
Glutamine
Glutamate

- Tyrosine is synthesized from phenylalanine. Cysteine is synthesized from Methionine so if inadequate intake of phenylalanine and Methionine in diet then Cysteine and Tyrosine become essential that's why we call Tyrosine and Cysteine called ***sparing amino acids***
- ***Semi-essential amino acids:*** they are essential in children and important for growth but become nonessential in adult (synthesized in adults) such as histidine and Arginine

Synthesis of amino acids

According to the precursor, amino acids are grouped into 6 families:

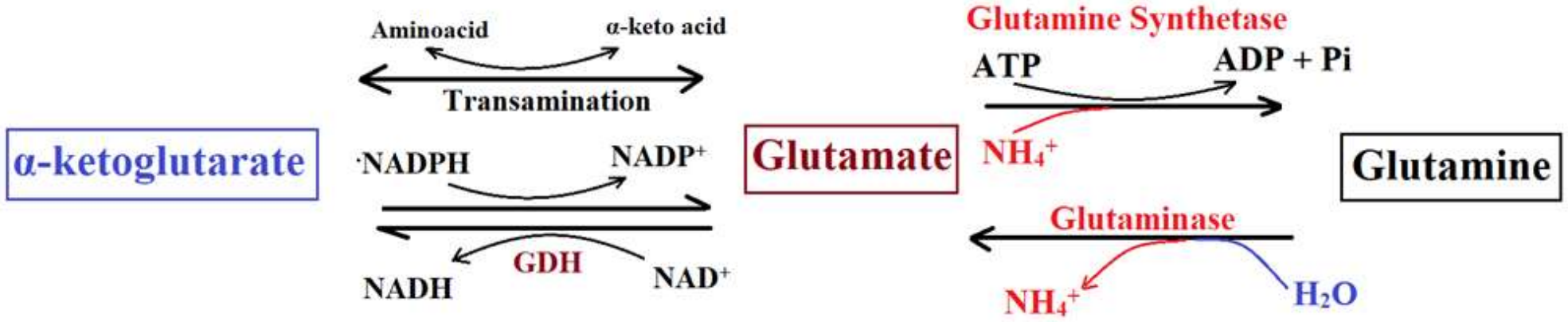
1. α-ketoglutarate family
2. Serine family
3. Aspartate family
4. Aromatic family
5. Pyruvate family
6. Histidine family



