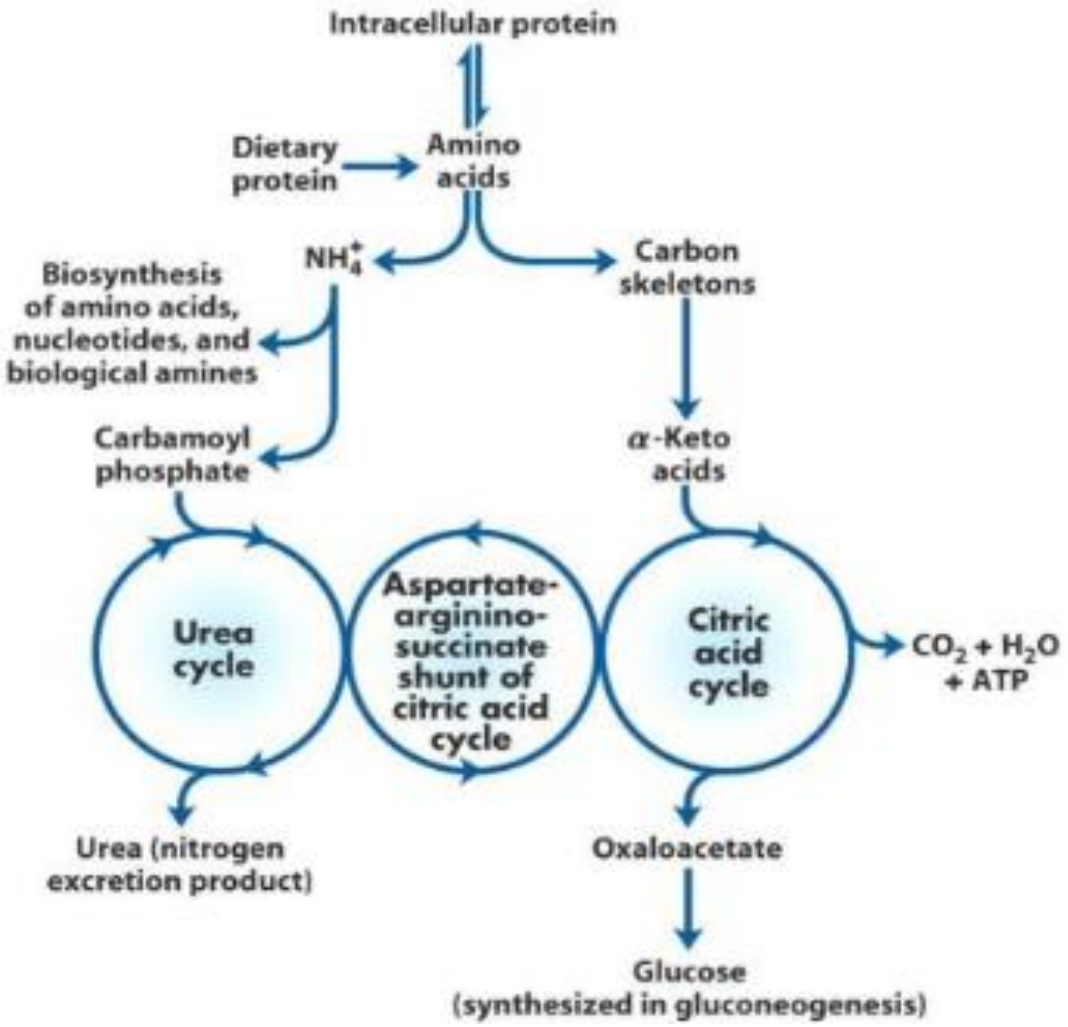
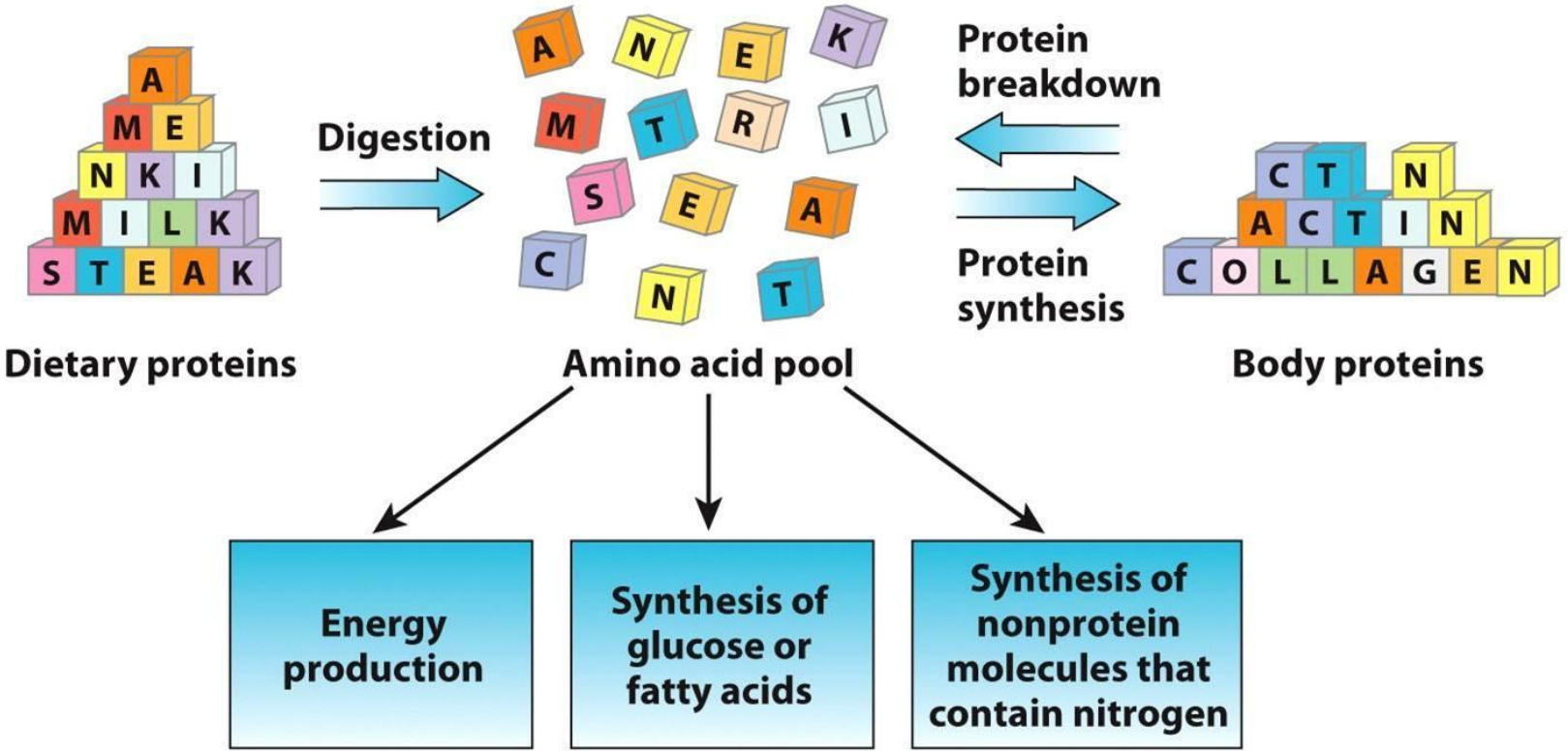
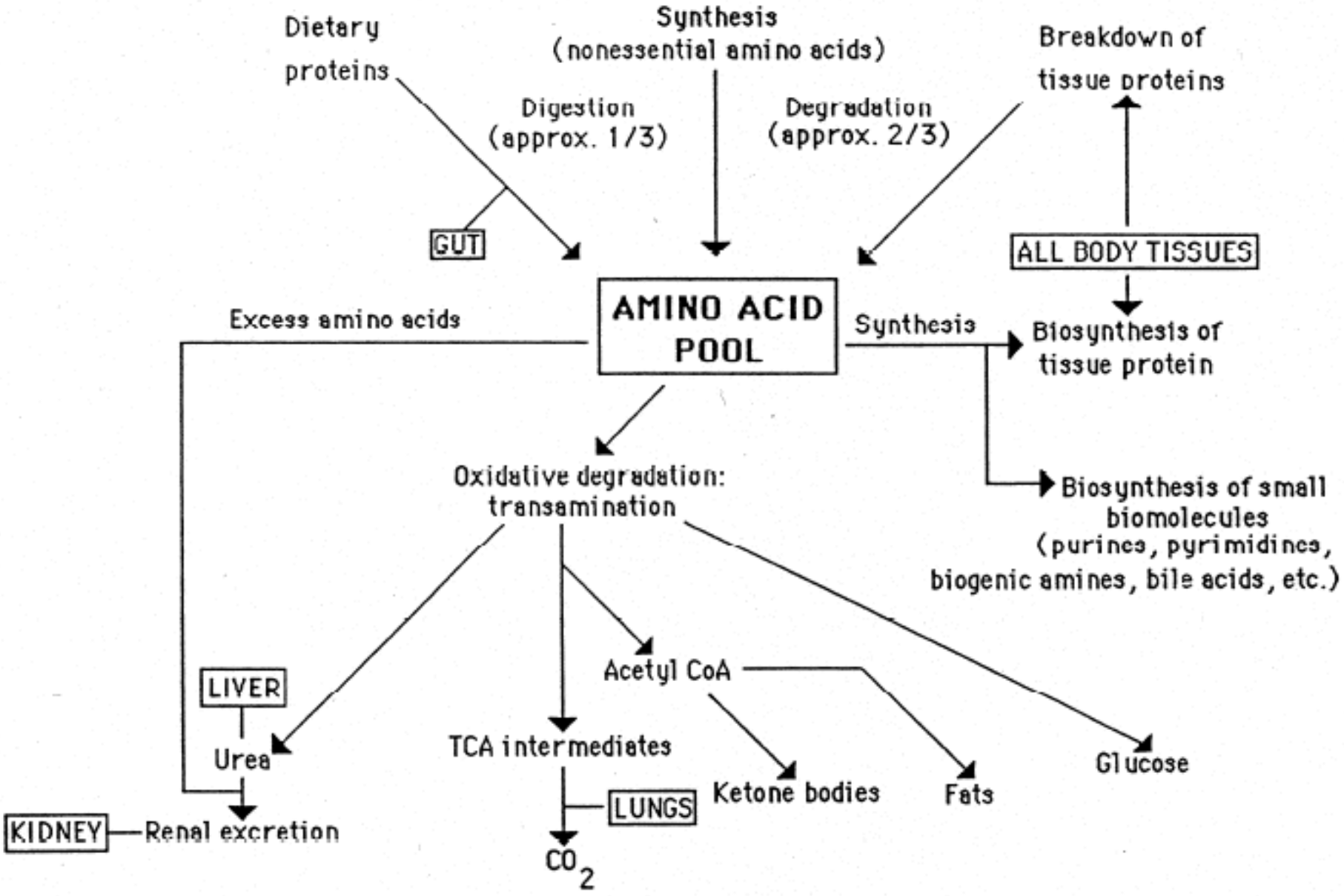
Amino Acids Metabolism



Amino Acid Pool

Unlike fats and carbohydrates, AAs are not stored by the body. Therefore, amino acids must be obtained from the diet, synthesized, or produced from normal protein degradation




Dietary proteins
Synthesis (nonessential amino acids)
Breakdown of tissue proteins
Digestion (approx. 1/3)
Degradation (approx. 2/3)
GUT
ALL BODY TISSUES
AMINO ACID POOL
Excess amino acids
Synthesis
Biosynthesis of tissue protein
Oxidative degradation: transamination
Biosynthesis of small biomolecules (purines, pyrimidines, biogenic amines, bile acids, etc.)
LIVER
Urea
Acetyl CoA
TCA intermediates
Glucose
Ketone bodies
Fats
KIDNEY
Renal excretion
LUNGS
CO_2

Catabolism of Amino Acids

The presence of the -amino group keeps AAs safely locked away from oxidative breakdown. Removing this amino group is **essential for producing energy** from any amino acid

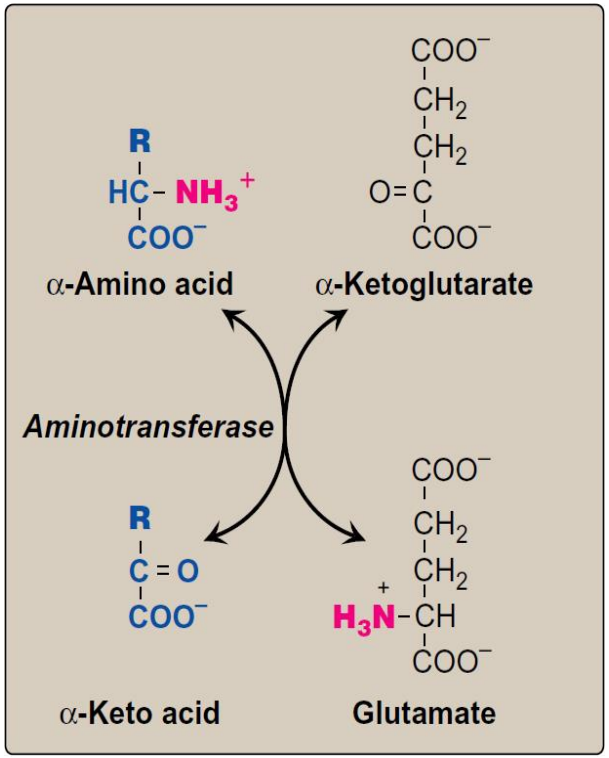
- The first phase of catabolism involves the removal of the **α-amino groups** (usually by transamination and subsequent oxidative deamination), forming ammonia (as NH4, Urea or Uric Ac. In different organisms) and the corresponding α-keto acid—the "carbon skeletons" of amino AA
- **Thus,C-skeleton** enters known pathways

Transamination

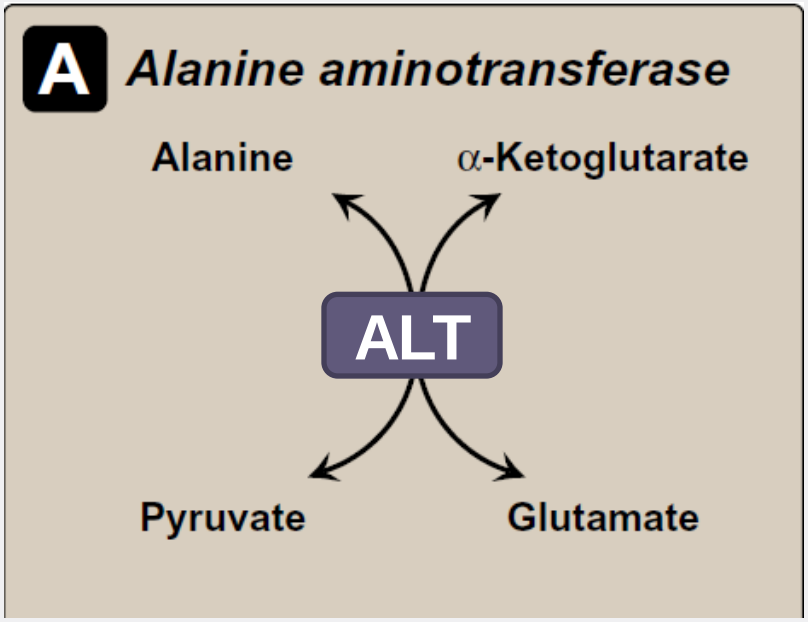
The first step in the catabolism of most AAs is the transfer of their α-amino group to α-ketoglutarate. The products are an α-keto acid and glutamate. This reaction occurs in the cytosol of hepatocytes.

