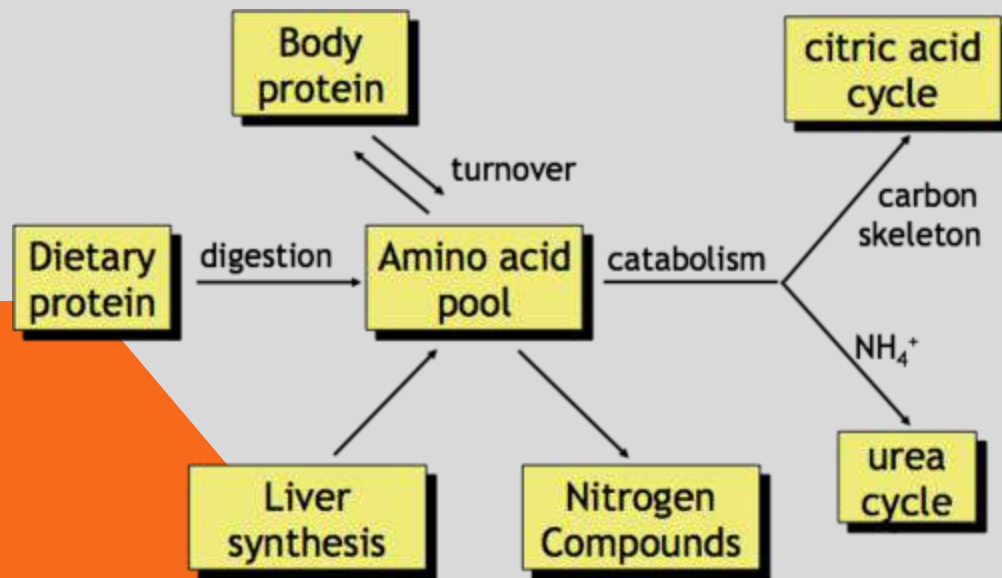


Metabolism of proteins & amino acids

by

Dr/ Heba M. Kareem



Essential amino acids :

Lysine, Leucine, Isoleucine, Valine, Methionine, Phenylalanine, Threonine, Tryptophan

Nonessential amino acids:

serine, tyrosine, Alanine, glycine, aspartate , glutamate, asparagine, proline , glutamine, cysteine ,

Histidine & arginine are semi essential. They are essential only for infants growth, but not for old children or adults where in adults histidine requirement is obtained by intestinal flora & arginine by urea cycle.

Nitrogen Balance (NB)

Nitrogen balance is a comparison between
Nitrogen intake (in the form of dietary protein)
and
Nitrogen loss (as undigested protein in feces ,
NPN as urea, ammonia, creatinine & uric acid in urine,
sweat & saliva & **losses** by hair, nail, skin).

- NB is important in defining
1. overall protein metabolism of an individual
 2. nutritional nitrogen requirement.

Three states are known for NB:

a) Normal adult: will be in nitrogen equilibrium,
Losses = Intake

b) Positive Nitrogen balance:

Nitrogen intake more than losses (High formation of tissue proteins) occurs in growing children, pregnancy, lactation and convalescence.

c) Negative Nitrogen balance:

Nitrogen losses more than intake occurs in:- (Low intake of proteins) in starvation, malnutrition, GIT diseases

- (High loss of tissue proteins) in wasting diseases like

burns, hemorrhage & kidney diseases with albuminuria

- (High breakdown of tissue proteins)

Biological Value for Protein (BV)

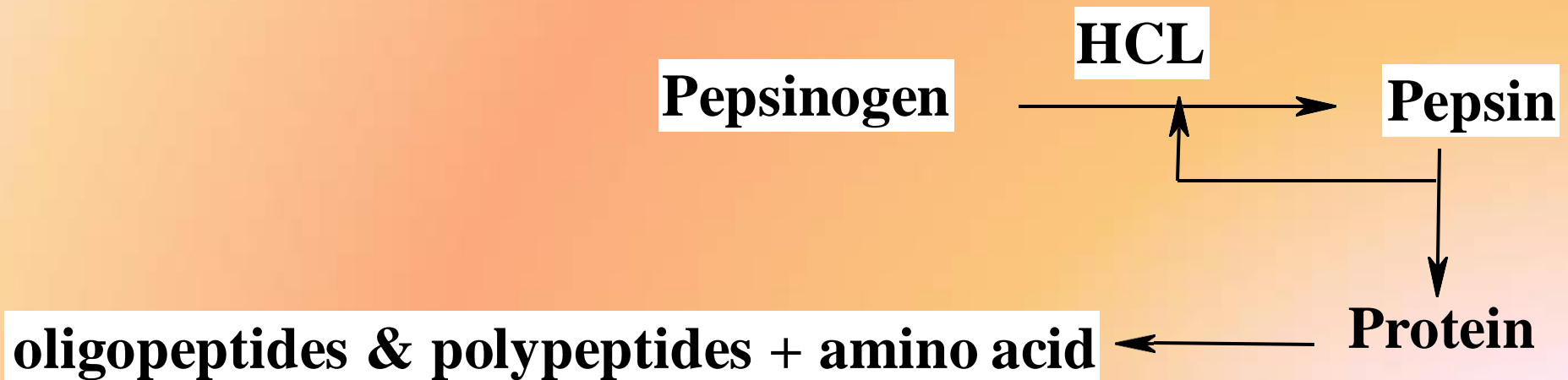
- * **BV** is : a measure for the ability of dietary protein to provide the **essential amino acids** required for tissue protein maintenance.
- * Proteins of animal sources (meat, milk, eggs) have high **BV** because they contain **all the essential amino acids**.
- * Proteins from plant sources (wheat, corn, beans) have low **BV** thus combination of **more than one** plant protein is required (**a vegetarian diet**) to increase its BV.

DIGESTION OF PROTEIN

- Proteins are broken down by hydrolyases (peptidases or proteases)
- **Endopeptidases** attack internal bonds and liberate large peptide fragments (pepsin, trypsin, Chymotrypsin & Elastase)
- **Exopeptidases** remove one amino acid at a time from – COOH or –NH₂ terminus (aminopeptidase & carboxypeptidase)
- **Endopeptidases** are important for initial breakdown of long polypeptides into smaller ones which then attacked by exopeptidases.
- Digestion of protein can be divided into: a gastric, pancreatic and intestinal phases.