1. α-ketoglutarate family: include Glutamate, Glutamine, Arginine and proline

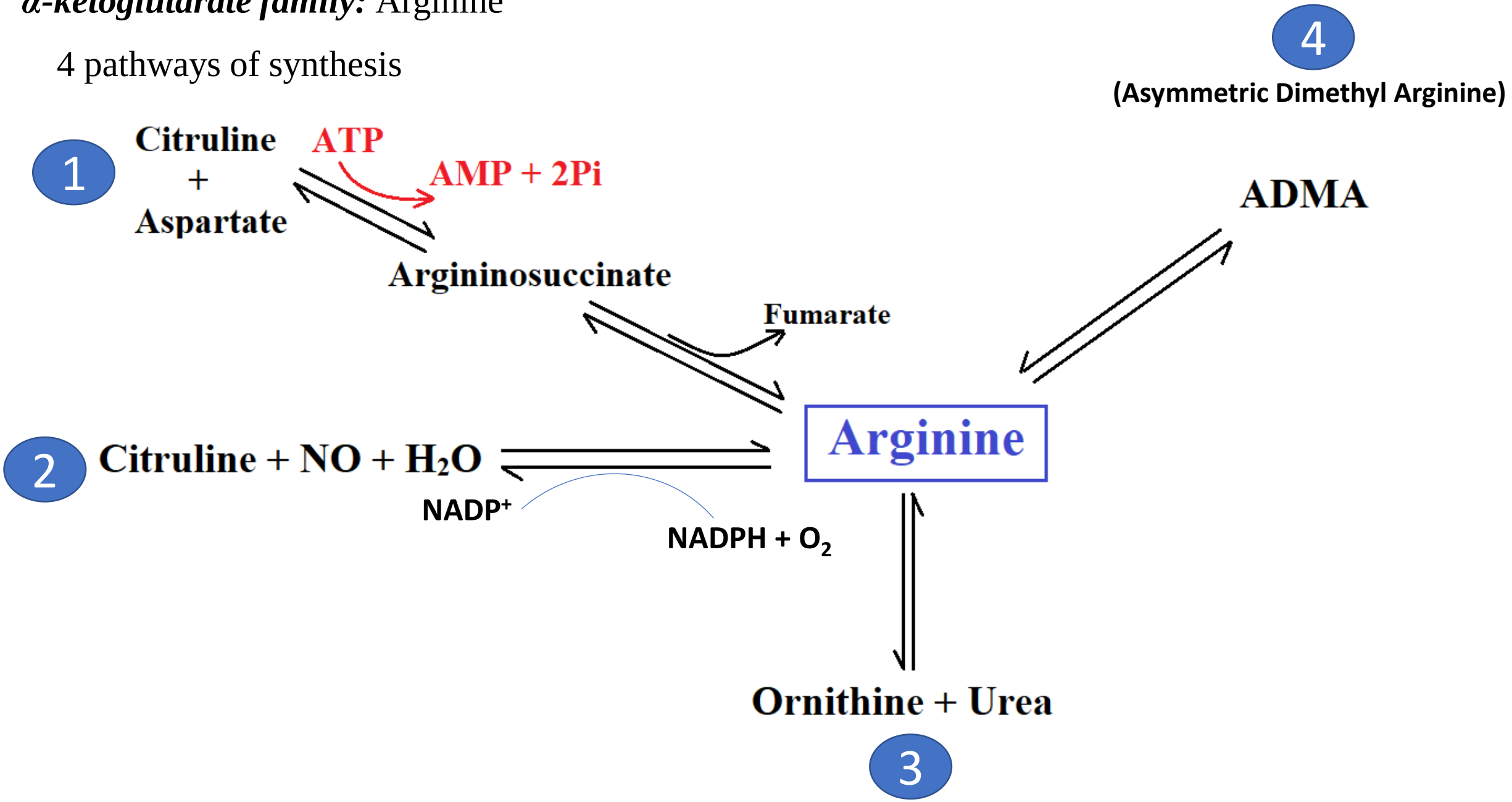
α-ketoglutarate family: Glutamate and Glutamine

Glutamate is synthesized from α-ketoglutarate by transamination or by reductive amination (GDH)
Glutamine is synthesized by amination of Glutamate (Glutamine Synthetase)
Glutamine is hydrolyzed to Glutamate and NH_4^+ by Glutaminase

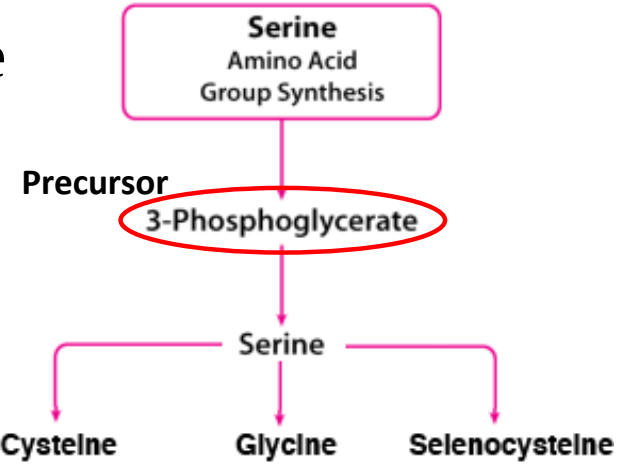


α-ketoglutarate family: Arginine

4 pathways of synthesis



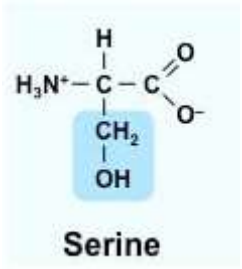
2. **Serine family:** includes Serine, Glycine, Cysteine, and Selenocysteine

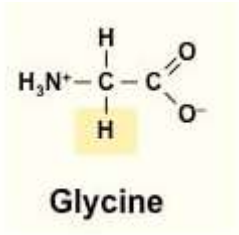


Serine family: Serine

Serine can be synthesized from a Glycolysis intermediate ***3-phosphoglycerate***