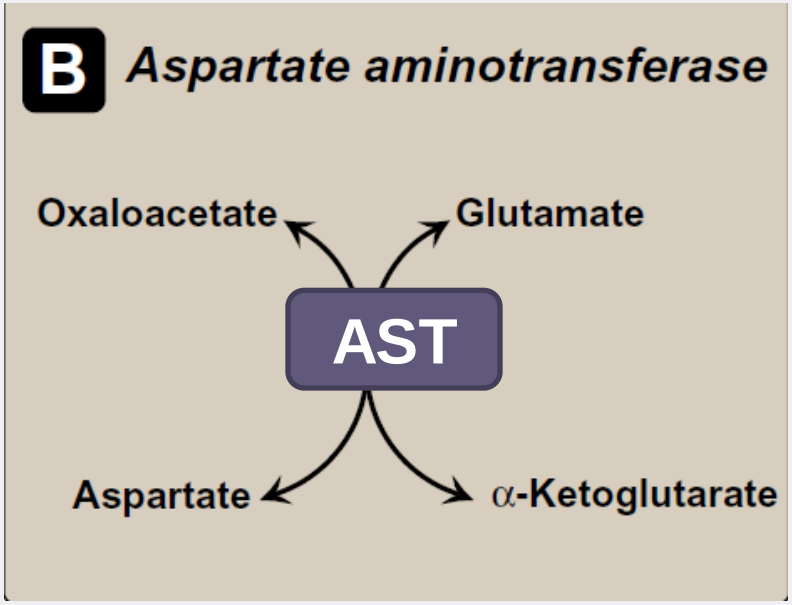
Ketoglutarate accepts the amino groups from most amino acids, becoming glutamate. All amino acids participate in transamination except lysine and threonine which lose their amino group by deamination.

The amino group that was removed is metabolized in the liver forming ammonia



All aminotransferases require the pyridoxal 5-phosphate (a derivative of vitamin B6) as a coenzyme to express its activity…





Aminotransferases are named after the specific amino group donor (the acceptor is almost always α-ketoglutarate).

The two most important aminotransferase reactions are catalyzed by ***alanine aminotransferase (ALT) and aspartate aminotransferase AST***

Deamination

Glutamate produced by transamination can be **oxidatively deaminated** by ***glutamate dehydrogenase*** *(in the metochondria of liver and kidney)*, or used as an amino group donor of non-essential AAs.

GD *uses NAD+ or NADP+ as coenzymes*

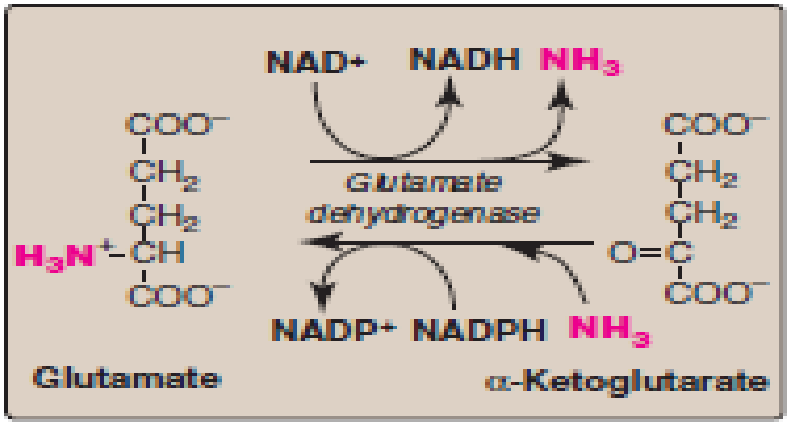
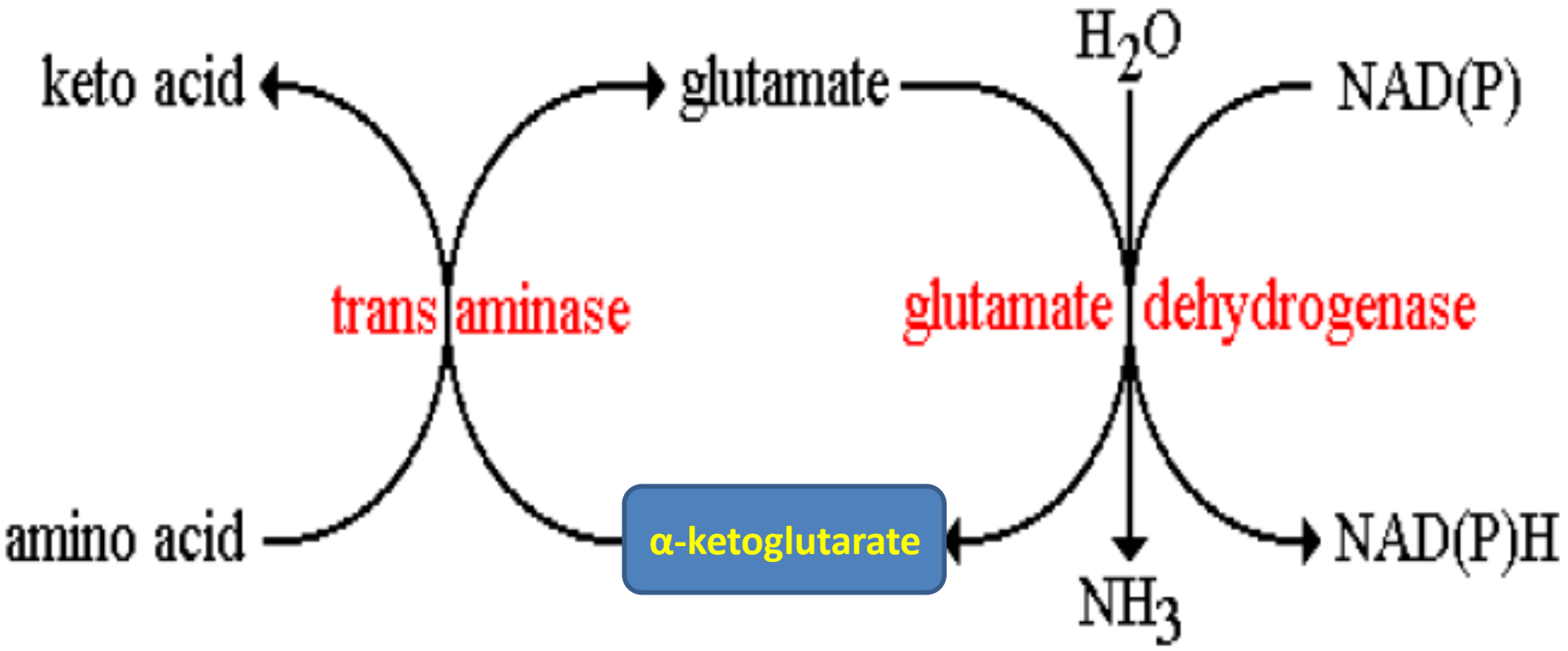


Figure 19.11
Oxidative deamination by *glutamate dehydrogenase.*

Transamination and oxidative deamination

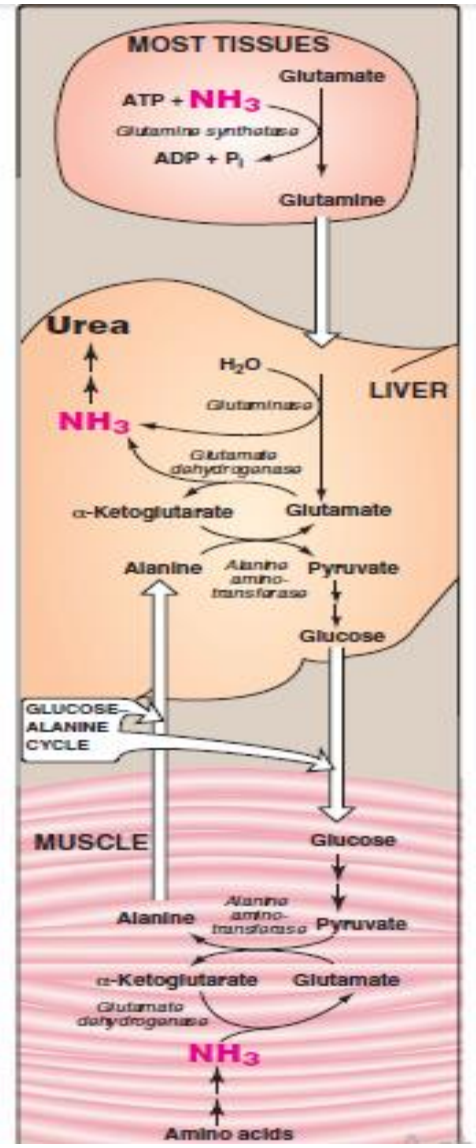


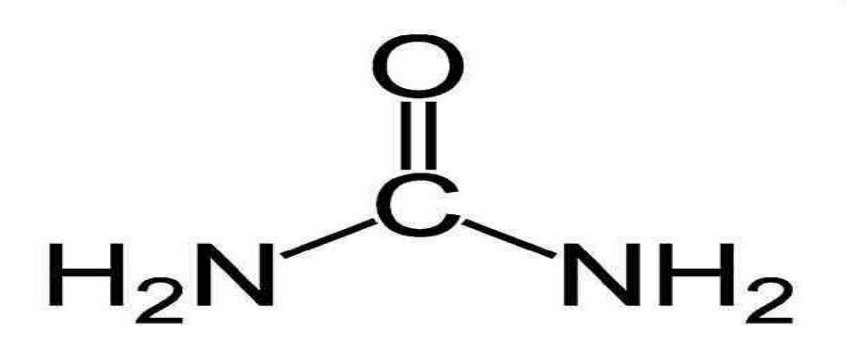
Transport of Ammonia to the Liver

Two mechanisms are available to transport ammonia from peripheral tissues to liver:

1-found in most tissues, uses **glutamine synthetase** to combine ammonia (NH3) with glutamate to form glutamine—). The glutamine is transported in the blood to the liver where it is cleaved by *glutaminase* to produce glutamate and free ammonia

2- used primarily by muscle, involves transamination of pyruvate (the end product of aerobic glycolysis) to form alanine, which is transported by the blood tothe liver, where it is converted to pyruvate





UREA CYCLE

BIOSYNTHESIS OF UREA

- Urea is the major end product in Nitrogen metabolism in humans and mammals.
- NH_3, the product of oxidative deamination reaction, is toxic in even small amount and must be removed from the body.
- **Urea cycle (Ornithine cycle) is the conversion reactions of NH_3 into urea**.

- This reaction occur in liver (certain occur in cytosol and mitochondria)
- The urea is transported to the kidney where it is excreted.
- The overall urea formation reaction is :-