I. Gastric Phase of Protein Digestion: (represents 15% of protein digestion)

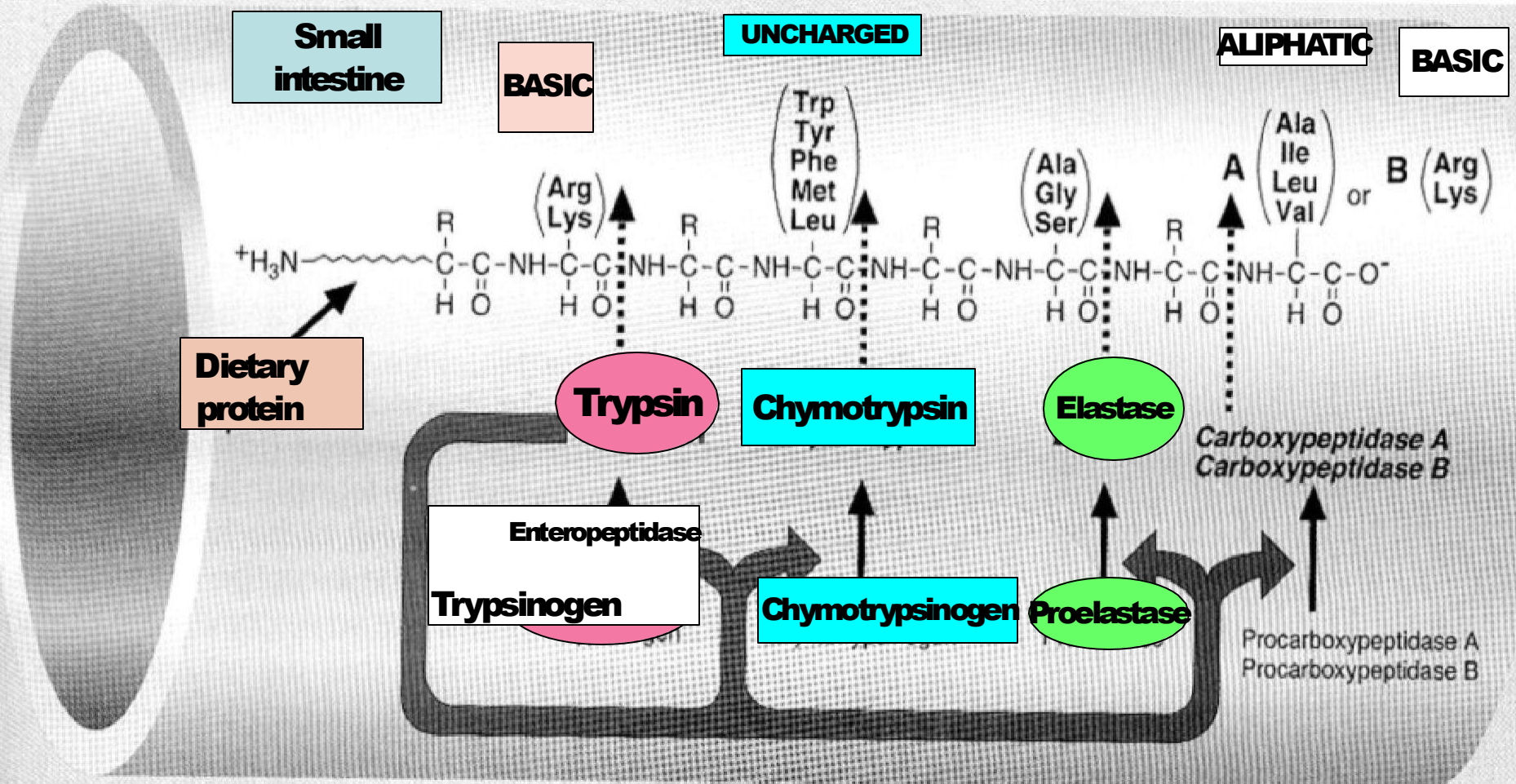
- 1 **Pepsin**: in adult stomach , secreted as pepsinogen. It is specific for peptide bond formed by aromatic or acidic amino acids



- 2 **Rennin**: in infants for digestion of milk protein (casein).

II. Pancreatic Phase of Protein Digestion

- This phase ends with **free amino acids** and **small peptides** of 2-8 amino acid residues which account for 60% of protein digestion



III. Intestinal Phase of protein digestion:

- Intestinal enzymes are:
aminopeptidases (attack peptide bond next to amino terminal of polypeptide) &
dipeptidases
- The end product is **free amino acids**
dipeptides & tripeptides.

Absorption of Amino Acids and Di- & Tripeptides:

***L-amino acids** are actively transported across the intestinal mucosa (need carrier, Na⁺ pump, Na⁺ ions, ATP).

Different carrier transport systems are:

- a) For **neutral** amino acids.
- b) For **basic** amino acids and **cysteine**.
- c) For **imino acids** and **glycine**.
- d) For **acidic** amino acids.
- e) For **B-amino acids** (B-alanine & taurine).

***D-isomers** transported by simple diffusion.

→ **Tri- & Dipeptides** can actively transported faster than their individual amino acids.

→ **intact proteins:**

1. **Immunoglobulins of colostrum** are absorbed by **neonatal intestines** through endocytosis without loss of their biological activity and thus provide **passive** immunity to the infants.

2. **Vaccines (undigested polypeptides)** in **children and adults** are absorbed without loss of their biological activity producing **antigenic** reaction and **immunologic** response.

METABOLIC FATES OF AMINO ACIDS:

1 Body **protein** biosynthesis.

2 Small **peptide** biosynthesis(GSH).

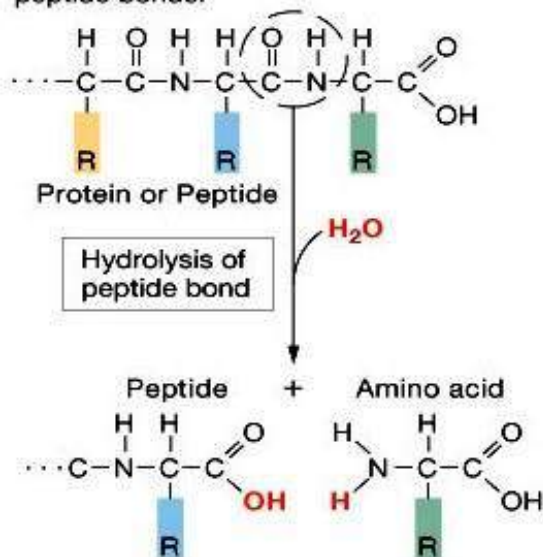
3-Synthesis of **non-protein nitrogenous (NPN)** compounds (creatine, urea, ammonia and uric acid)

4- **Deamination & Transamination** to synthesized a new amino acid or glucose or ketone bodies or produce energy in starvation.

Protein Catabolism

(a) Protein catabolism

Proteins are broken into amino acids by hydrolysis of their peptide bonds.

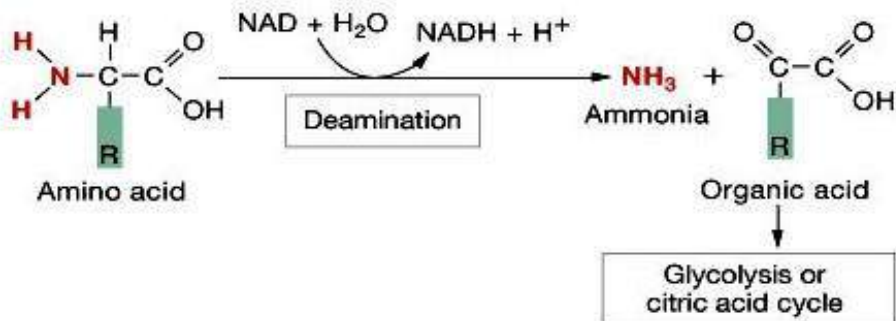


(c) Ammonia is toxic and must be converted to urea.