Serine family: Glycine

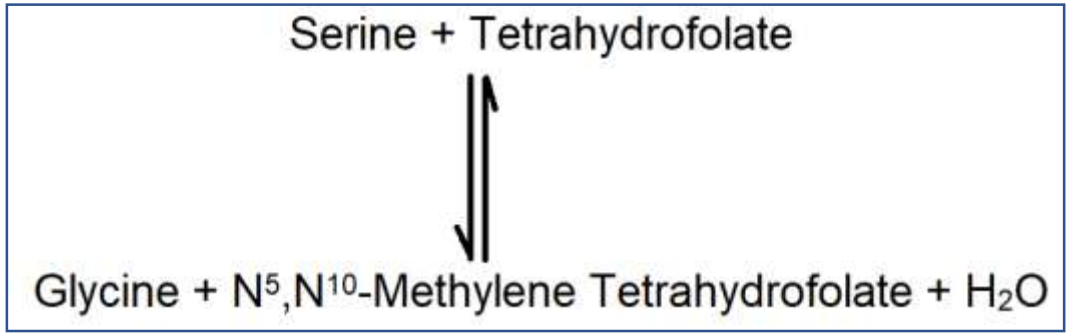




The difference between Serine and Glycine is **One Carbon unit**

So glycine can be synthesized from serine by removing this carbon unit from the side chain

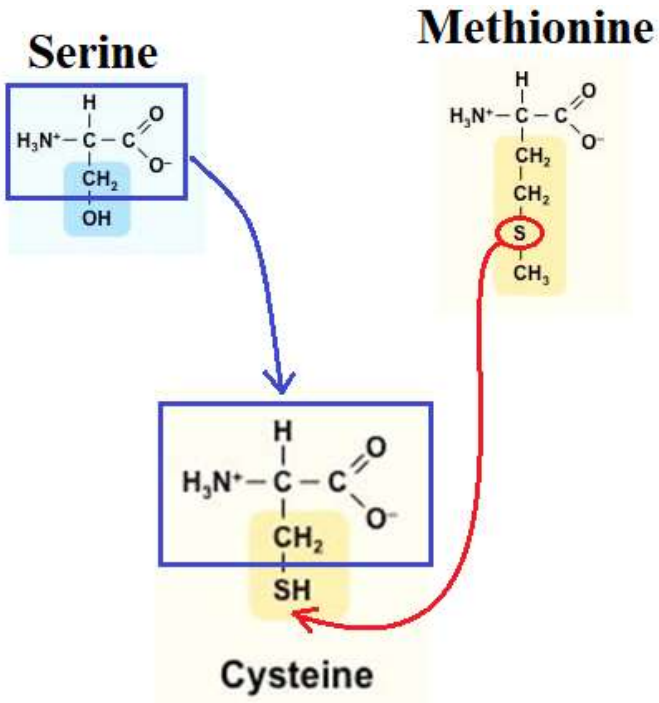
The acceptor of this 1C unit is Tetrahydrofolate (THF) the active form of folate (B9) become N^5,N^{10}-Methylene THF



This reaction is reversible, so Serine can be synthesized from Glycine using N^5,N^{10}-Methylene THF as one C unit donor

Serine family: *Cysteine*

The backbone of Cysteine is derived from Serine, and the Sulfur (S) atom is derived from Methionine



Increased level of Homocysteine is associated to cardiovascular diseases (Myocardial Infarction and Stokes)