Aspartate +2 NH_3 + CO_2 + 3ATP ---> urea + fumarate + H_2O + 3 ADP

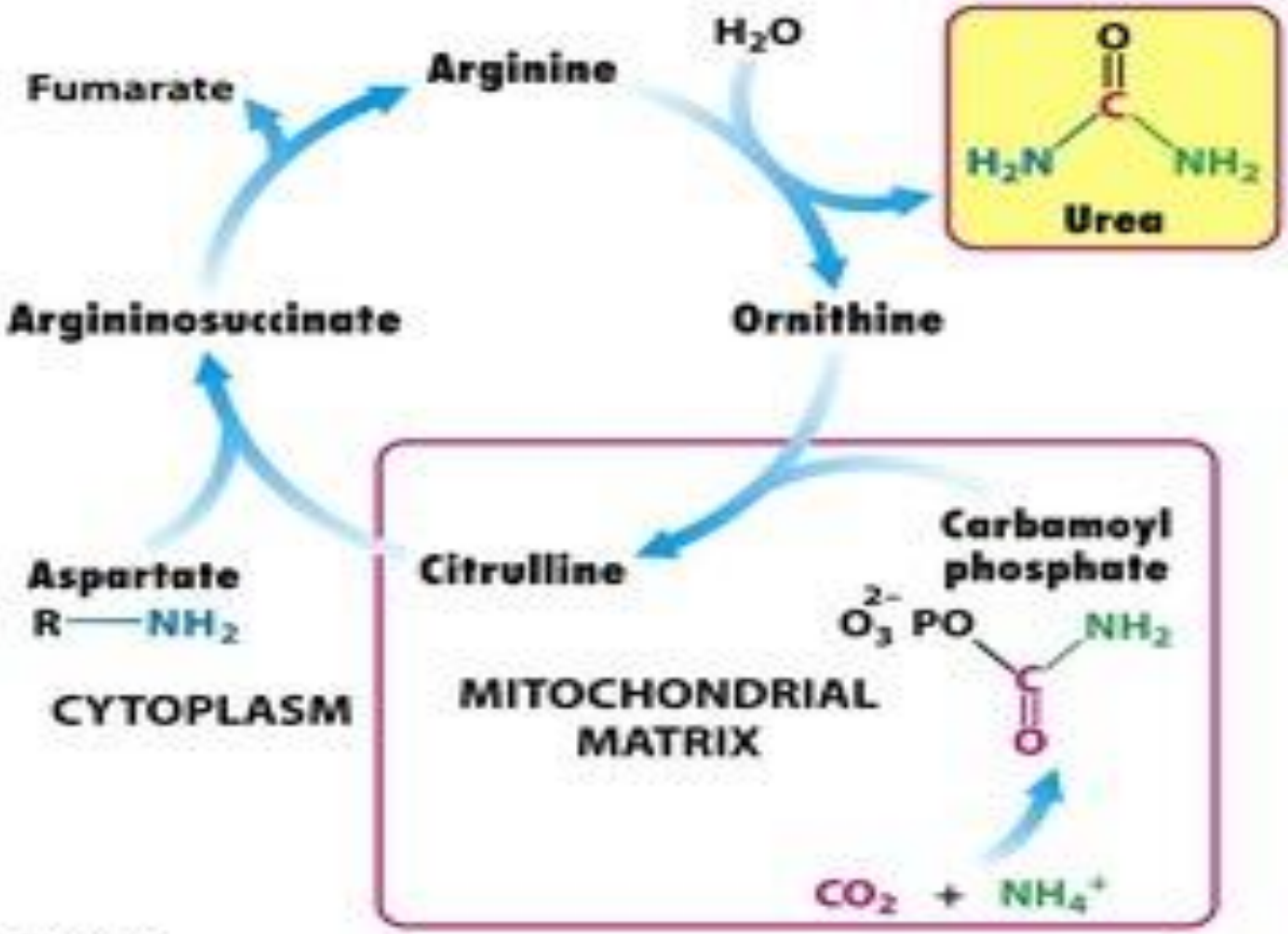
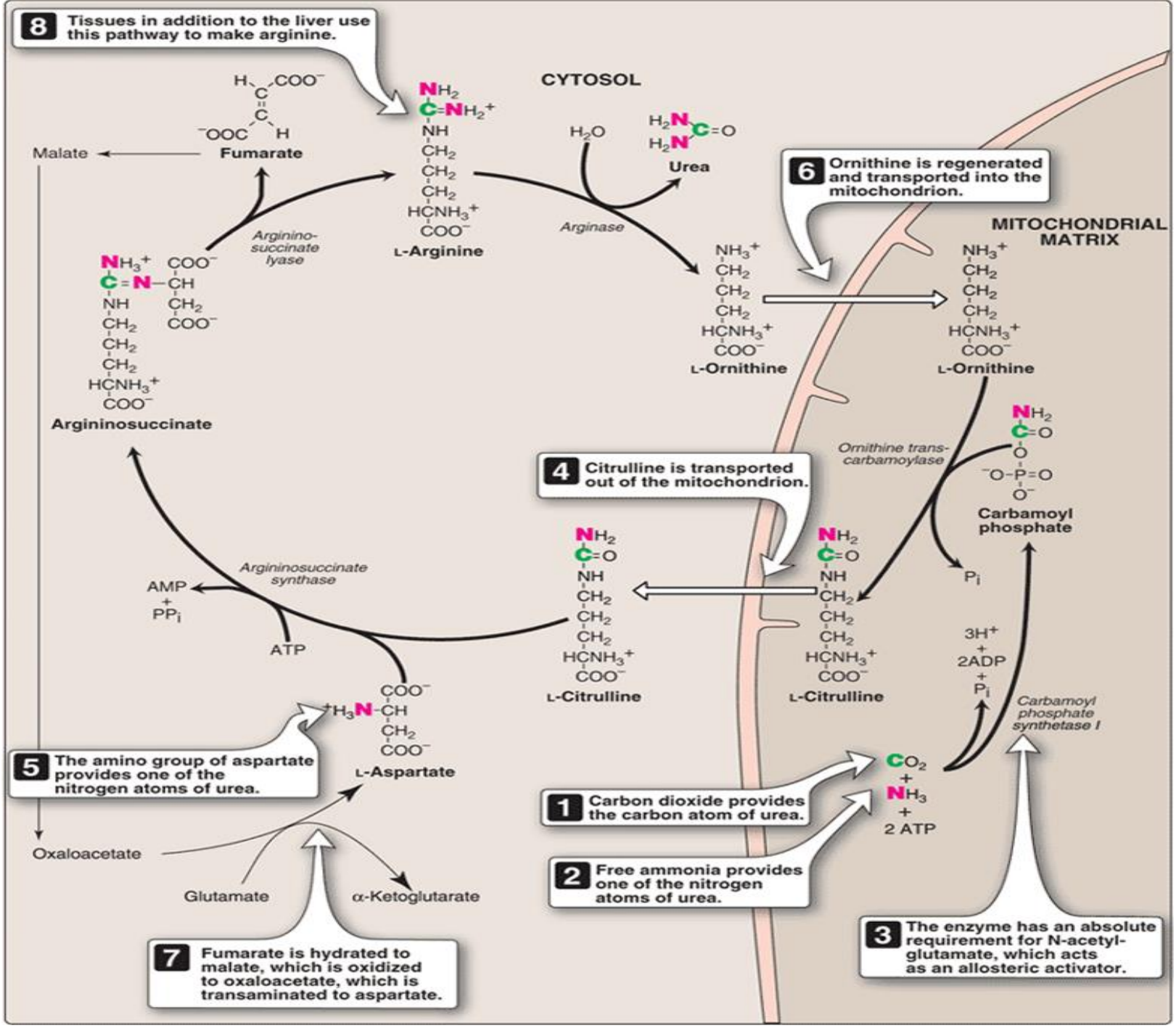


Figure 23-17
Biochemistry, Sixth Edition


8 Tissues in addition to the liver use this pathway to make arginine.
CYTOSOL
Fumarate
Malate
L-Arginine
Urea
Arginino-succinate lyase
Arginase
6 Ornithine is regenerated and transported into the mitochondrion.
MITOCHONDRIAL MATRIX
L-Ornithine
L-Ornithine
Argininosuccinate
Ornithine trans-carbamoylase
Carbamoyl phosphate
4 Citrulline is transported out of the mitochondrion.
Argininosuccinate synthase
AMP + PPi
ATP
Pi
L-Citrulline
L-Citrulline
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
L-Aspartate
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
CO2 + NH3 + 2 ATP
1 Carbon dioxide provides the carbon atom of urea.
Oxaloacetate
2 Free ammonia provides one of the nitrogen atoms of urea.
Glutamate
α-Ketoglutarate
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.

Steps in urea cycle

1. **Synthesis of carbamoyl phosphate:**

   Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyzes the condensation of NH_4^+ ions with CO_2 to form carbamoyl phosphate. This step consumes 2 ATP and is **irreversible**, and **rate-limiting**.

Steps in urea cycle

2. **Formation of citrulline** : Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase. Ornithine is regenerated and used in urea cycle. Therefore, its role is comparable to that of oxaloacetate in citric acid cycle. Ornithine and citrulline are never found in protein structure (due to lack of codons). Citrulline produced in this reaction is transported to cytosol by a transporter system.

Steps in urea cycle

3. **Synthesis of arginosuccinate** : Arginosuccinate synthase condenses citrulline with aspartate to produce arginosuccinate. The second amino group of urea is incorporated in this reaction. This step requires ATP which is cleaved to AMP and pyrophosphate (PPi). The latter is immediately broken down to inorganic phosphate (Pi).

Steps in urea cycle

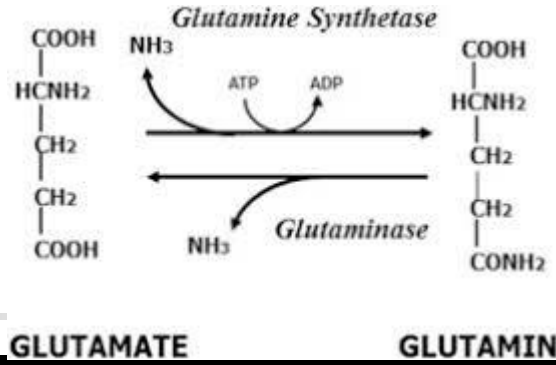
4. **Cleavage of arginosuccinate** : Arginosuccinase cleaves arginosuccinate to give arginine and fumarate. Arginine is the immediate precursor for urea. Fumarate liberated here provides a connecting link with TCA cycle, gluconeogenesis etc.

Steps in urea cycle

5. **Formation of urea** : Arginase is the fifth and final enzyme that cleaves arginine to yield urea and ornithine. Ornithine, so regenerated, enters mitochondria for its reuse in the urea cycle. Arginase is activated by Co^{2+} and Mn^{2+}.

Arginase is mostly found in the liver, while the rest of the enzymes (four) of urea cycle are also present in other tissues.

Fate of Ammonia



1 Amination of keto acids

2 ketoglutarate to glutamate

AMMONIA

3 Glutamate to Glutamine

4 Formation of Urea

Ammonia toxicity. **Ammonia** is highly **toxic**. Normally blood **ammonium** concentration is < 50 μmol /L, and an increase to 100 μmol /L can lead to disturbance of consciousness. A blood **ammonium** concentration of 200 μmol /L is associated with coma and convulsions.

One of the causes of hyperammonaemia is a urea cycle defect. Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle defect in adults. It is an X-linked disorder due to **deleterious mutations in the OTC gene**.

Deficiencies of urea cycle enzymes

Inherited Disorders of urea cycle

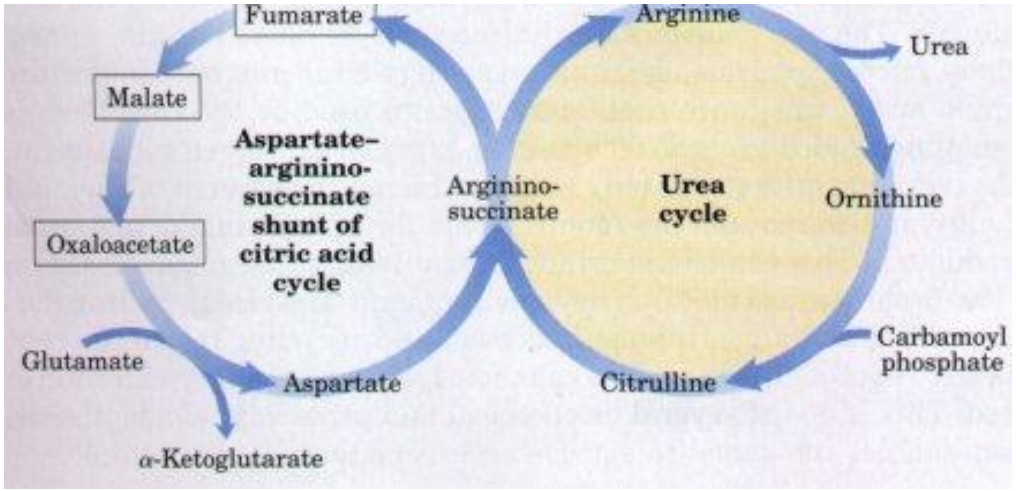
Disoeders	Defective Enzyme	Products accumulated
Hyperammonaemia-1	Carbamoyl Phosphate Syntethase -1	Ammonia
Hyperammonaemia-2	Ornithine transcarbomylase (orotic aciduria-most common)	Ammonia
Citrullinemia	Argininino succinate Synthethase	Citrulline
Arginosuccinic aciduria	Argininosuccinate lyase	Arginosuccinate
Argininemia	Arginase	Arginine

Symptoms

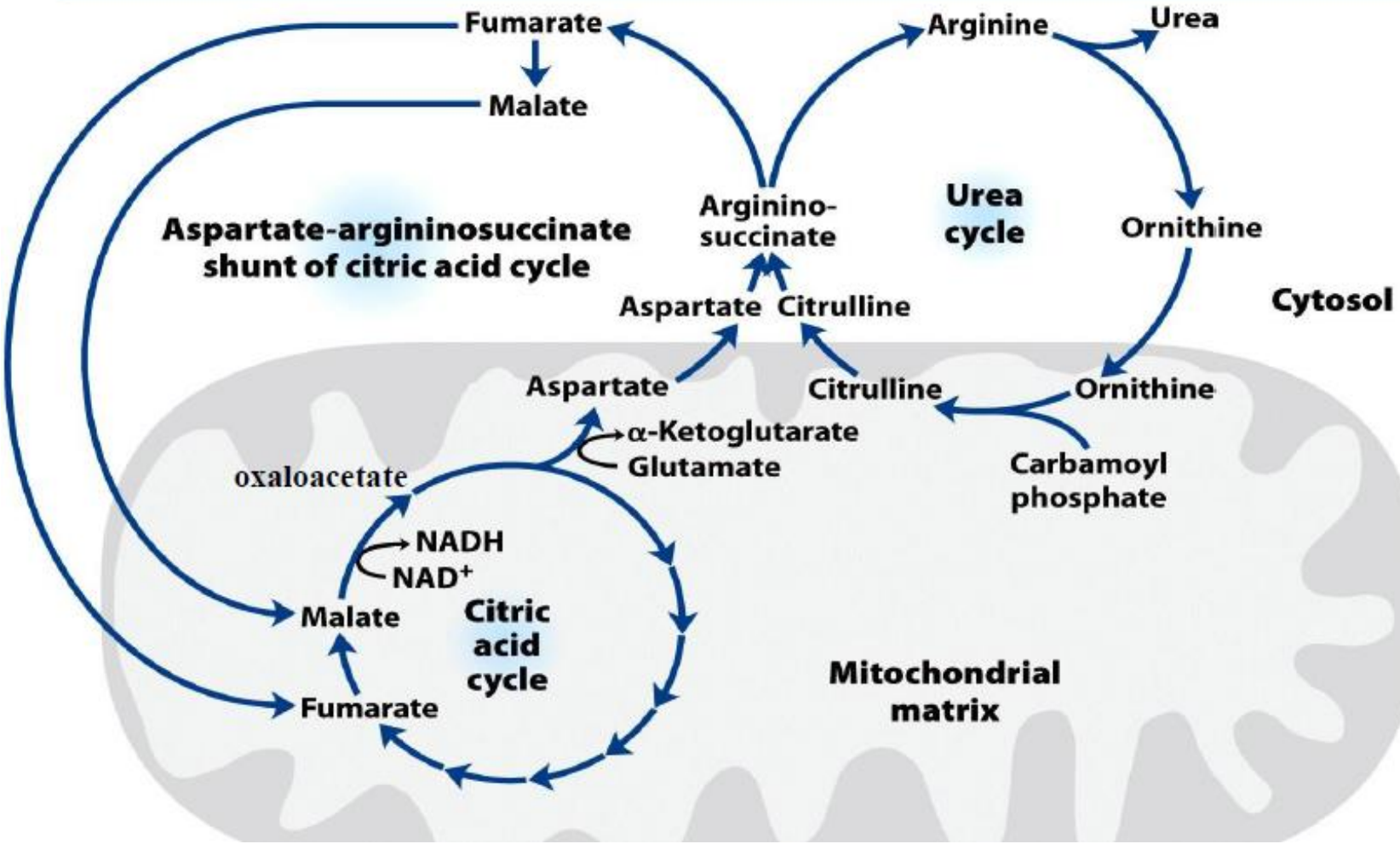
- Increased levels of ammonia results in
- Slurring of speech
- Blurring of the vision ضبابية الرؤية
- Convulsions اختلاجات
- Nausea, Vomiting
- Neurological Deficits عجز عصبي
- Mental Retardation
- Coma & Death.