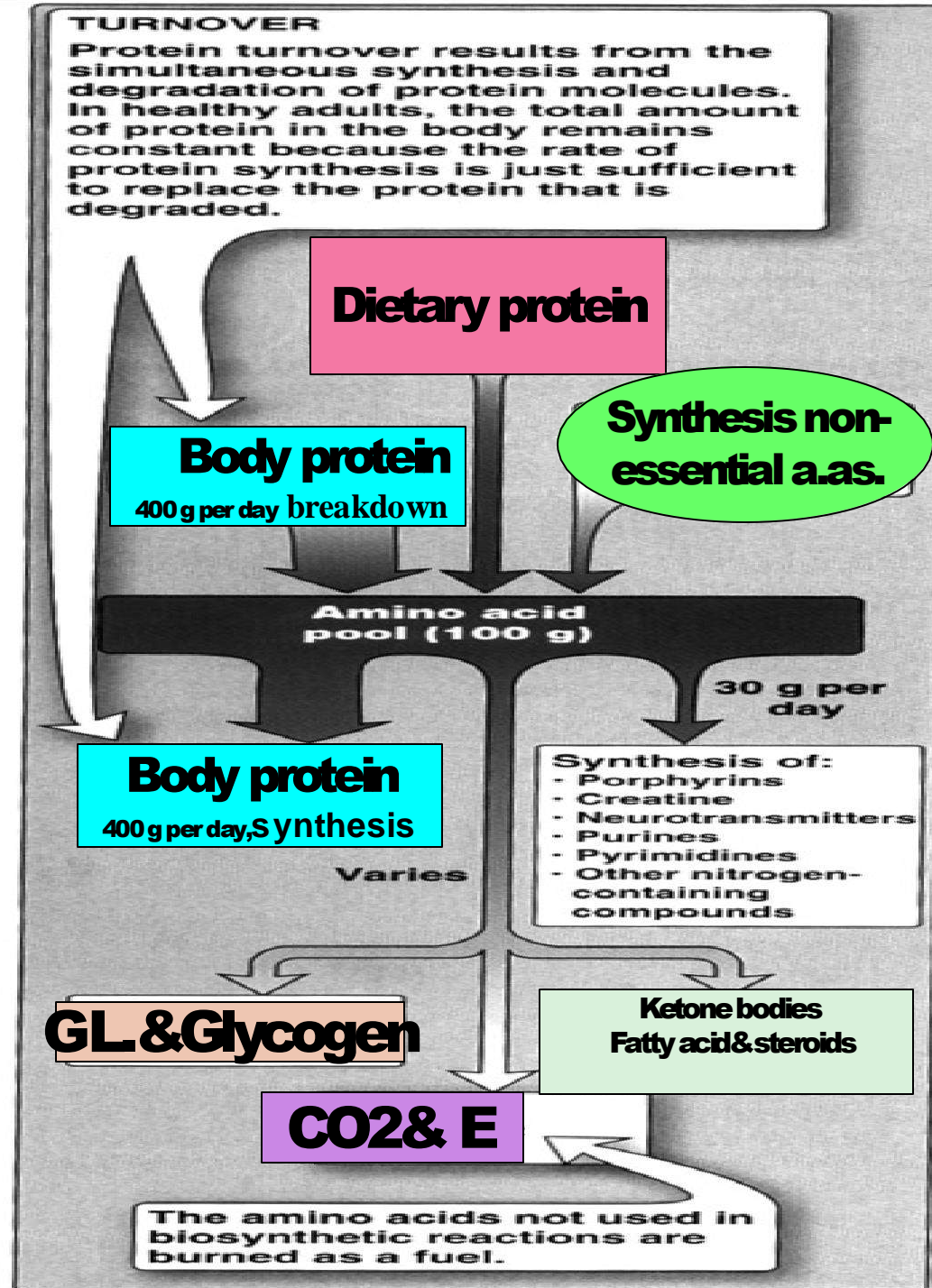
(b) Deamination

Removal of the amino group from an amino acid creates ammonia and an organic acid.



Sources & fates of amino acids:

- Protein turnover : (results from simultaneous **synthesis & breakdown** of proteins molecules)
- Total amount of protein in body of healthy adult is **constant** (due to rate of protein **synthesis** is equal to the rate of its **breakdown**).



Metabolism OF AMINO ACIDS:

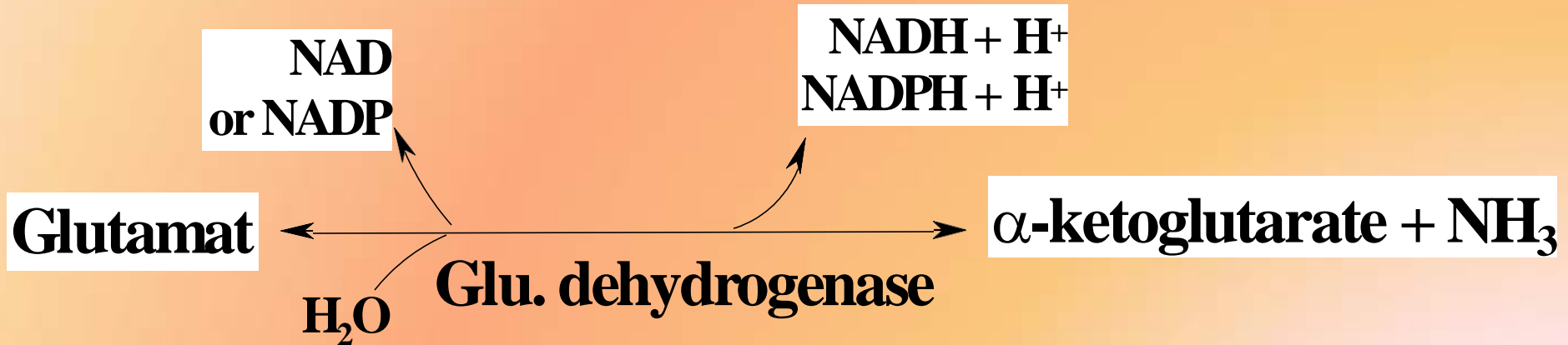
1. Removal of ammonia by :
- $$\text{NH}_2 - \underset{\downarrow}{\overset{\text{R}}{\text{CH}}} - \text{COOH}$$
- Deamination
 - **Oxidative deamination**
 - 1) glutamate dehydrogenase in mitochondria
 - 2) amino acid oxidase in peroxisomes
 - **Direct deamination (nonoxidative)**
 - 1) dea. by dehydration (-H₂O)
 - 2) dea. by desulhydration (-H₂S)
 - Transamination (GPT & GOT)
 - and transdeamination.
2. Fate of carbon-skeletons of amino acids
3. Metabolism of ammonia

Deamination of Amino Acids



a) Oxidative Deamination:

-1 Glutamate dehydrogenase , mitochondrial , potent, major deaminase



It is allosterically stimulated by ADP
inhibited by ATP, GTP & NADH.