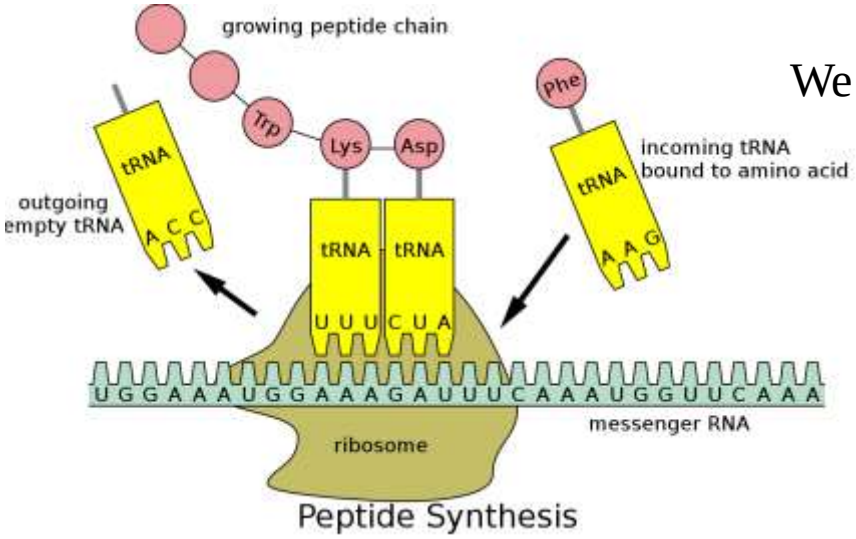
Genetic deficiency of this enzyme leads to Homocysteinurea, increased plasma level of Cystathionine and increased risk of cardiovascular diseases
For these patients Cysteine become essential amino acid

Serine family: Selenocysteine

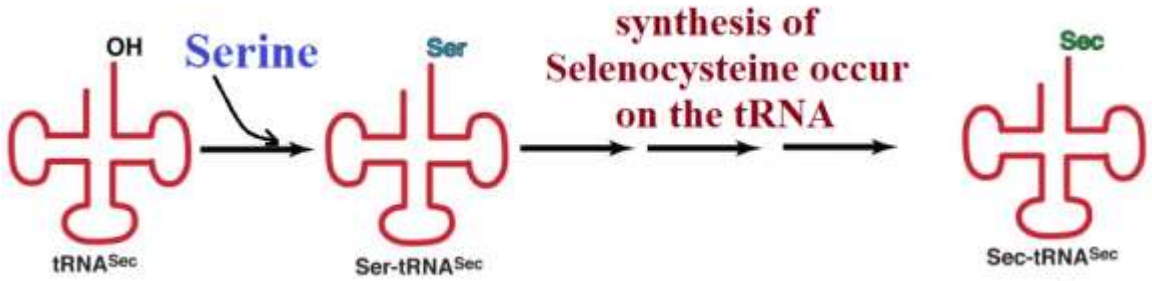
- Its important for many anti-oxidant enzymes
- Thus uncommon amino acid is incorporated to the polypeptide chain during the synthesis, but not specified directly by the genetic code

So, how its incorporated to the polypeptide??

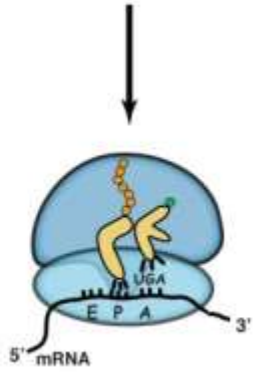
tRNA: transfer RNA responsible for transferring the correct amino acids to their corresponding codon in the mRNA



We have specific tRNA that can bind to the stop codon **UGA** under special conditions



1. Serine bind to this special tRNA
2. Serine is converted to Selenocysteine on the tRNA
3. This tRNA bind to the stop codon UGA on the mRNA

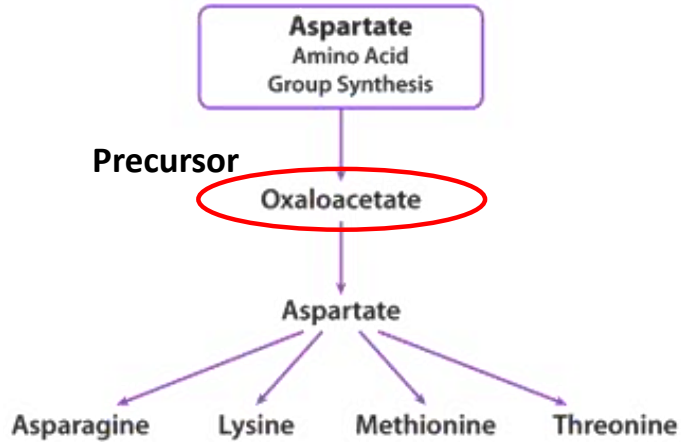


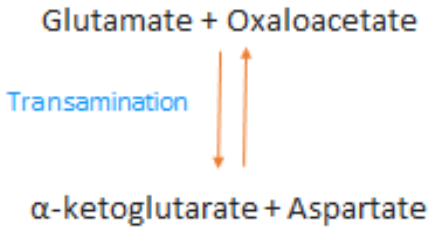
3. ***Aspartate family:*** include Aspartate, Asparagine, Lysine, Methionine, and Threonine