Links between Urea Cycle and Citric Acid Cycle

The pathways linking the citric acid and urea cycles are known as the **aspartate-argininosuccinate shunt**; these effectively link the fates of the amino groups and the carbon skeletons of amino acids.



Aspartate –Arginosuccinate Shunt Links Urea Cycle and Citric Acid Cycle



Aspartate –Arginosuccinate Shunt Links Urea Cycle and Citric Acid Cycle

- Fumarate production connects the urea cycle and the citric acid cycle (fumarate → malate → oxaloacetate).
- In the citric acid cycle fumarate is converted to oxaloacetate.
- Oxaloacetate is transaminated to aspartate.
- Aspartate carries the amino groups of other amino acids into the urea cycle.

The Fate of the Carbon Skeleton in AA breakdown

- **Amino acids**, when deaminated, yield **α-keto acids** that, directly or via additional reactions, feed into major metabolic pathways (e.g., Krebs Cycle).
- As previously mentioned, Amino acids are grouped into 2 classes, based on whether or not their carbon skeletons can be converted to glucose:
  - **glucogenic**
  - **ketogenic**.

- Carbon skeletons of **glucogenic** amino acids are degraded to:

◆**pyruvate**, or

◆a **4-C or 5-C intermediate of Krebs Cycle**.

These are precursors for gluconeogenesis.

- Glucogenic amino acids are the major carbon source for **gluconeogenesis** when glucose levels are low.
- They can also be catabolized for **energy**, or converted to glycogen or fatty acids for energy **storage**.

Carbon skeletons of **ketogenic** amino acids are degraded to:

- **acetyl-CoA**, or
- **acetoacetyl CoA,**

Acetyl CoA, & its precursor acetoacetate, cannot yield net production of oxaloacetate, the gluconeogenesis precursor. Thus, Carbon skeletons of ketogenic amino acids can be catabolized for **energy** in Krebs Cycle, or converted to **ketone bodies** or **fatty acids**, they **cannot be converted to glucose**.

For every 2-C acetyl residue entering Krebs Cycle, 2 C leave as CO_2.

THE FATE OF CARBON-SKELETONS OF AMINO ACIDS

a) Simple degradation:

(amino acid → Common metabolic intermediate)

Alanine → Pyruvate

Glutamate → α-ketoglutarate

Aspartate → Oxaloacetate

b) Complex degradation:

(amino acid--- Keto acid----- **complex** pathway---- Common metabolic intermediate)

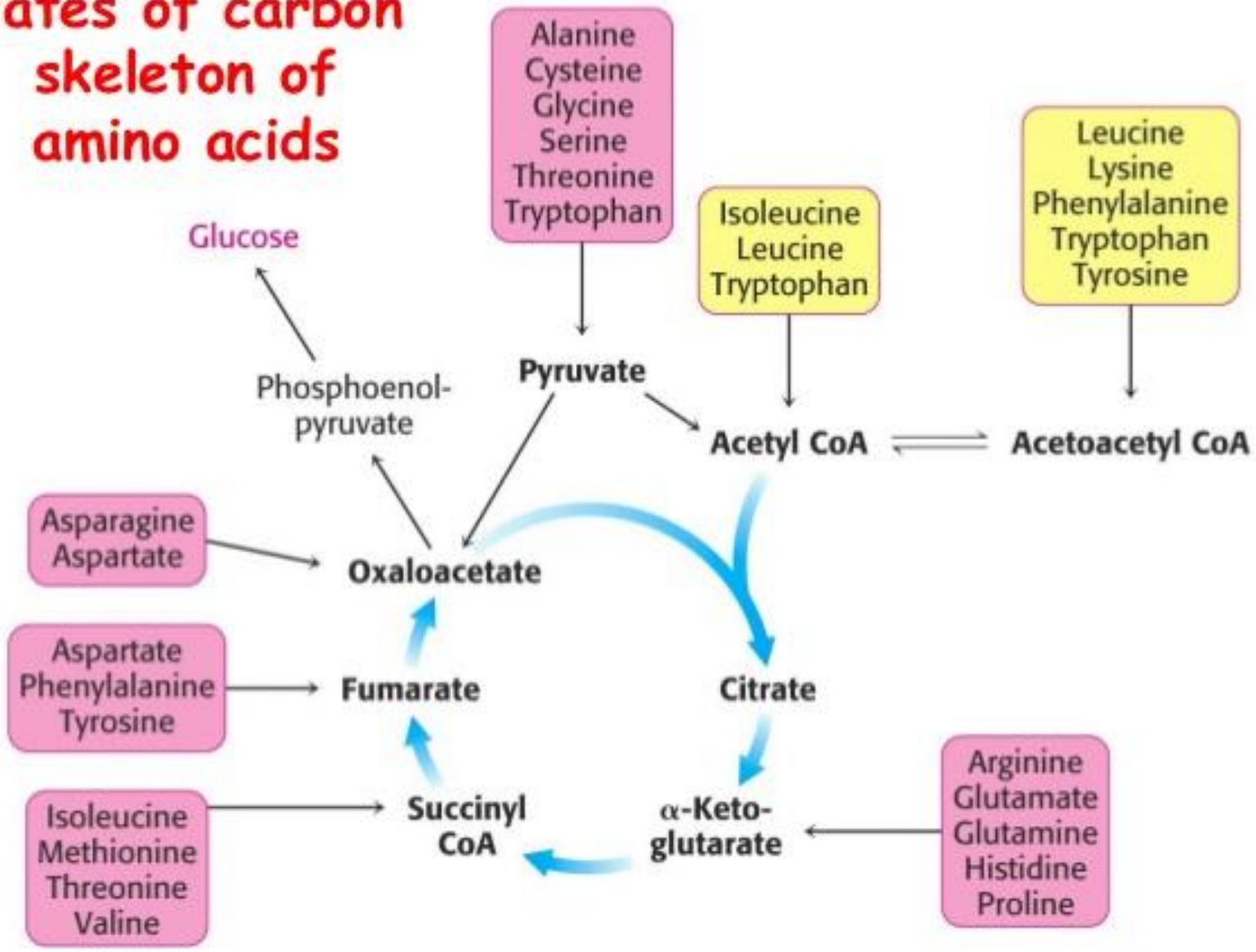
Amino acids whose ketoacids are metabolized via **more complex** pathway **e.g. Tyrosine, Lysine, Tryptophan**

c) Conversion of one amino acid into another amino acid before degradation:

Phenylalanine is converted to **tyrosine** prior to its further degradation.

- Seven to acetyl-CoA
  - Leu, Ile, Thr, Lys, Phe, Tyr, Trp
- Six to pyruvate
  - Ala, Cys, Gly, Ser, Thr, Trp
- Five to α-ketoglutarate
  - Arg, Glu, Gln, His, Pro
- Four to succinyl-CoA
  - Ile, Met, Thr, Val
- Two to fumarate
  - Phe, Tyr
- Two to oxaloacetate
  - Asp, Asn

Fates of carbon skeleton of amino acids



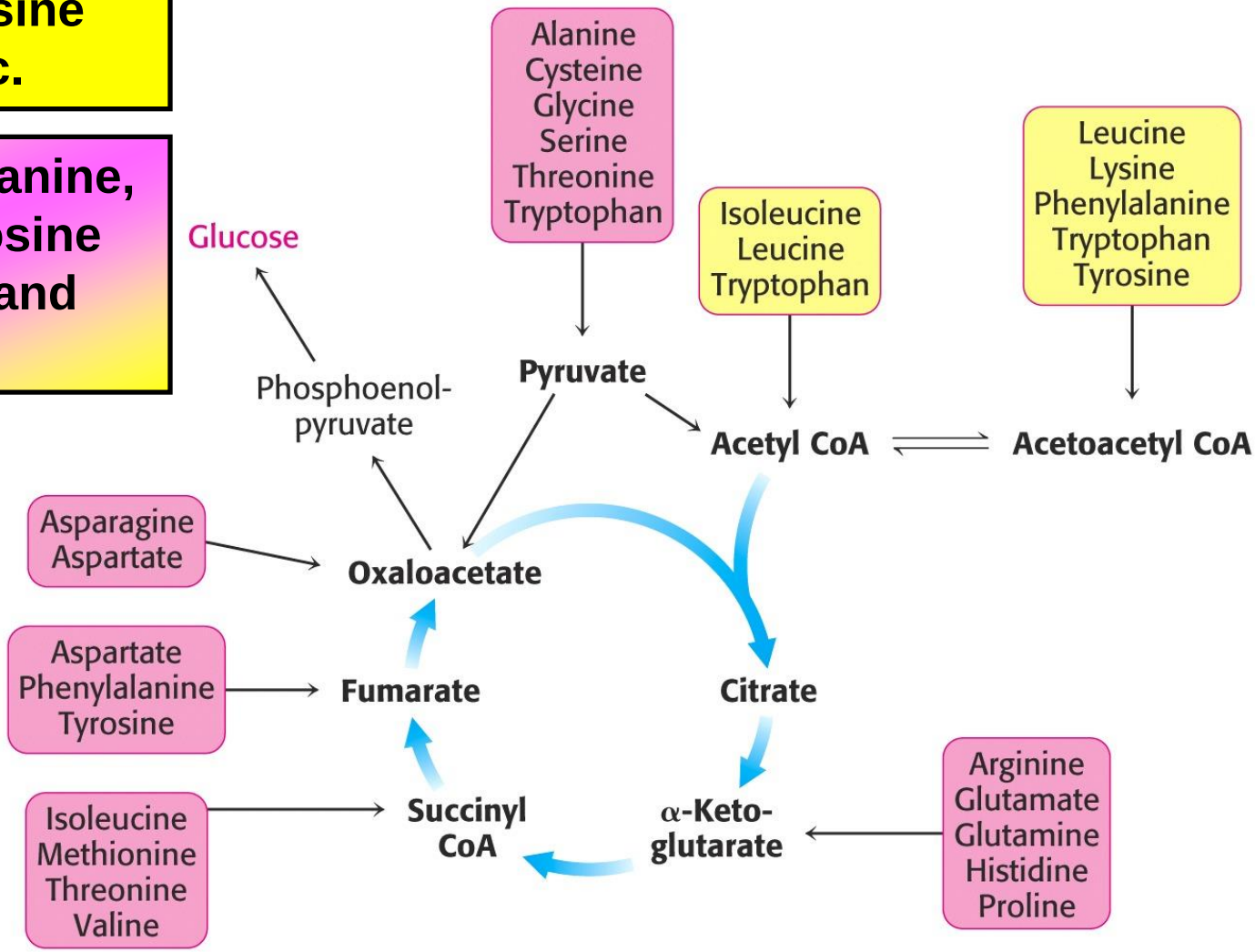
Glucogenic Amino Acids: amino acids (aa) that are converted to metabolites that can be converted to **glucose.** TCA cycle intermediates and pyruvate can be converted to phosphoenolpyruvate and then glucose.

Ketogenic Amino Acids: aa that give rise to **ketone** bodies or fatty acids.

Only leucine and lysine are solely ketogenic.

Isoleucine,phenylalanine, tryptophan and tyrosine are both ketogenic and glucogenic.

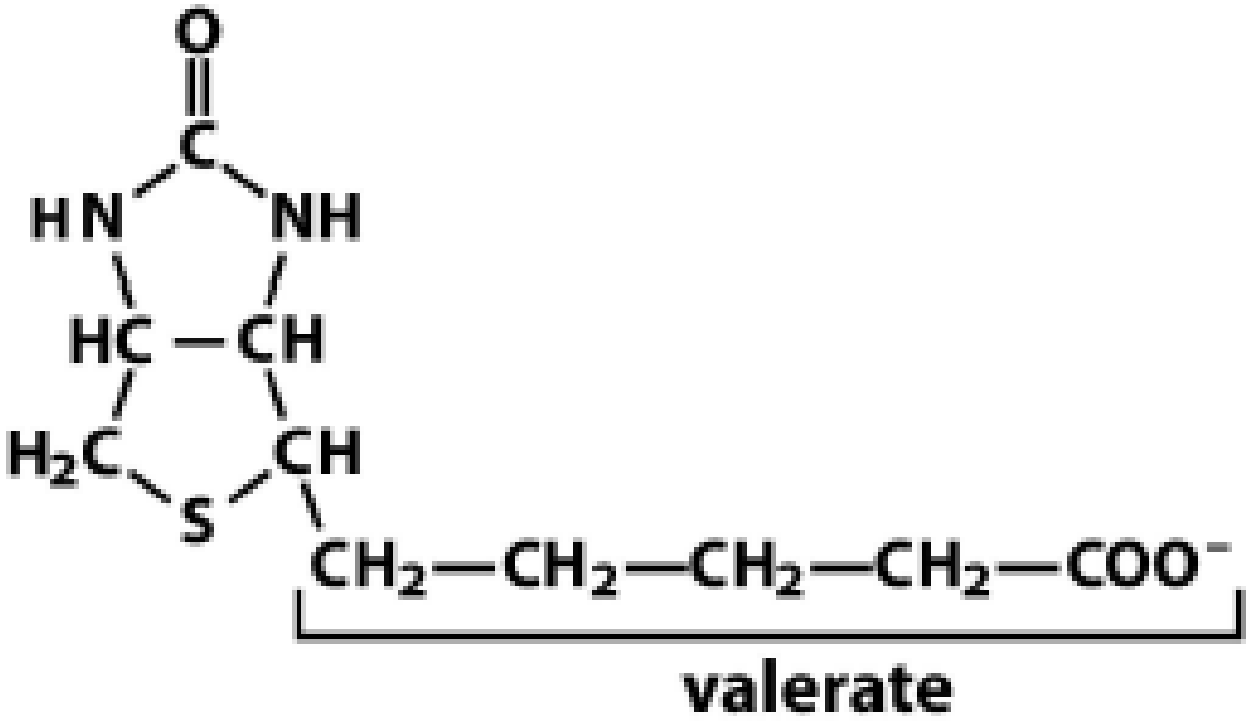
Remaining 14 amino acids are solely glucogenic.