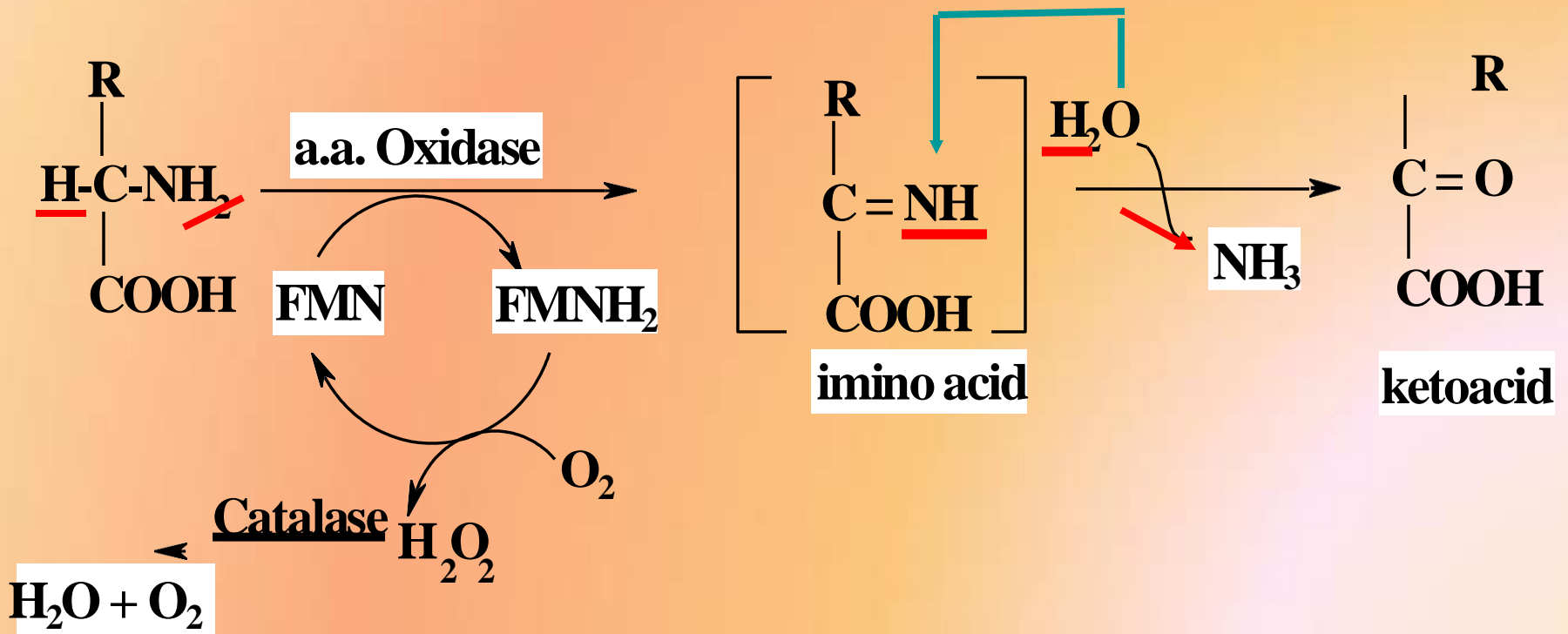
Thus, high ADP (low caloric intake) increases protein degradation
high ATP (well fed-state) decreases deamination of amino acids & increases protein synthesis.

-2 Amino Acid Oxidases:

The **minor** pathway for deamination of amino acids.

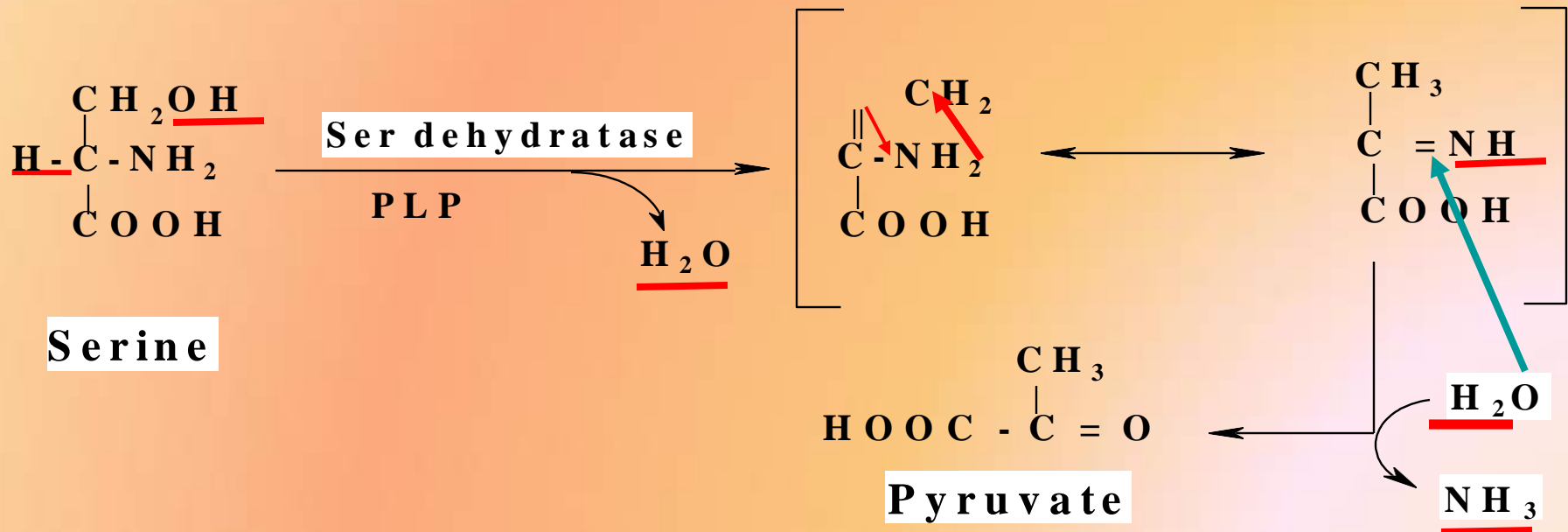
They are found **in peroxisomes** of liver and kidney.

L-amino acid oxidases utilize **FMN** while **D**-a.a. oxidases utilize **FAD**.