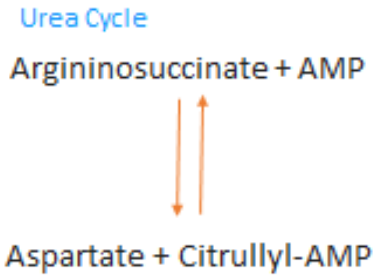
Precursor: Oxaloacetate

Aspartate family: Aspartate

- Aspartate can be synthesized for Oxaloacetate by transamination reaction
- Aspartate can be synthesized from Urea cycle intermediate Arginosuccinate

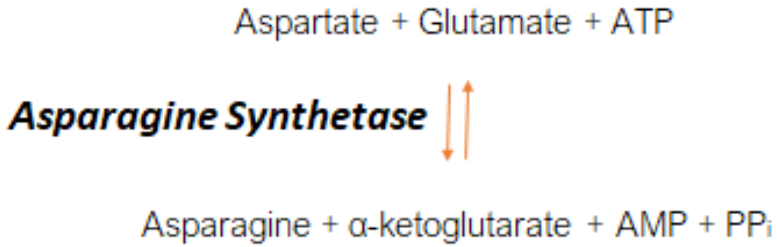




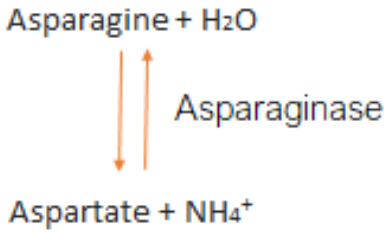


Aspartate family: Asparagine

- Asparagine is synthesized from Aspartate by transamination reaction catalyzed by ***Asparagine synthetase*** (Transaminase) using Glutamate as source of amine and consuming ATP to AMP



- Asparagine can be hydrolyzed to Aspartate and NH_4^+ by ***Asparaginase***

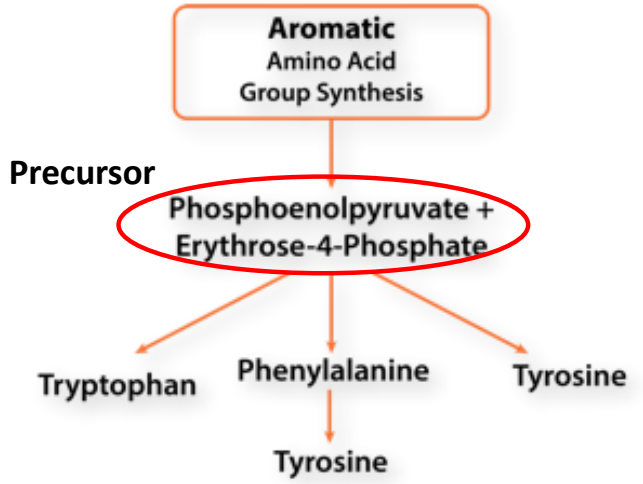


This can be considered third pathway of Aspartate synthesis
Asparagine is the only Amino acid in Aspartate family that can give Aspartate

4. Aromatic family: include Tryptophan, Phenylalanine, and Tyrosine

Precursor: Phosphoenolpyruvate + Erythrose-4-P

- Shikimic Acid and Chorismic Acid are intermediates during the synthesis



Aromatic Family

Tryptophan

Melatonin
هرمون النوم
sleep and circadian rhythm

Serotonin
هرمون السعادة
Mood and appetite

Niacin (B3)
NAD+, NADP+

Auxins
Cell division

Phenylalanine

Hydroxylation by ***phenylalanine hydroxylase***
(if deficient → phenylketonuria "PKU")