- Several **enzyme cofactors** play important roles in amino acid catabolism:
  - ❖ Transamination requires pyridoxal phosphate
  - ❖ One Carbon transfer requires:
    - Biotin
    - Tetrahydrofolate
    - S-adenosylmethionine

Biotin – single C transfers as CO_2

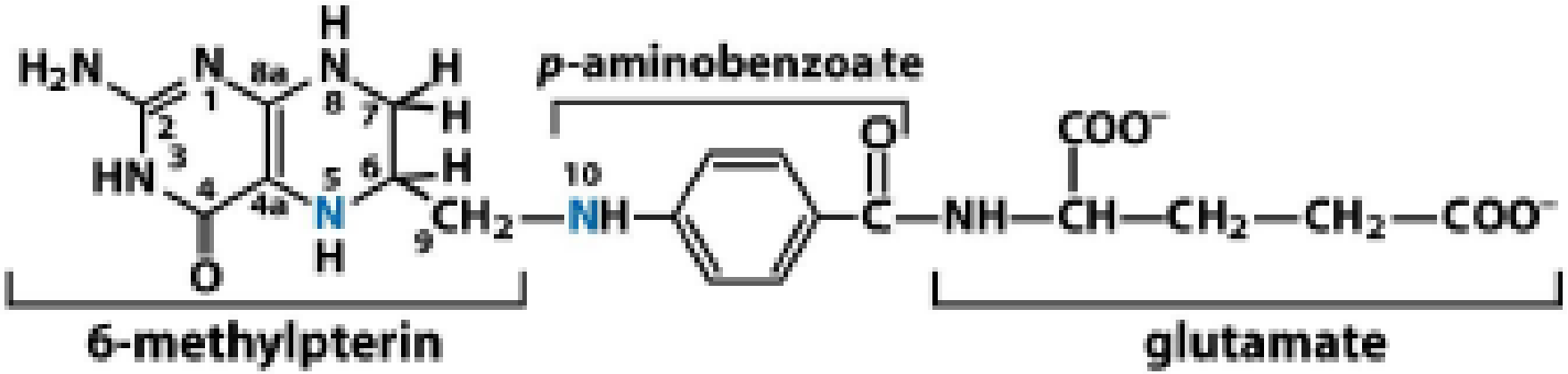
- Eg. Pyruvate Carboxylase



Biotin

Tetrahydrofolate

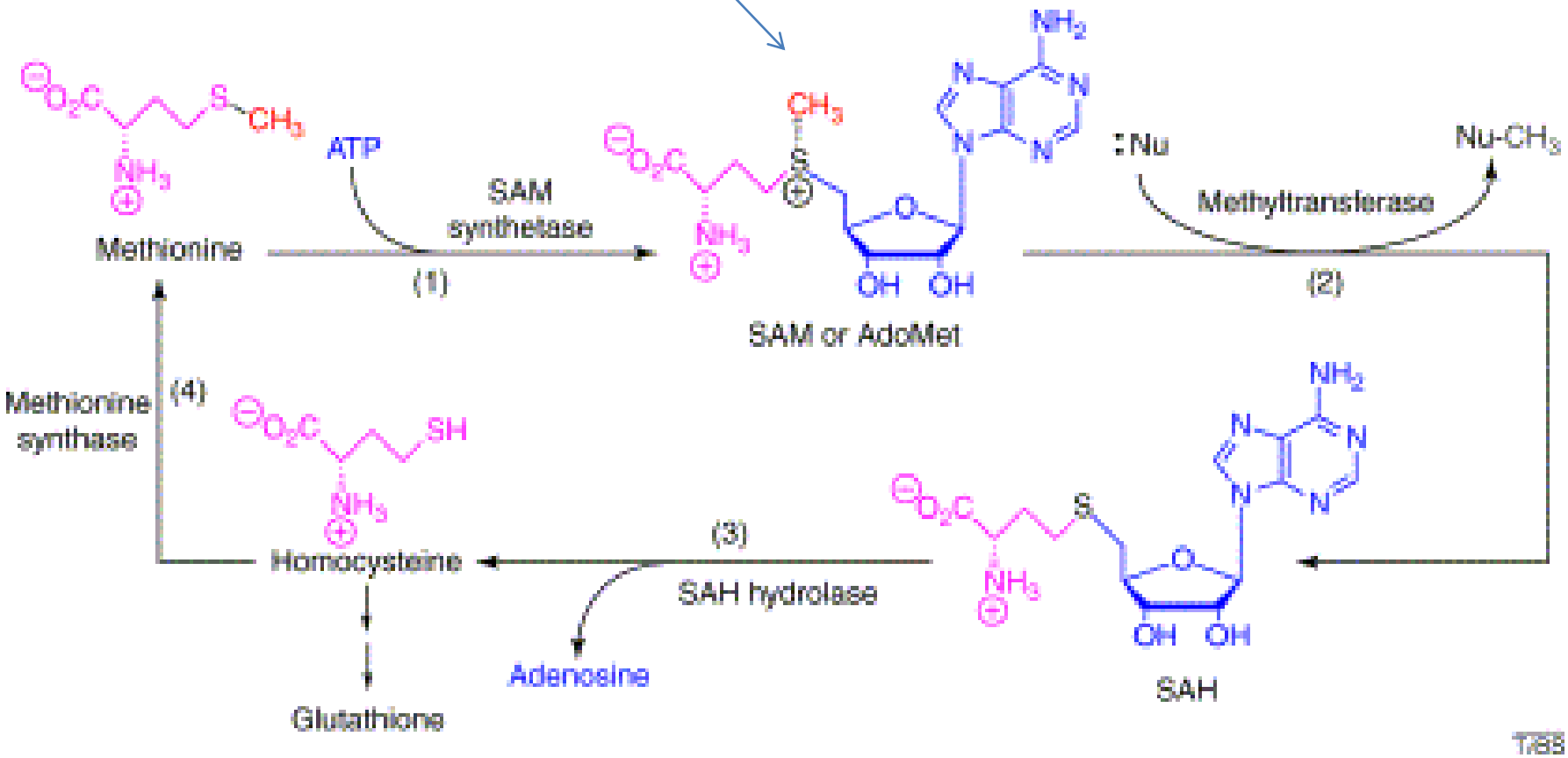
- Single Carbon Transfers – intermediate oxidation state – methylene, formyl, …



Tetrahydrofolate (H_4 folate)

S-Adenosyl Methionine

- Methyl Transfers

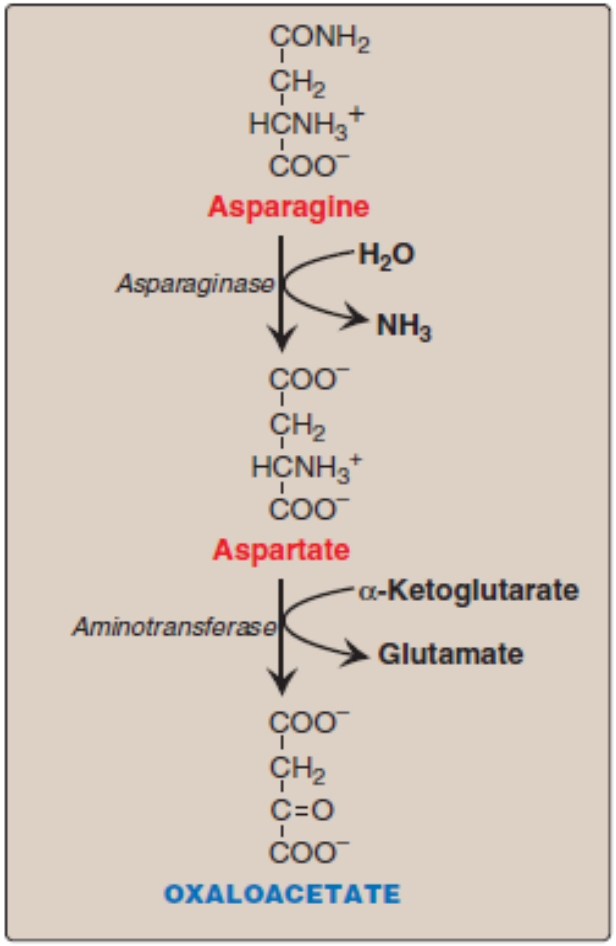


T/83

CATABOLISM OF THE CARBON SKELETONS OF AMINO ACIDS

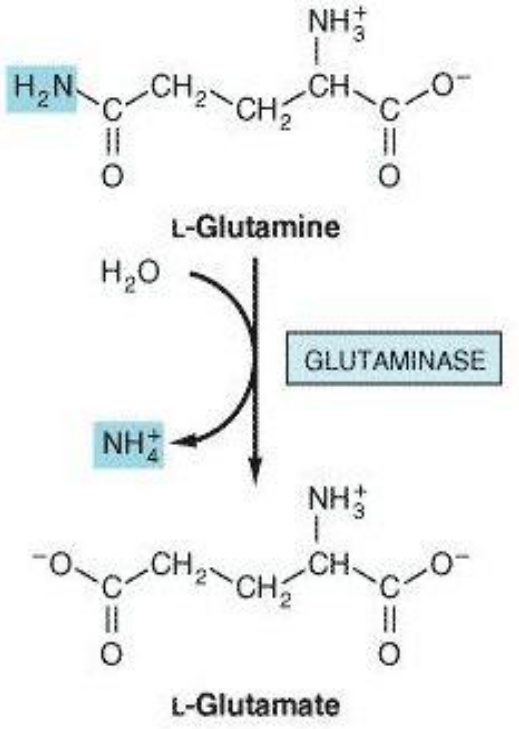
A. **Amino acids that form oxaloacetate:**

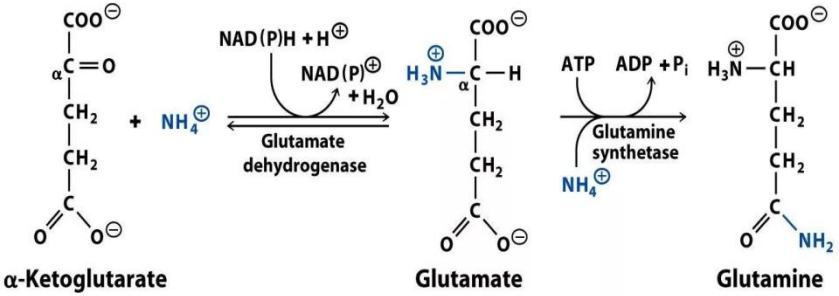
Asparagine is hydrolyzed يحلل مائيا by asparaginase, liberating ammonia and aspartate. Aspartate loses its amino group by trans - amination to form oxaloacetate



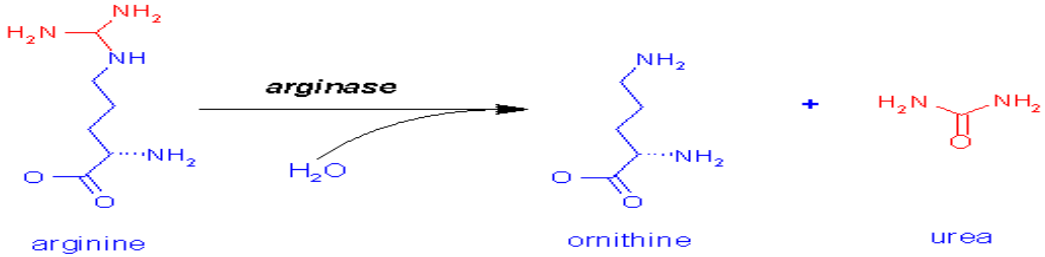
B. Amino acids that form -ketoglutarate via glutamate:

- **1. Glutamine:** This amino acid is converted to glutamate and ammonia by the enzyme glutaminase. Glutamate is converted to α-keto glutarate by transamination, or through oxidative deamination by glutamate dehydrogenase
- **2. Proline:** This amino acid is oxidized to glutamate.