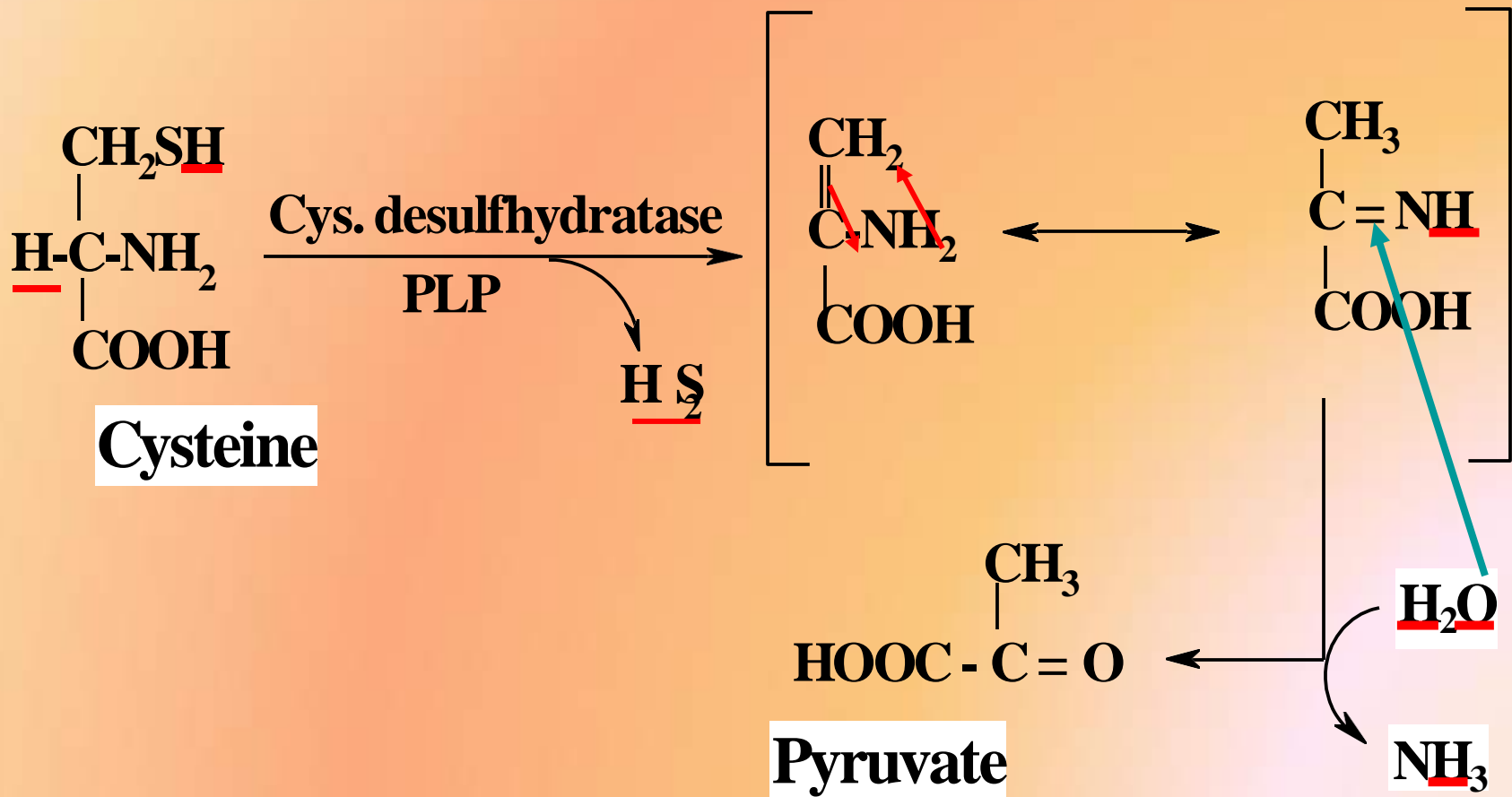


b) Non-oxidative deamination: (Direct Deamination)

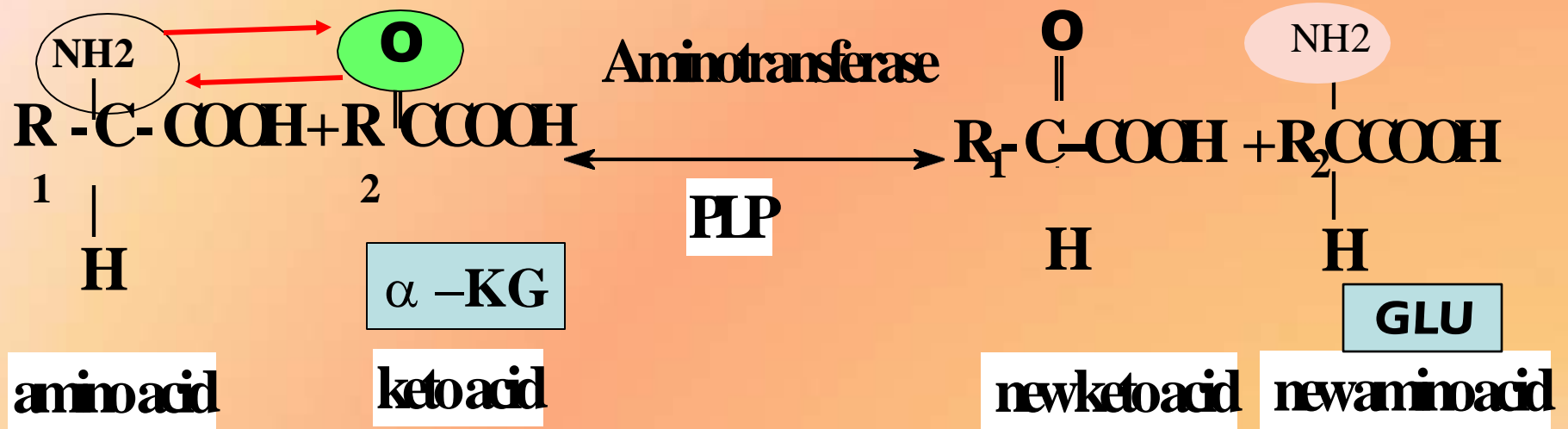
-1 Deamination by dehydration: Serine & Threonine



-2 Deamination by desulfhydration : (cysteine)



Transamination:



Aminotransferases are **active** both in cytoplasm and mitochondria e.g.:

1. Aspartate aminotransferase (**AST**), Glutamate oxaloacetate transaminase (**GOT**)

2. Alanine aminotransferase (**ALT**), Glutamate pyruvate transaminase, (**GPT**)

In all transamination reactions, α -ketoglutarate (α -**KG**) acts as amino group acceptor.

Most, but not all amino acids undergo transamination reaction with few exceptions (**lysine, threonine and imino acids**)

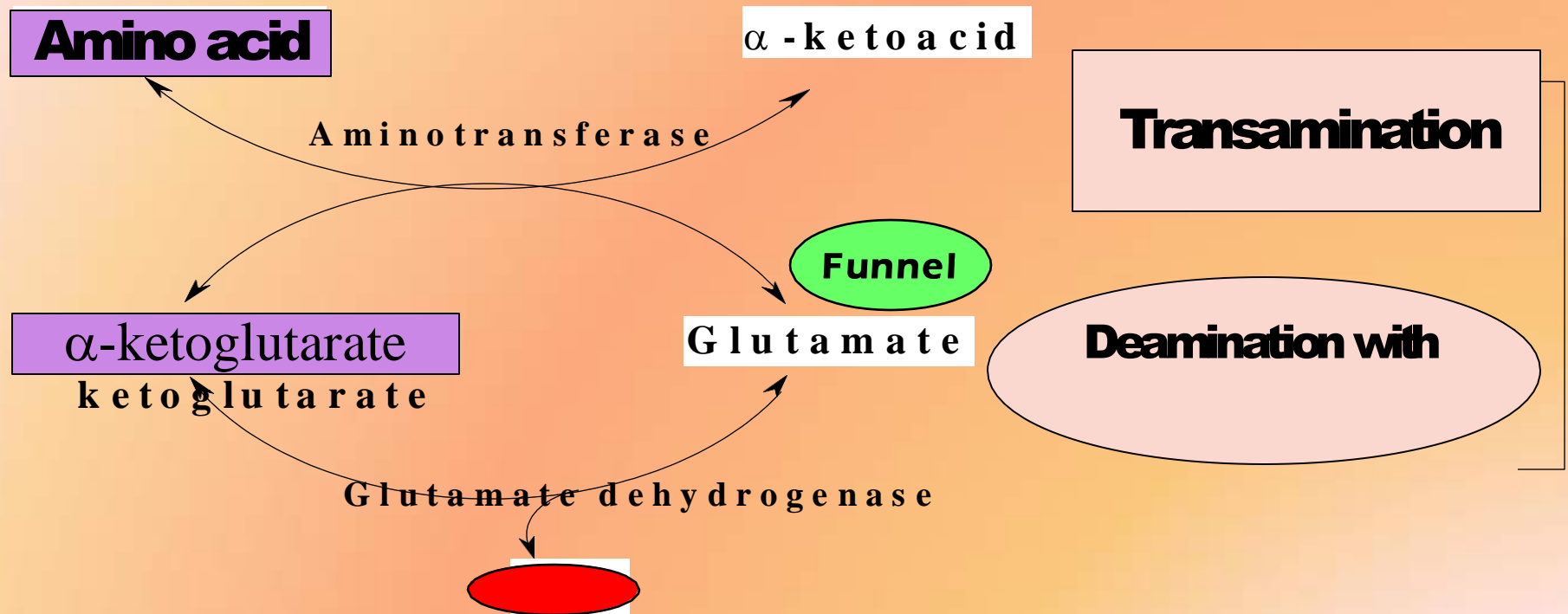
Metabolic Significance of Transamination Reactions