Tyrosine

Catecholamines
L-Dopa
Dopamine
Norepinephrine
Epinephrine
Neurotransmitters

Melanin
Skin and hair pigment

Thyroxines (T4 and T3)
Thyroid gland hormones

Derivative of Aromatic amino acids

Tryptophan derivatives:

- **Melatonin:** Circadian Rhythm Sensing, affect Sleep, Mood, and blood pressure
- **Serotonin:** Happy Feelings, Enhances Memory/Learning
- **Niacin** (Vitamin B_3) Derived From it NAD^+ & $NADP^+$ (Deficiency of B_3 Leads to disease called ***Pellagra***)
- **Auxins** (Indole-3-Acetic Acid Most Important one) Stimulate Cell Division and Rooting in Plants

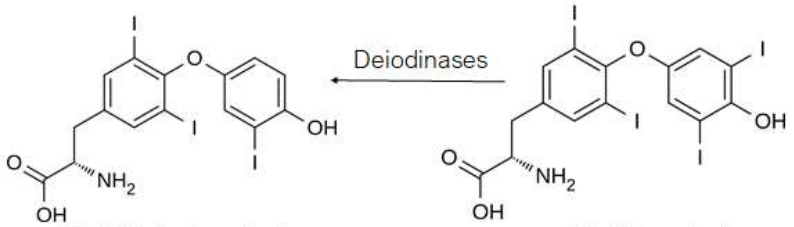
Tyrosine derivatives:

- Tyrosine is synthesized from phenylalanine by hydroxylation reaction catalyzed by ***phenylalanine hydroxylase***
- Tyrosine is nonessential amino acid if phenylalanine is available, (insufficient intake of phe → Try become essential)
- Phenylalanine hydroxylase deficiency leads to accumulation of phenylalanine which that cause mental retardation a disease called ***Phenylketonuria (PKU)*** here Tyrosine become essential amino acid
- PKU patients must restrict dietary phenylalanine throughout their lives to prevent mental retardation
- ***Aspartame (NutraSweet®)*** a sucrose substituent contain phenylalanine so should be avoided in PKU

Tyrosine is important amino acid it's the precursor of:

1. **Catecholamine:** L-dopa, Dopamine, Norepinephrine and Epinephrine
   - Dopamine deficiency leads to Parkinson disease
2. **Melanin:** skin and hair pigment
3. **Thyroxines:** Thyroid gland hormone
   - T4 has 4 Iodine (most abundant but less active form)
   - T3 has 3 Iodine (the active form)

T3 is derived from T4 by ***Deiodinases*** "Se-containing enzymes"