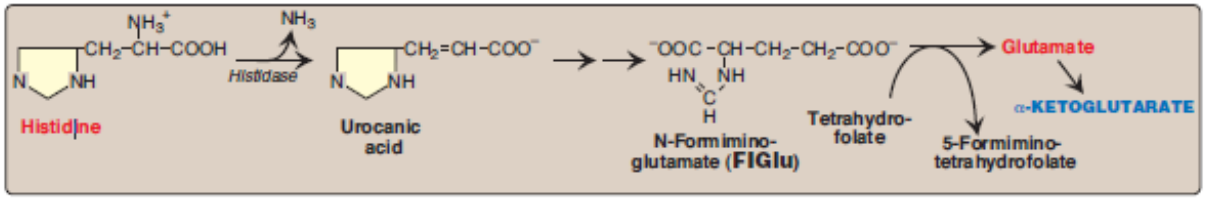


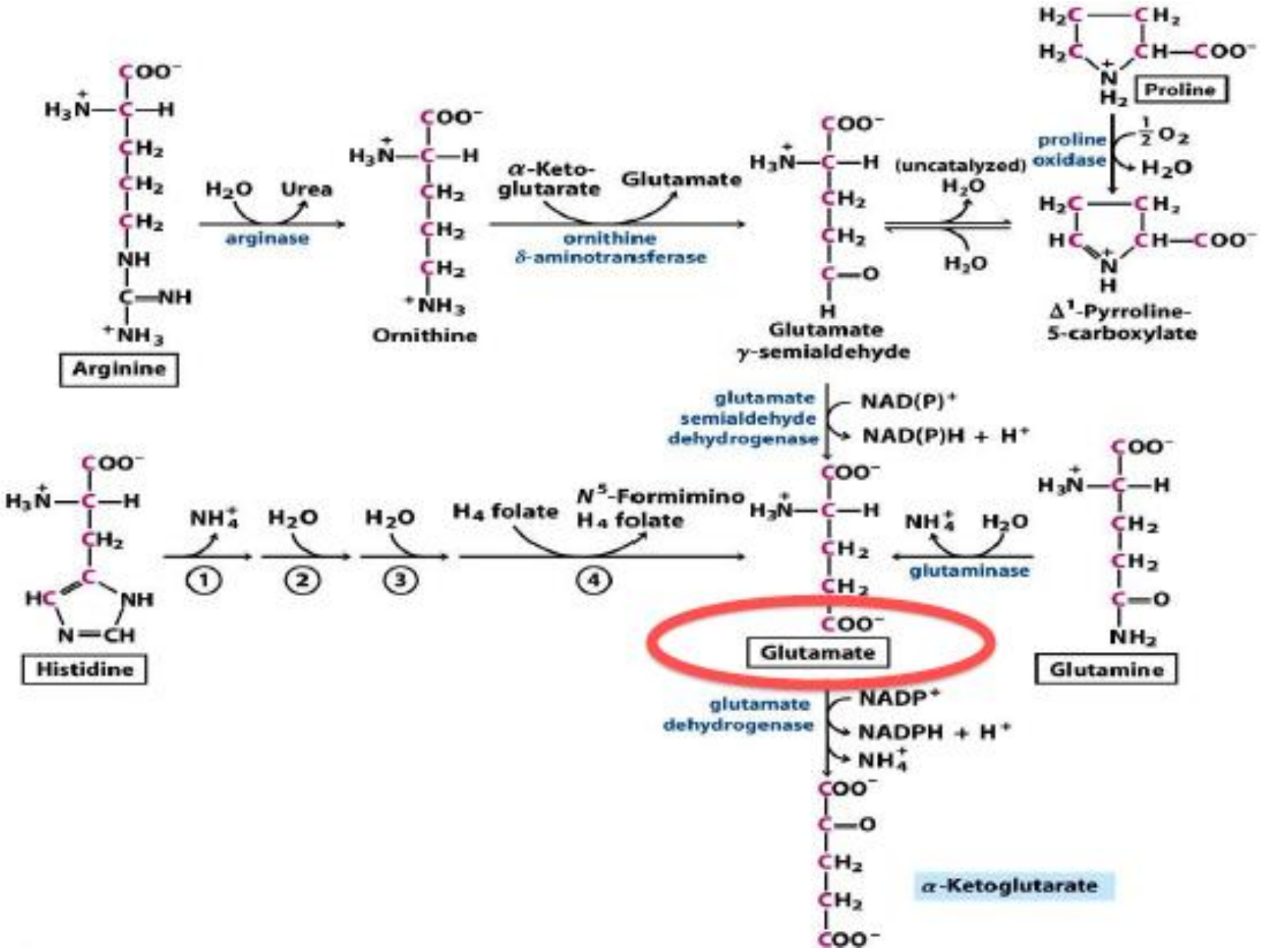


- **3. Arginine:** This amino acid is cleaved by arginase to produce ornithine. Ornithine is subsequently converted to α-keto glutarate.



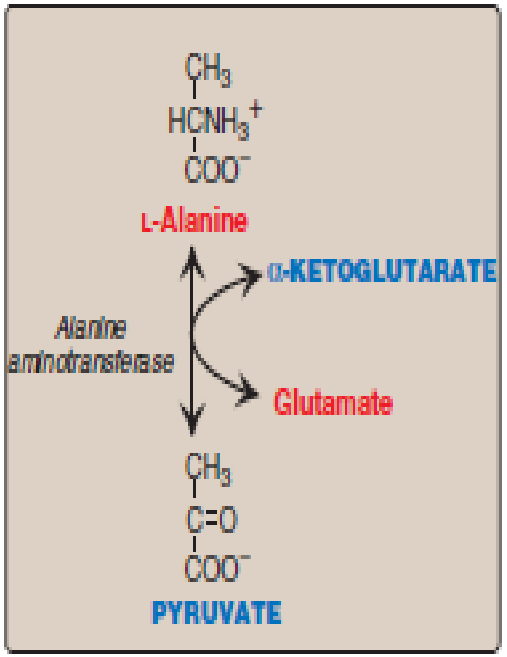
- **4. Histidine:** This amino acid is oxidatively deaminated by histidase to urocanic acid, which subsequently forms N-formimino glutamate



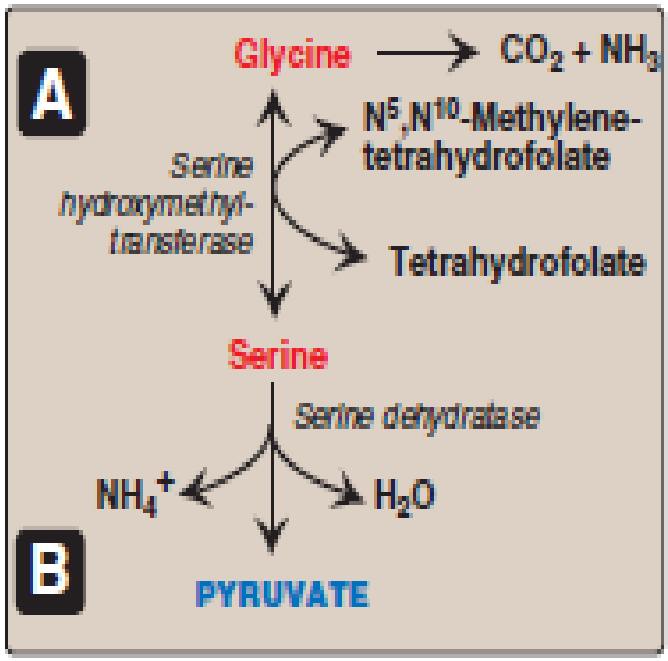

Arginine
H2O
Urea
arginase
Ornithine
α-Keto-glutarate
Glutamate
ornithine δ-aminotransferase
Glutamate γ-semialdehyde
(uncatalyzed)
H2O
H2O
Proline
proline oxidase
½ O2
H2O
Δ1-Pyrroline-5-carboxylate
glutamate semialdehyde dehydrogenase
NAD(P)+
NAD(P)H + H+
Histidine
NH4+
H2O
H2O
H4 folate
N5-Formimino H4 folate
1
2
3
4
NH4+
H2O
glutaminase
Glutamate
Glutamine
glutamate dehydrogenase
NADP+
NADPH + H+
NH4+
α-Ketoglutarate

C. Amino acids that form pyruvate

- **1. Alanine:** This amino acid loses its amino group by reversible transamination to form pyruvate.
- **2. Serine:** This amino acid can be converted to glycine and N_5,N_{10}-methylenetetra hydrofolate. Serine can also be converted to pyruvate by serine dehydratase

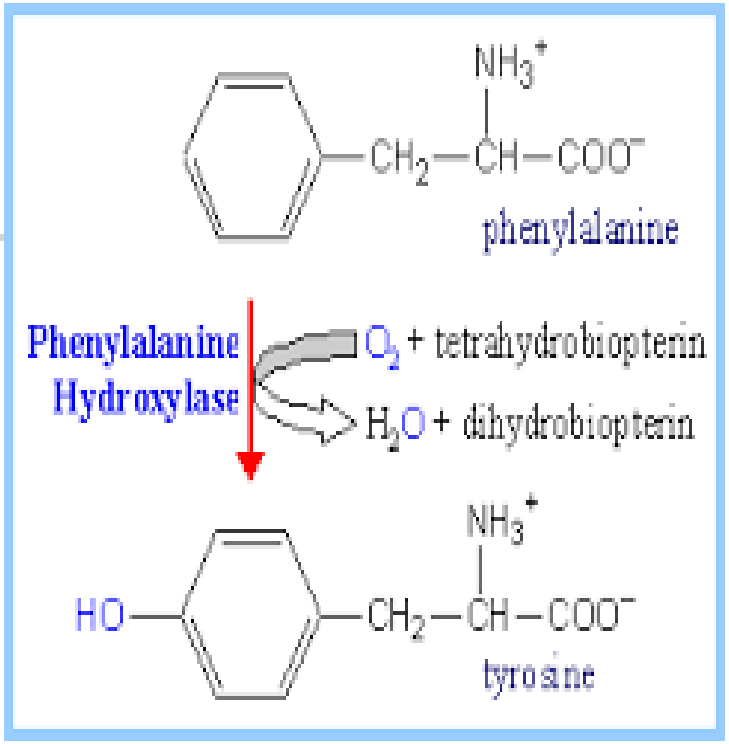


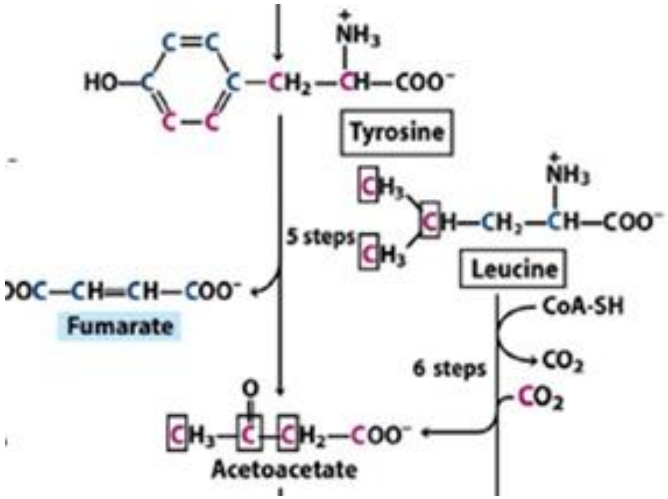
- **3. Glycine:** This amino acid can be converted to serine by the reversible addition of a methylene group from N_5,N_{10}-methylene tetrahydrofolic acid or oxidized to CO_2 and NH_3.
- **4. Cystine:** This amino acid is reduced to cysteine, using NADH + H. **Cysteine** undergoes <u>desulfuration</u> to yield pyruvate.
- **5. Threonine:** This amino acid is converted to pyruvate or to α-ketobutyrate



D. Amino acids that form fumarate

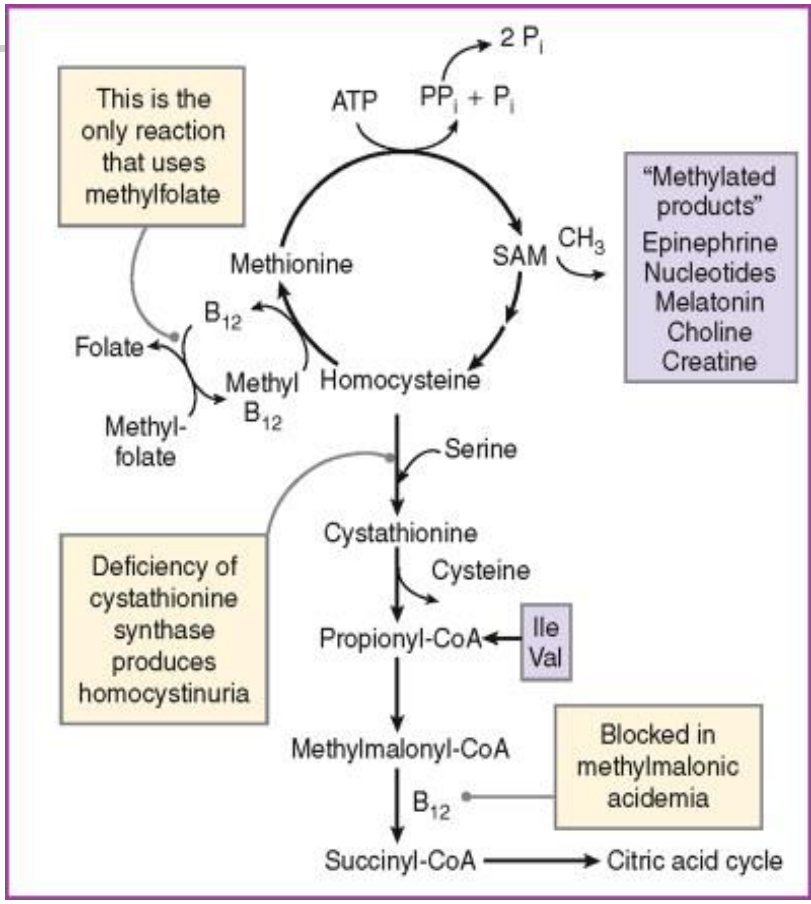
- **1. Phenylalanine and tyrosine:** Hydroxylation of phenylalanine produces tyrosine. This reaction, catalyzed by tetra - hydrobiopterin-requiring phenylalanine hydroxylase, initiates the catabolism of phenyl alanine.