- It is an **exchange of amino nitrogen** between the molecules without a net loss

This metabolically important because:

- 1) There is **no mechanism for storage** of a protein or amino acids.
- 2) In case of low energy (caloric shortage), the organism depends on **oxidation of the ketoacids** derived from transamination of amino acids.
- 3) It is important for formation of the **non-essential amino acids**

Transdeamination:



So... the most **important** and **rapid** way to deamination of amino acids **is first** transamination with α -ketoglutarate **followed** by deamination of glutamate.

Therefore **glutamate** through transdeamination serves to a **funnel** ammonia from all amino acids.



THE FATE OF CARBON-SKELETONS OF AMINO ACIDS

a) Simple degradation:



b) Complex degradation:

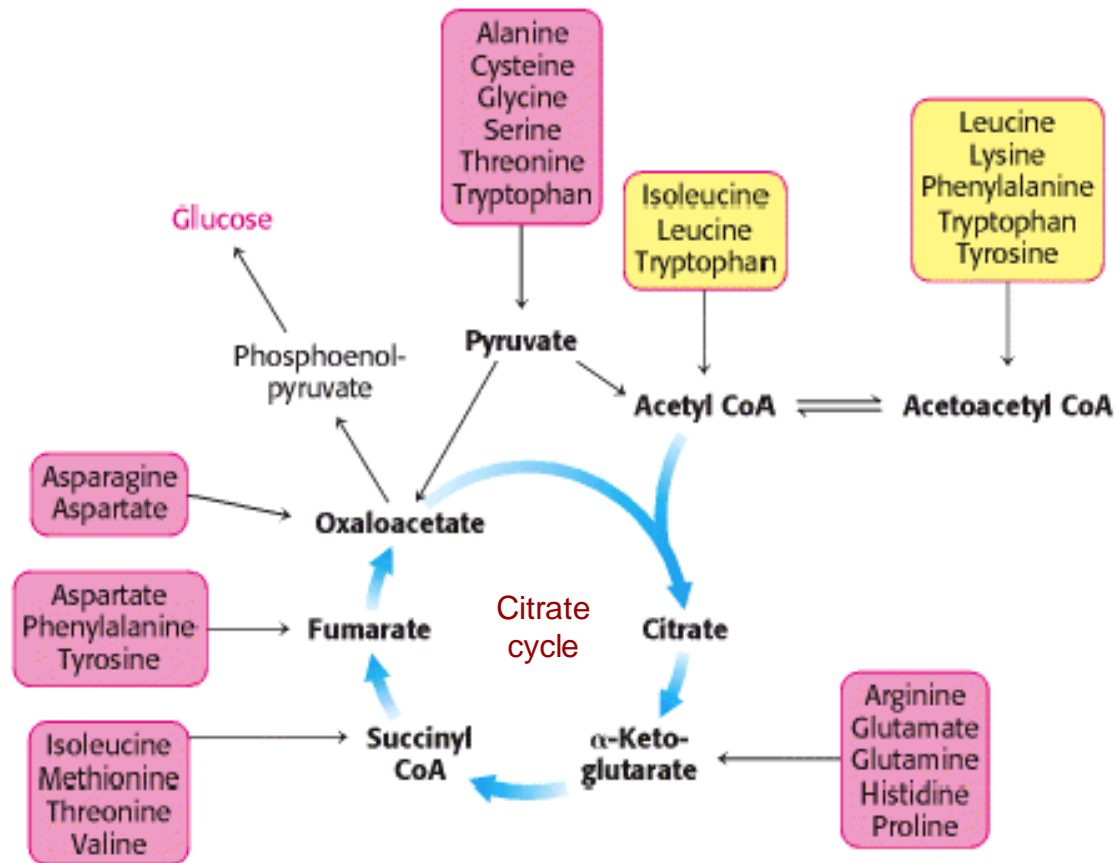
(amino acid--- Keto acid----- **complex** pathway----- Common metabolic intermediate)

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.

The common metabolic intermediates that arise from the degradations of amino acids are: acetyl CoA, pyruvate, one of the krebs cycle intermediates (α -ketoglutarate, succinyl CoA, fumarate & oxaloacetate)



Fates of the Carbon Skeletons of Amino Acids. Glucogenic amino acids are shaded red, and ketogenic amino acids are shaded yellow. Most amino acids are both glucogenic and ketogenic.

Metabolism of the Common Intermediates

- 1. Oxidation:** amino acids can be oxidized in TCA cycle with **energy** production
- 2. Fatty acids synthesis:** some amino acids provide **acetyl CoA** e.g. leucine and lysine (ketogenic amino acids).
- 3. Gluconeogenesis:** ketoacids derived from amino acids are used for synthesis of **glucose** (is important in starvation).

Glucogenic

Ala, Ser, Gly, Cys,
Arg, His, Pro, Glu,
Gln, Val, Met, Asp, Asn.

Ketogenic

Leu , Lys

Glucogenic & Ketogenic

Phe, Tyr, Trp, Ile, Thr

METABOLISM OF AMMONIA

Ammonia is formed in body from:

a) *From amino acids:* 1. Transdeamination in liver
2. amino acid oxidases and amino acid deaminases in liver and kidney.

b) *Deamination of physiological amines:* by monoamine oxidase
(histamine, adrenaline, dopamine and serotonin)

c) *Deamination of purine nucleotides:* especially adenine nucleotides



d) *Pyrimidine catabolism.*

e) *From bacterial action in the intestine on dietary protein & on urea in the gut.*

NH₃ is also produced by glutaminase on glutamine .