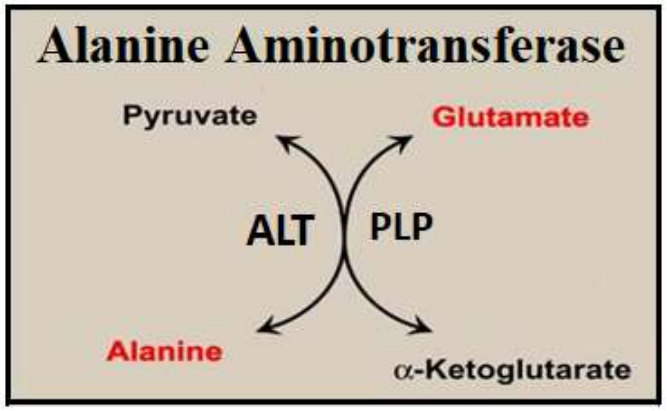


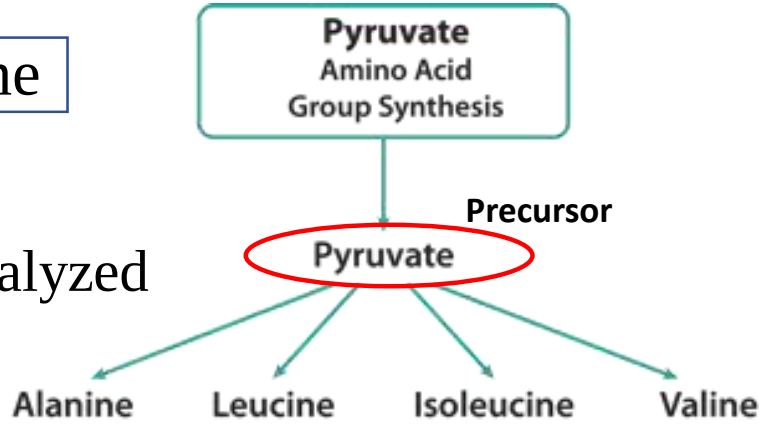
Branched chain amino acids

5. Pyruvate family: include Alanine, Leucine, Isoleucine , and Valine

pyruvate family: Alanine

Alanine can be synthesized from pyruvate by transamination reaction catalyzed by Alanine amino transferase

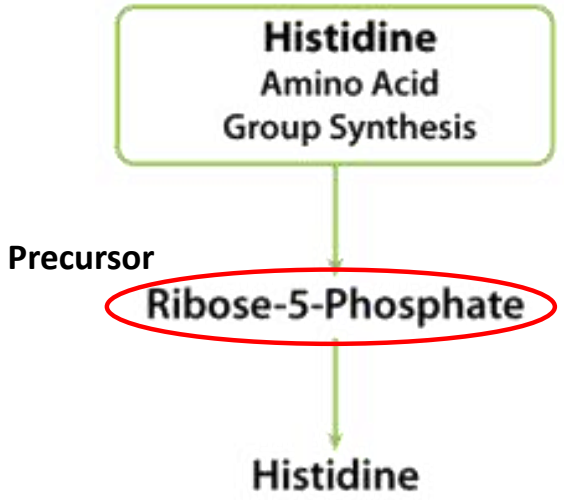




6. Histidine family: include Histidine only

Precursor: Ribose-5-P

- Ribose-5-Phosphate and PRPP "phosphoribosyl-pyrophosphate" are common intermediate in nucleotides and Histidine synthesis
- **Overlaps Nucleotide Metabolism**