E. Amino acids that form succinyl CoA:

Methionine: This sulfur-containing AA is converted to S-adenosyl methionine (SAM), the major methyl-group donor in metabolism. Methionine is also the source of homocysteine—a metabolite associated with atherosclerotic vascular disease



F. Other amino acids that form succinyl CoA:

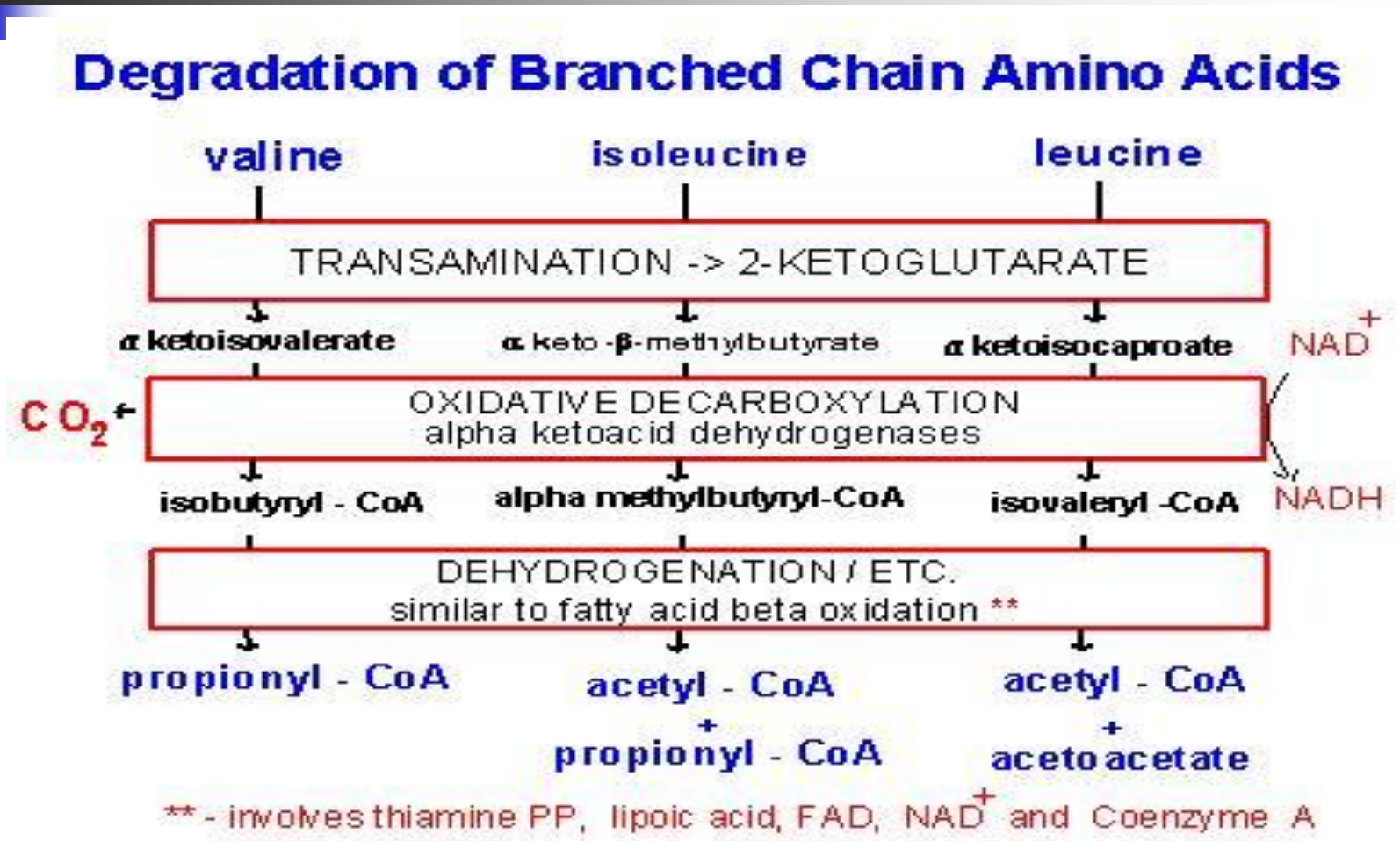
- Degradation of valine, isoleucine, and threonine also results in the production of succinyl CoA—a tricarboxylic acid (TCA) cycle intermediate and glucogenic compound.

G. Amino acids that form acetyl CoA or acetoacetyl CoA

- Leucine, isoleucine, lysine, and tryptophan form acetyl CoA or aceto acetyl CoA directly, without pyruvate serving as an intermediate (through the pyruvate dehydrogenase reaction).

Phenylalanine and tyrosine also give rise to acetoacetate during their catabolism.

H. Catabolism of the branched-chain amino acids



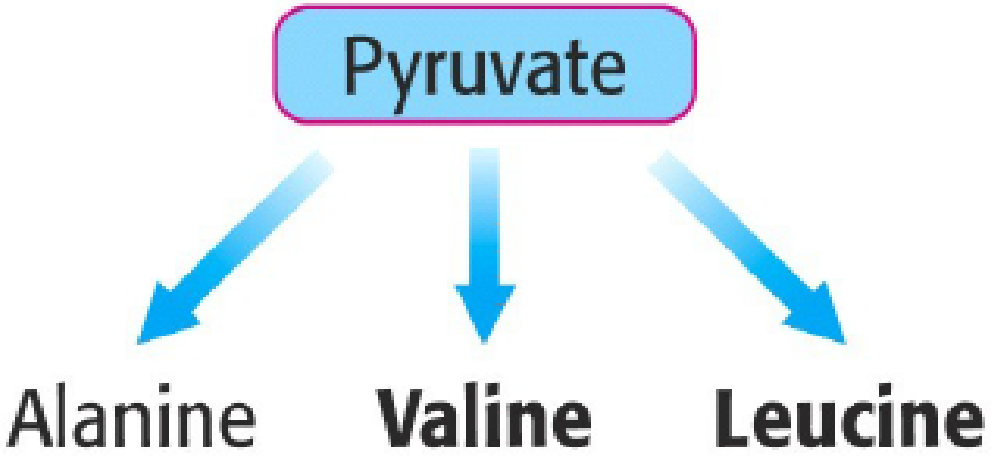
BIOSYNTHESIS OF Some Amino Acids

The pathways for the biosynthesis of amino acids are diverse

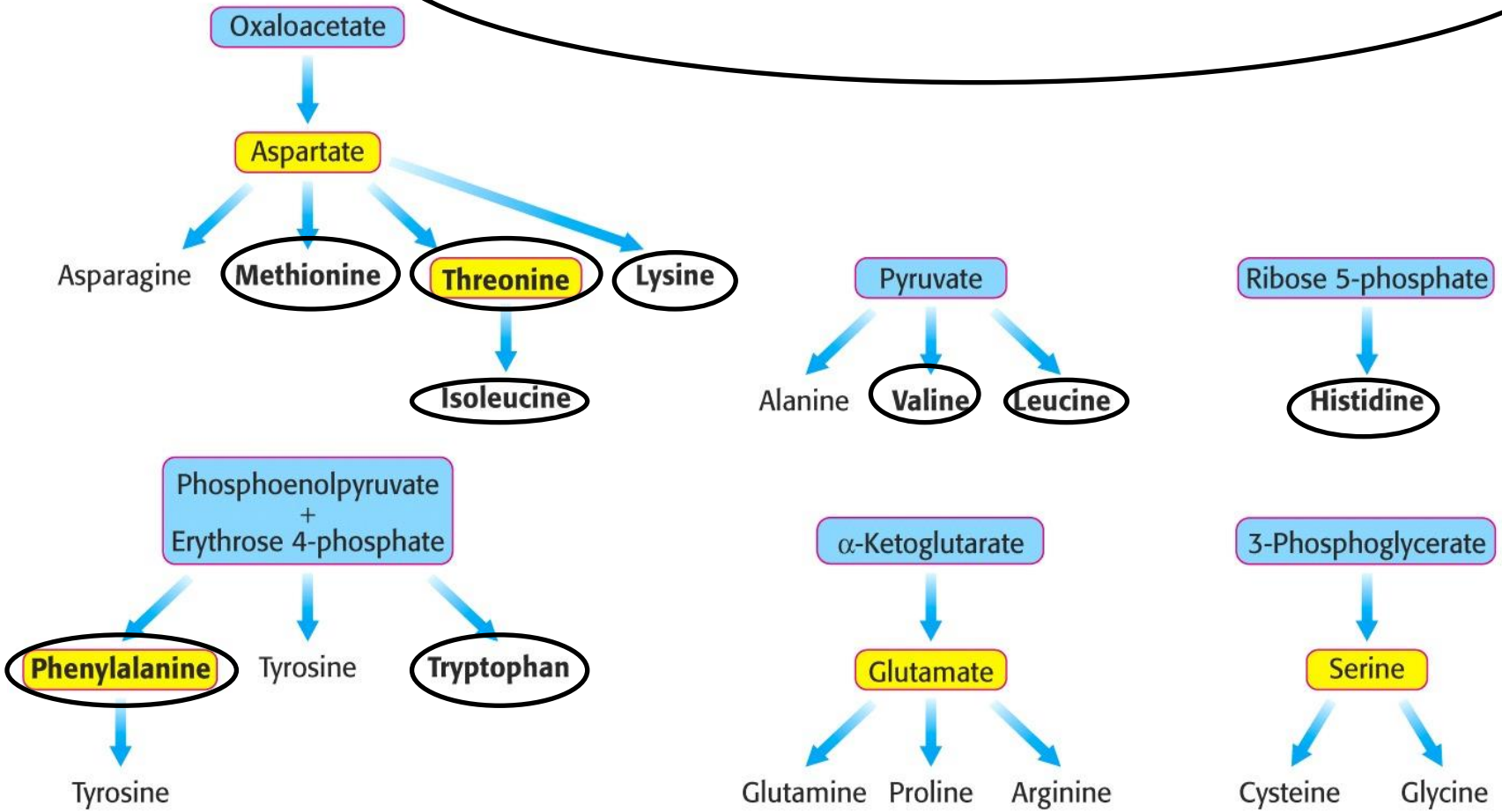
Common feature: *carbon skeletons come from intermediates of*

- *glycolysis,*
- *pentose phosphate pathway,*
- *citric acid cycle.*

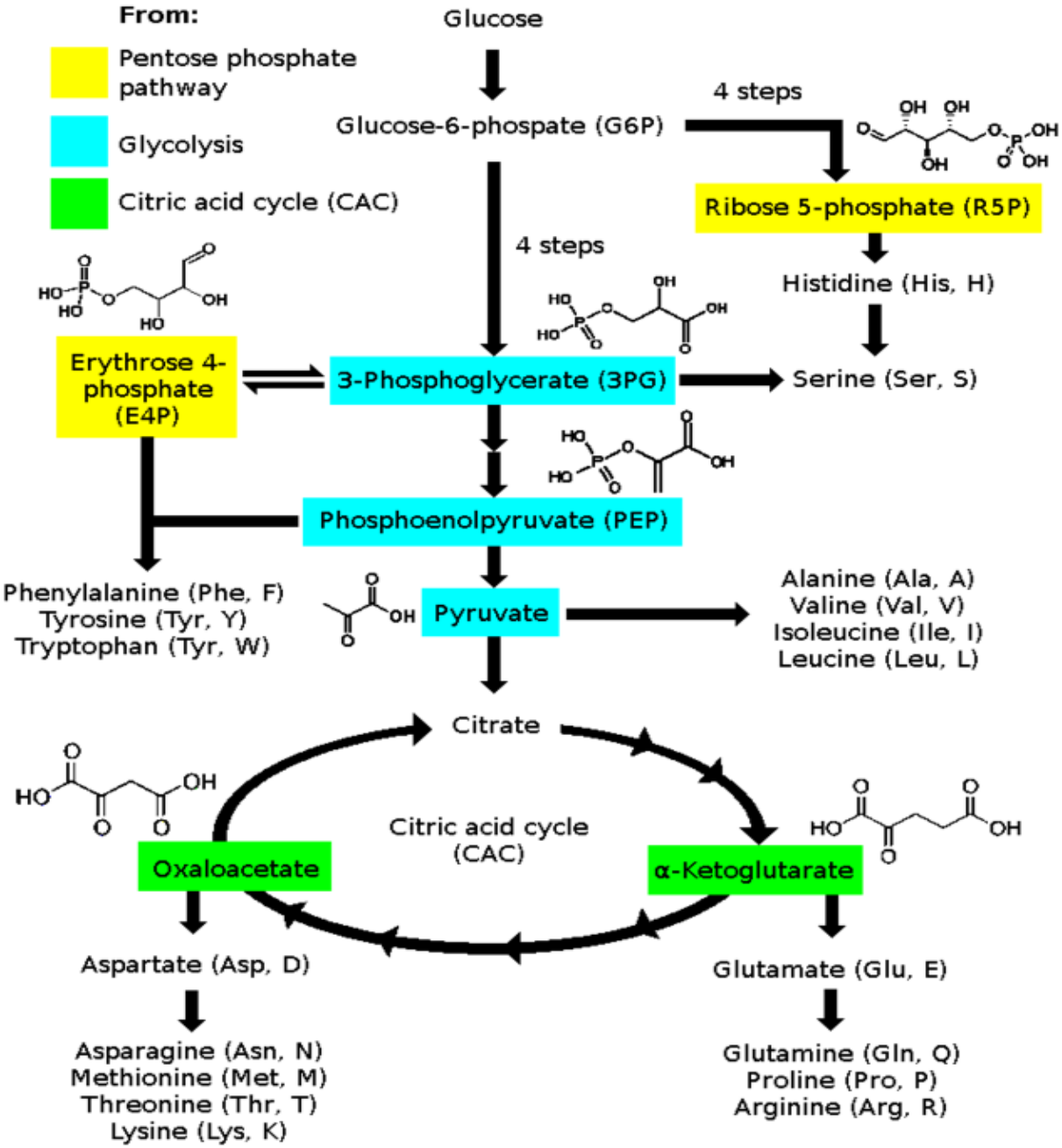
All amino acids are grouped into families according to the intermediates that they are made from



The essential amino acids cannot be made by humans and must be obtained in the diet.



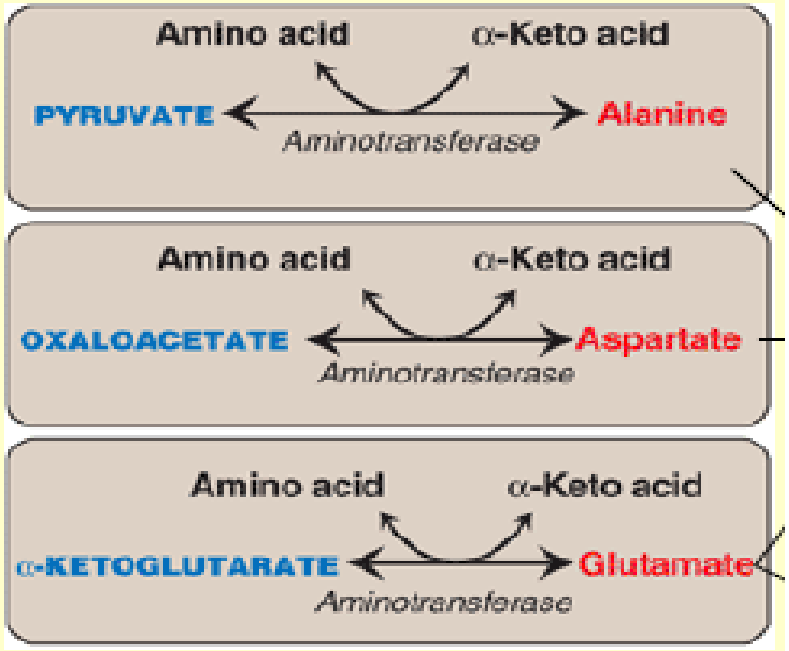
Amino Acids Synthesis



A. Synthesis from -keto acids:

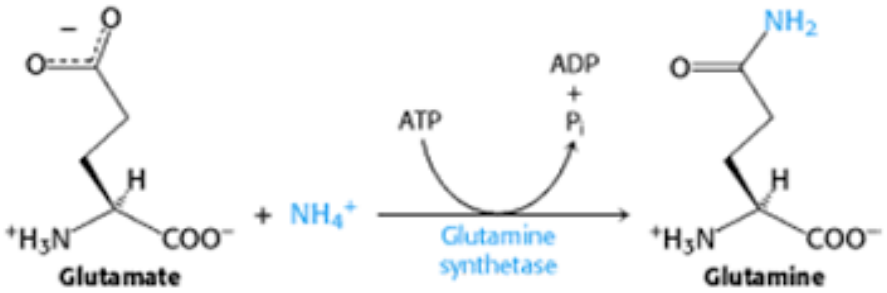
Alanine, aspartate, and glutamate are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-keto - glutarate, respectively.

glutamate, aspartate, alanine and glutamine are present in mammalian cells at much higher concentrations than the other 16 AA.