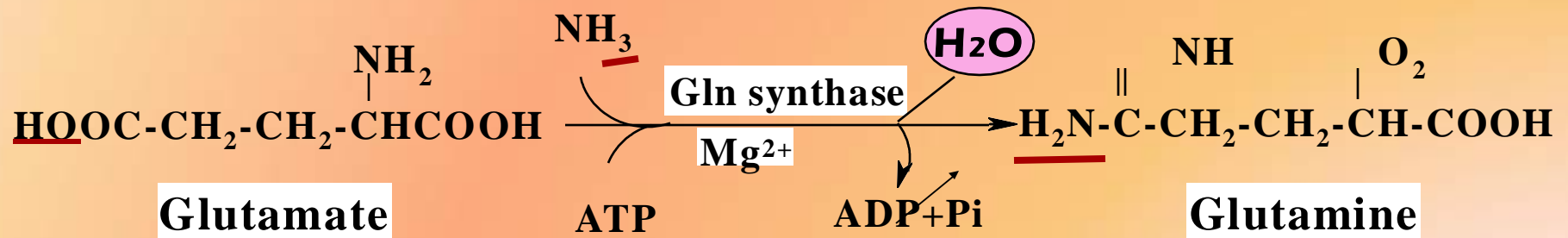
Metabolic Disposal of Ammonia

Ammonia is toxic to CNS, it is fixed into nontoxic metabolite for reuse or excretion according to the body needs:

a) Formation of Glutamate:



b) Glutamine Formation: Muscle, brain



Glutamine is storehouse of ammonia & transporter form of ammonia.

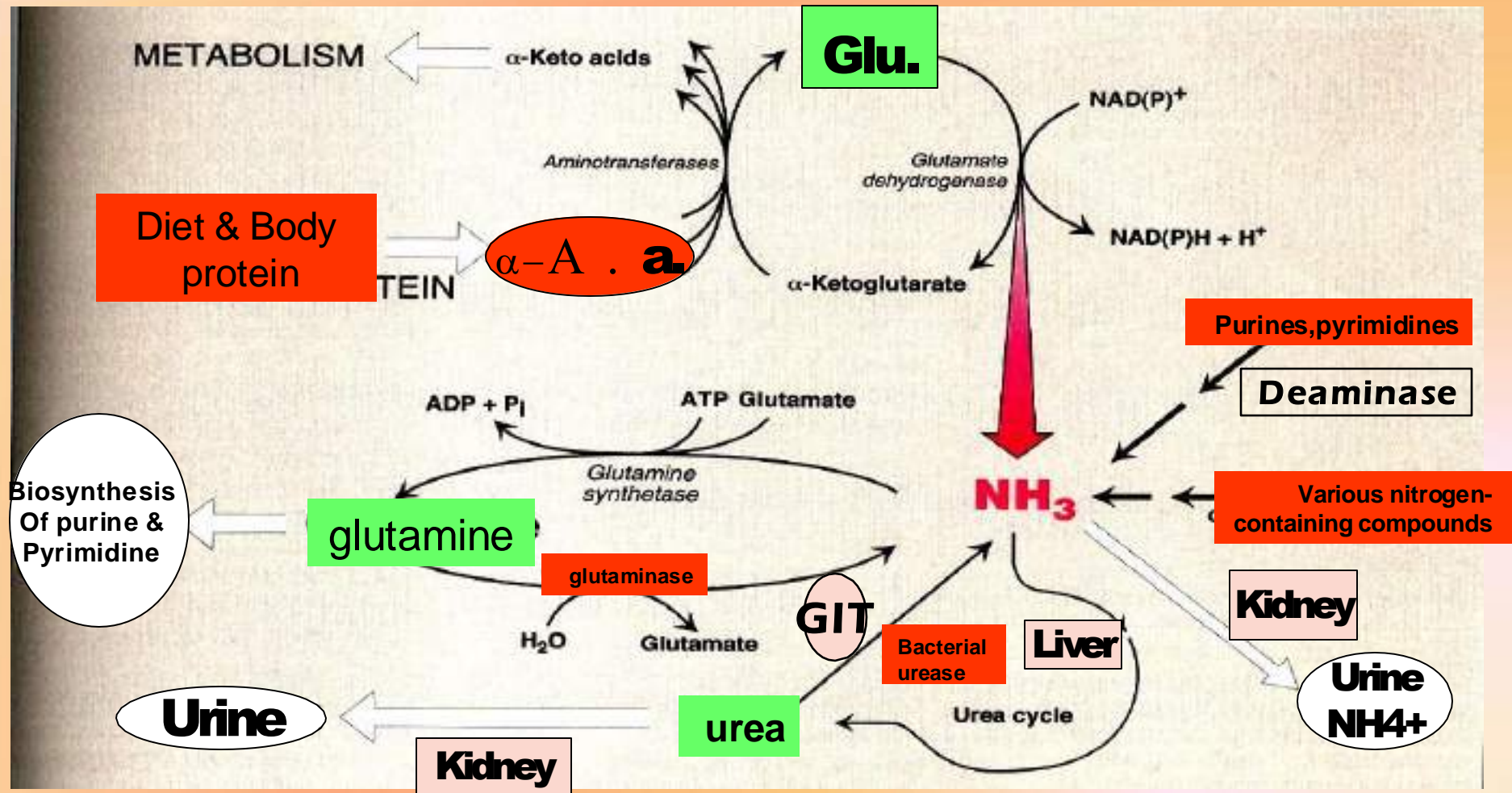
In brain, glutamine is the major mechanism for removal of ammonia while in liver is urea formation.

..Circulating glutamine is removed by kidney, liver and intestine where it is deamidated by glutaminase .

c) Urea formation



This reaction is important to **kidney** due to kidney excretes NH_4^+ ion to keep extracellular Na^+ ion in body **and** to maintain the acid-base balance.



c) Urea Formation

- ⌘ Urea is the **principal end-product** of protein metabolism in humans.
- ⌘ It is important route for **detoxication** of NH_3 .
- ⌘ It is **operated** in liver, **released** into blood and **cleared** by kidney.
- ⌘ Urea is **highly soluble, nontoxic** and has a **high nitrogen content (46%)**, so ...it represents about **80-90% of the nitrogen** excreted in urine per day in man
- ⌘ **Biosynthesis of urea in man is an energy- requiring process.**
- ⌘ **It takes place partially in mitochondria and partially in cytoplasm.**

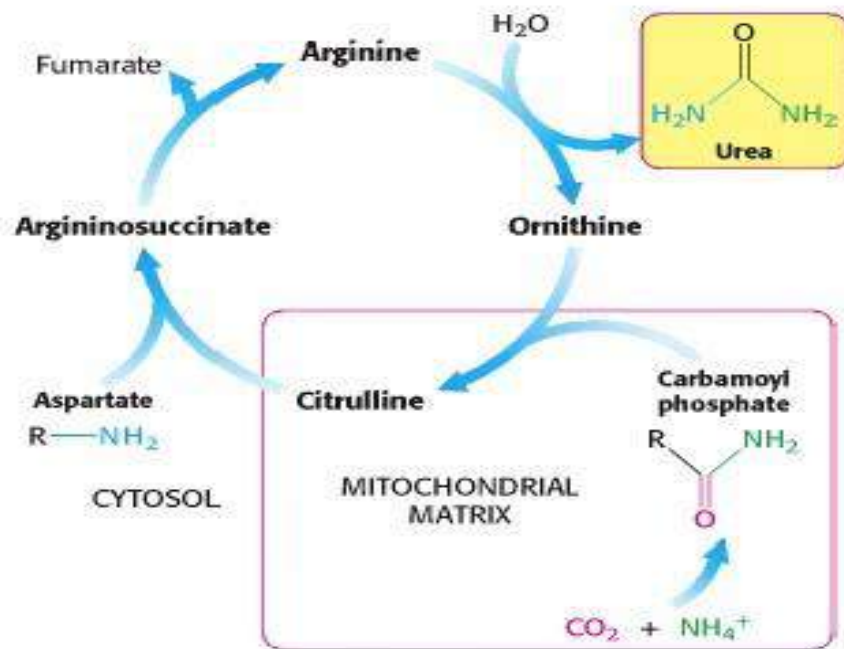


Figure 23.16. The Urea Cycle.