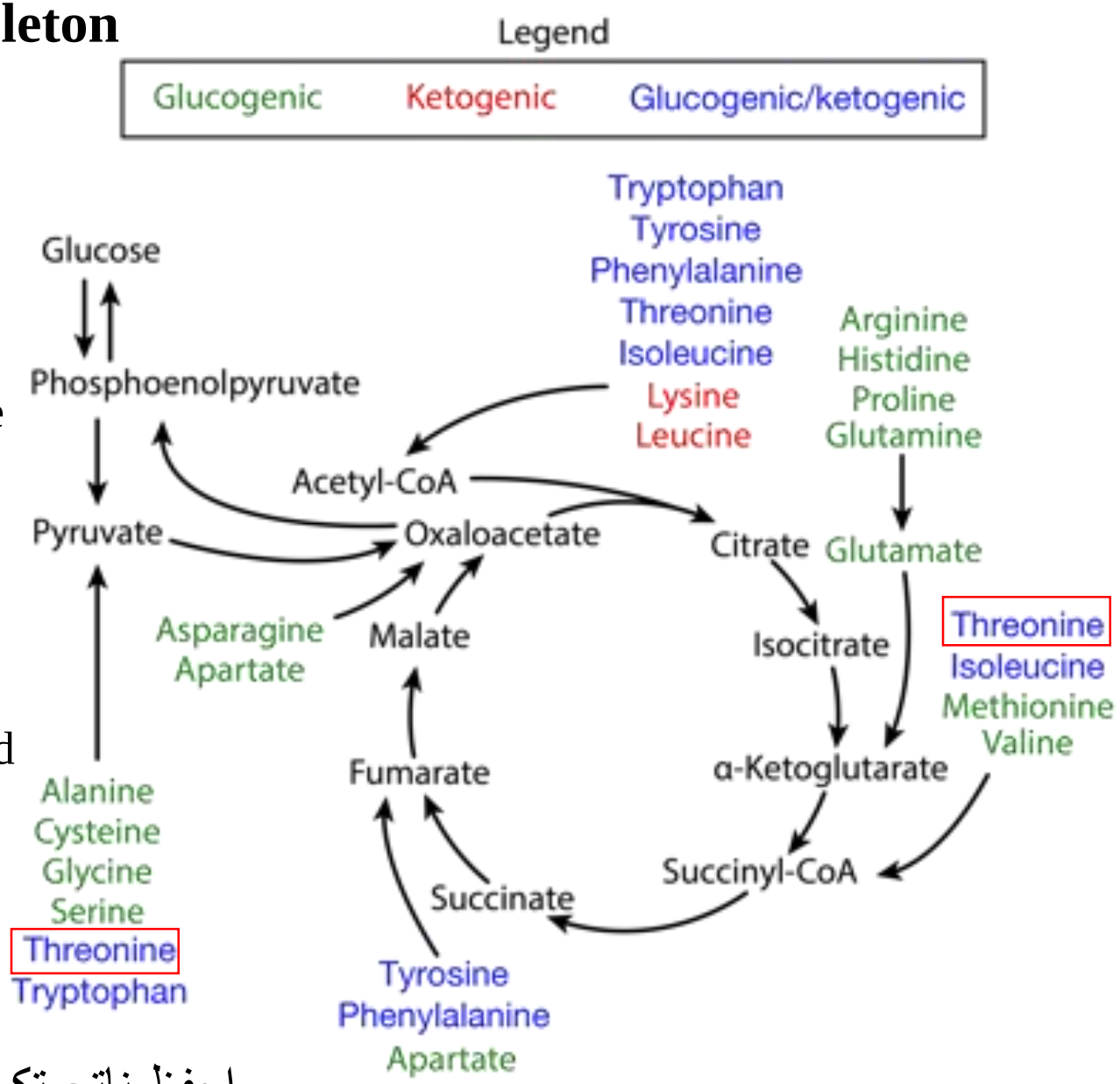


The product of the amino acid's Carbon skeleton

- If the carbon skeleton of the amino acid produce pyruvate or TCA-cycle intermediate → can be used to synthesize Glucose → ***Glucogenic amino acids***

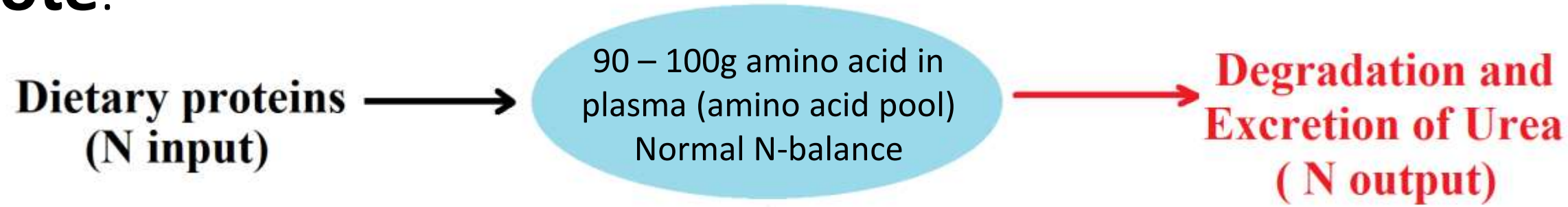
- - If the carbon skeleton of the amino acid produce Acetyl-CoA → cannot be used to synthesize Glucose and can be used to synthesize Ketone bodies → ***Ketogenic amino acids (Lysine and Leucine)***

- - If the carbon skeleton of the amino acid produce pyruvate or TCA-cycle intermediate in addition to Acetyl-CoA→ can be used to synthesize Glucose and Ketone bodies → ***Mixed both glucogenic and ketogenic amino acids (Aromatic + Thr + Ile)***



احفظ ناتج تكسير الهيكل الكربوني لكل حمض اميني من الصورة والالوان بسهل عليك

Note:



Some Nutritional Terms:

- If N-input = N-output → ***Nitrogen Equilibrium (normal Nitrogen balance)***; the case in healthy adult
- If N-input > N-output → ***Positive Nitrogen balance***; the case in children and convalescent adult
- If N-input < N-output → ***Negative Nitrogen balance***; the case in food deprivation, illness, aging and deficiency of essential amino acids that will inhibit protein synthesis and degradation of unused amino acids

اتمنى لكم
التوفيق جميعا
و اعتذر عن اي
تقصير
طارق جبريل