2. B. Synthesis by amidation:

- **1. Glutamine:** This AA is formed from glutamate by glutamine synthetase. The reaction is driven by the hydrolysis of ATP

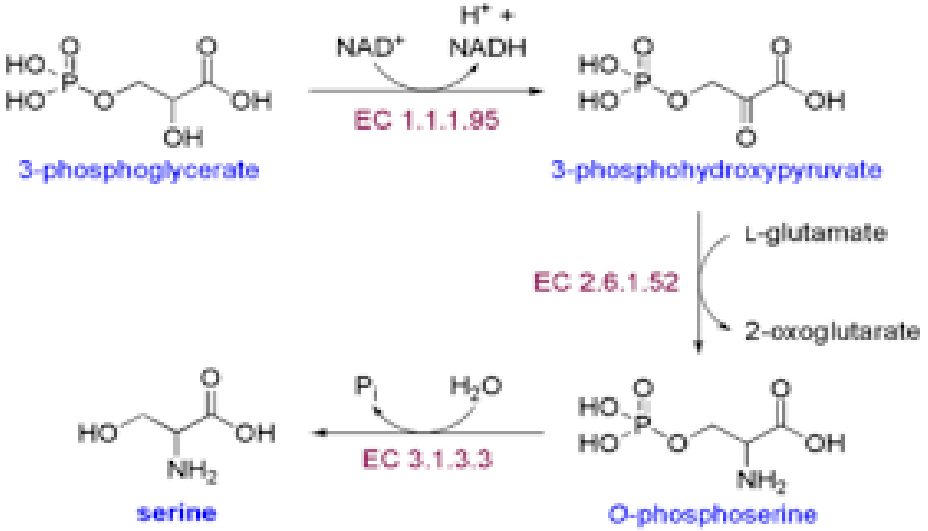


- **Asparagine:** This AA, is formed from aspartate by asparagine synthetase, using glutamine as the amide donor.

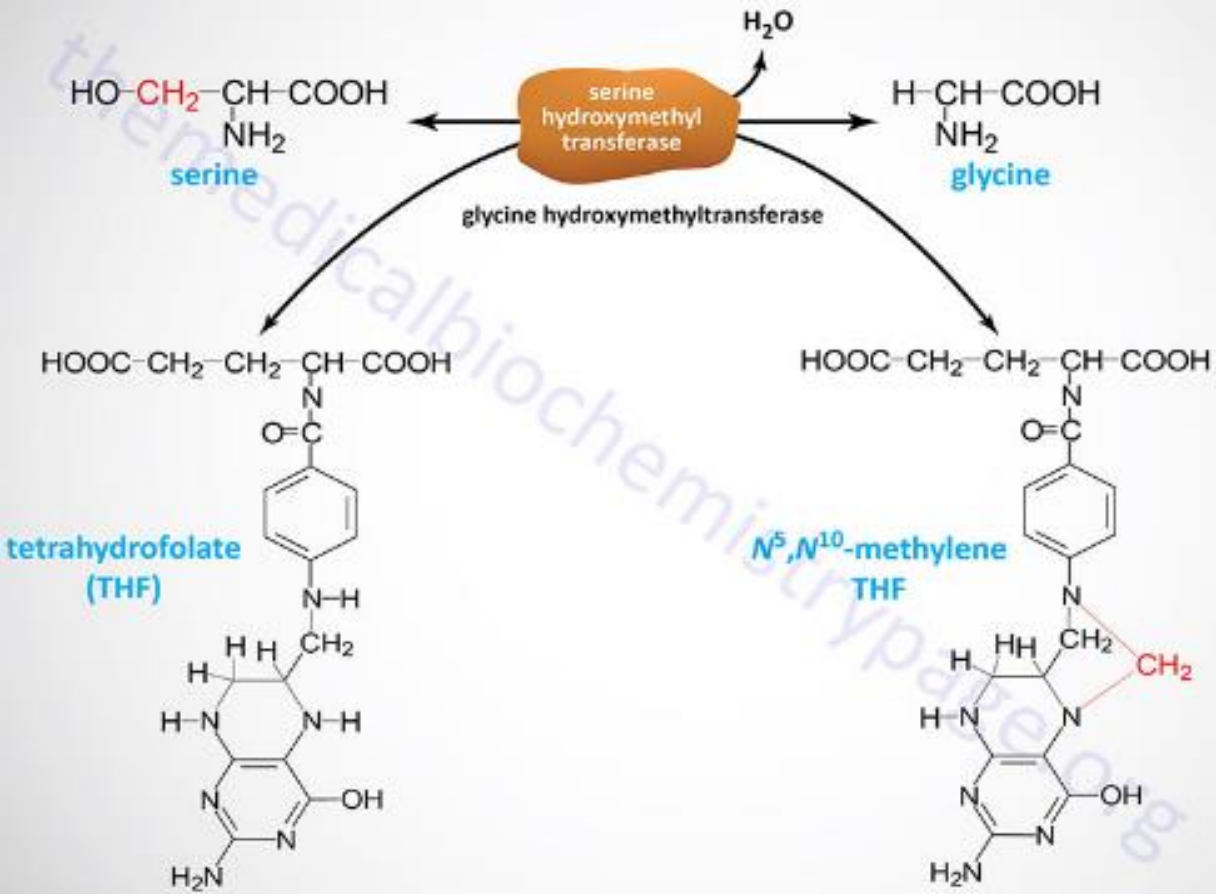
C. Proline: Glutamate is converted to proline by cyclization and reduction reactions.

D. Serine, glycine, and cysteine

1. **Serine:** This amino acid arises from 3-phosphoglycerate (intermediate in glycolysis), which is first oxidized to 3-phosphopyruvate, and then transaminated to 3-phospho serine. Serine is formed by hydrolysis of the phosphate ester.



- **2. Glycine:** This amino acid is synthesized from serine by removal of a hydroxy-methyl group (also by serine hydroxymethyl transferase).



Functions of Glycine:

1.Required for protein synthesis.

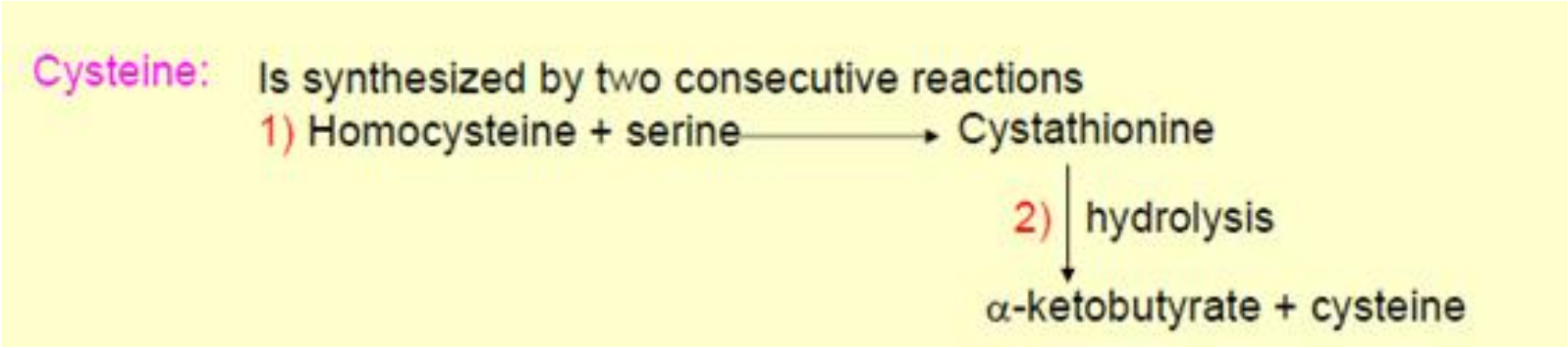
2.It forms many biologically important compounds – glucose, serine (a non-essential amino acid), heme, conjugated bile acids, creatine, glutathione and purines

3.It provides its carbon atom for one carbon pool.

4.It is required for certain detoxification reactions.

4.It acts as a neurotransmitter

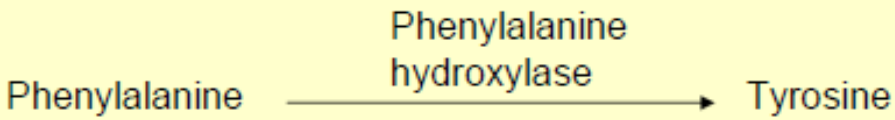
- **3. Cysteine:** First, homo cysteine combines with serine, forming cystathionine that, in turn, is hydrolyzed to ⟨ -ketobutyrate and cysteine. Homocysteine is derived from methionine



Biosynthesis of nonessential amino acids

E. Tyrosine

The reaction requires molecular oxygen and the coenzyme tetra hydrobiopterin (BH4)



Tyrosine and Cysteine are non essential AA. But there synthesis is dependent on the essential AAs phenylalanine and methionine resp.
Hence, these AAs are non essential only when there is an adequate supply of essential AA.

Conversion of AA to specialized products

Amino acids are precurseors for:

Porphyrines

-Heme

Catecholamines (Dopamine, epinephrine, Norepinephrine)

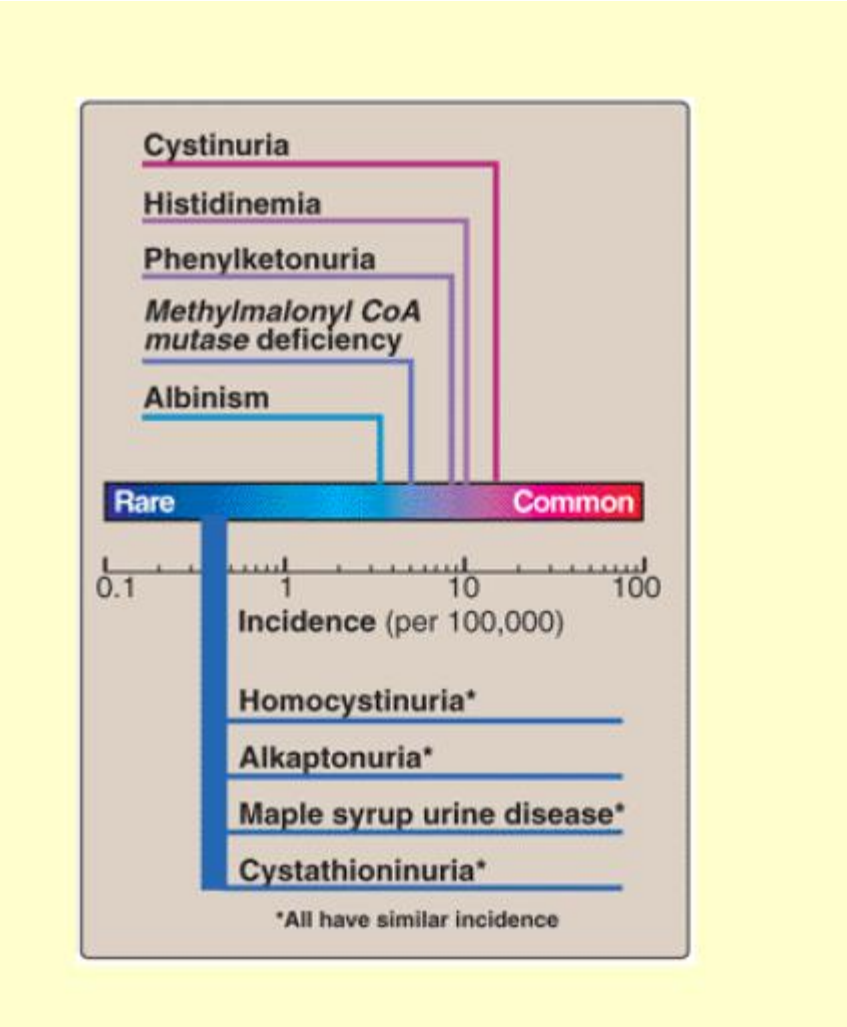
Histamine

Serotonine

Creatine

Melanin

Examples of Metabolic Defects in Amino Acids Metabolism



بعض الاضطرابات الجينيّة البشريّة التي تؤثّر على استقلاب الحموض الأمينيّة:

المرض	سببه
البَهَق Albinism	عوز أنزيم تيروزين ٣-مونو أوكسيجيناز
بيلة الألكابتون Alkabtonuria	عوز أنزيم هوموجينتيزات ٢,١-دي أوكسيجيناز
بيلة شراب القَيْقَب Maple syrup urine diseasse	عوز أنزيم ديهيدروجيناز الخاصّ بالأحماض الكيتونيّة من نوع ألفا ذات السلاسل المتفرّعة، وسمّي هذا المرض بهذا الاسم لأنّ بول المرضى به له رائحة شبيهة برائحة شجرة القيقب
Hartnup's disease داء هارتنب (سوء استقلاب النيكوتيناميد)	النقل الكلوي للأنزيم المحايد AA

Phenylketonuria

Cause

- PKU is caused by a defect in the gene that helps create **phenylalanine hydroxylase**
- Unable to break down phenylalanine.
- This causes a buildup of phenylalanine in the body

Symptoms

- Seizures
- Tremors, or trembling and shaking
- Stunted growth
- Hyperactivity
- A musty odor of their breath, skin, or urine

Albinism – genetically determined lack or deficit of enzyme **tyrosinase**

Tyrosinase in melanocytes oxidases tyrosine to DOPA and DOPA-chinone