Figure 23.17. Metabolic Integration of Nitrogen Metabolism. The urea cycle, the citric acid cycle, and the transamination of oxaloacetate are linked by fumarate and aspartate.

Metabolic Significant Aspects of Urea Cycle

A) Energy Cost: Three ATP molecules and four high-energy phosphate bonds are utilized in the reactions..

B) urea cycle is related to TCA cycle:

1. CO₂

2. **Aspartate arises via transamination of oxaloacetate with glutamate.** Thus, depletion of oxaloacetate will decrease urea formation

3. **Fumarate** enters TCA cycle

C) Sources of Nitrogen in urea : free NH₃ and **aspartate**.

N.B. **glutamate** is the **immediate source** of both **NH₃** (via oxidative deamination by Glu. Dehyd.) and **aspartate** nitrogen (through transamination of oxaloacetate by AST).

Importance of Urea Cycle

1. Formation of arginine (in organisms synthesizing arginine) & formation of urea (in ureotelic organisms, man) due to presence of arginase.
2. **Liver** shows much **higher** activity of arginase than brain or kidney for formation of urea while **in brain or kidney** is the synthesis of arginine.
3. Synthesis of **non-protein amino acids** (ornithine and citrulline) in body.

Regulation of Urea Cycle

1) Activity of individual enzymes:

THE RATE LIMITING STEPS

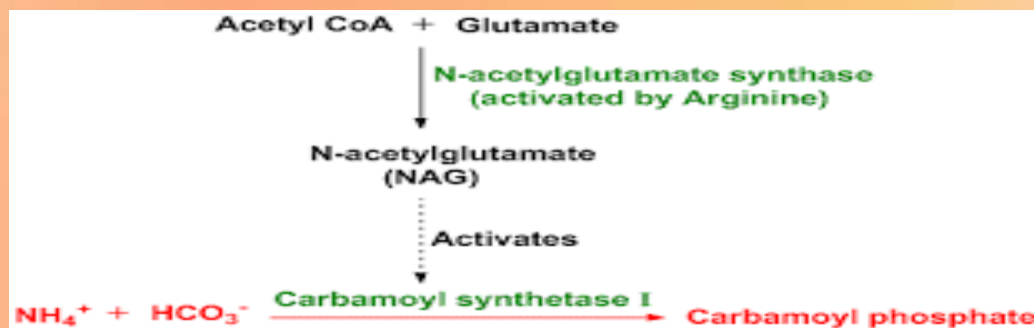
- a) carbamoyl phosphate synthase-1
- b) Ornithine transcarbamylase.
- c) Arginase.

⊗ ***N-acetylglutamate*** is activator for carbamoyl phosphate synthase-1

It enhances its affinity for ATP.

It is synthesized from acetyl CoA and glutamate.

its hepatic concentration increases after intake of a **protein diet**, leading to an increased rate of urea synthesis.



⊗ ***Activity of ornithine transcarbamylase*** is limited by the concentration of its co-substrate "ornithine".

-2 Regulation of the flux through the cycle:

a) Flux of ammonia:

1. by amino acids release from muscle
(alanine, glutamine),
2. metabolism of glutamine in the intestine
3. amino acids degradation in the liver.

b) Availability of ornithine.

c) Availability of aspartate:

since aspartate is required in equimolar amounts with ammonia, this is satisfied by of transdeamination .

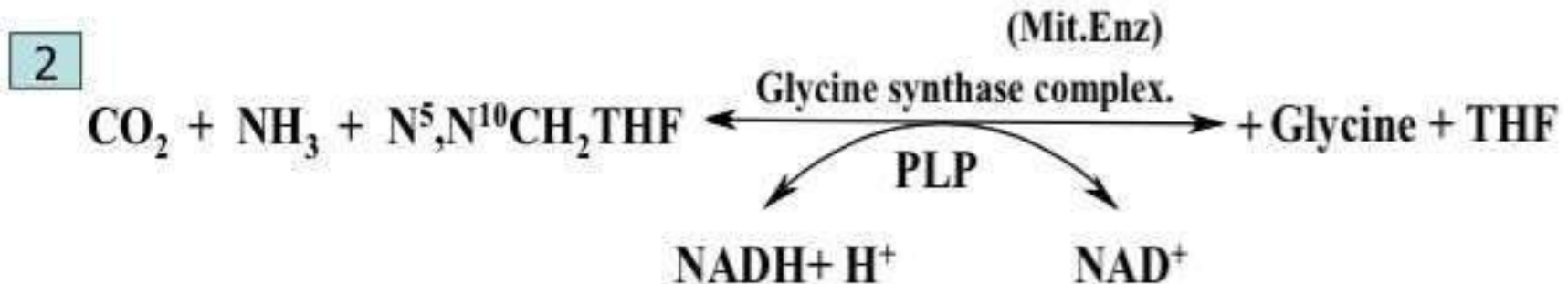
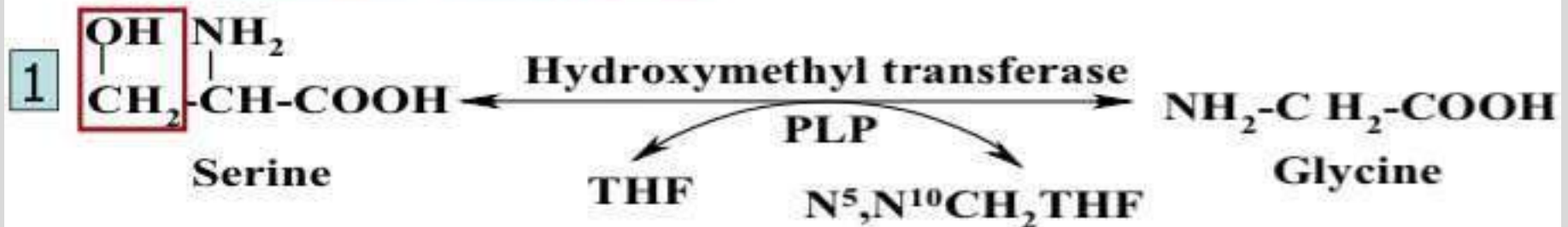
-3 Change in the level of Enzymes:

- **Arginase & other urea-forming enzymes** are adaptive enzymes thus
- a **protein-rich diet** will increase their **biosynthesis** rate & the opposite is true for **low protein diet**.
- However, **in starvation**, where the body is forced to use its own tissue protein as fuel, there is an **increase in urea-forming enzymes**.

METABOLISM OF INDIVIDUAL AMINO ACIDS

1. Metabolism of Glycine: nonessential, glucogenic.

Biosynthesis of glycine:



Special Functions of Glycine:

a-Protein, Hormones & enzymes.

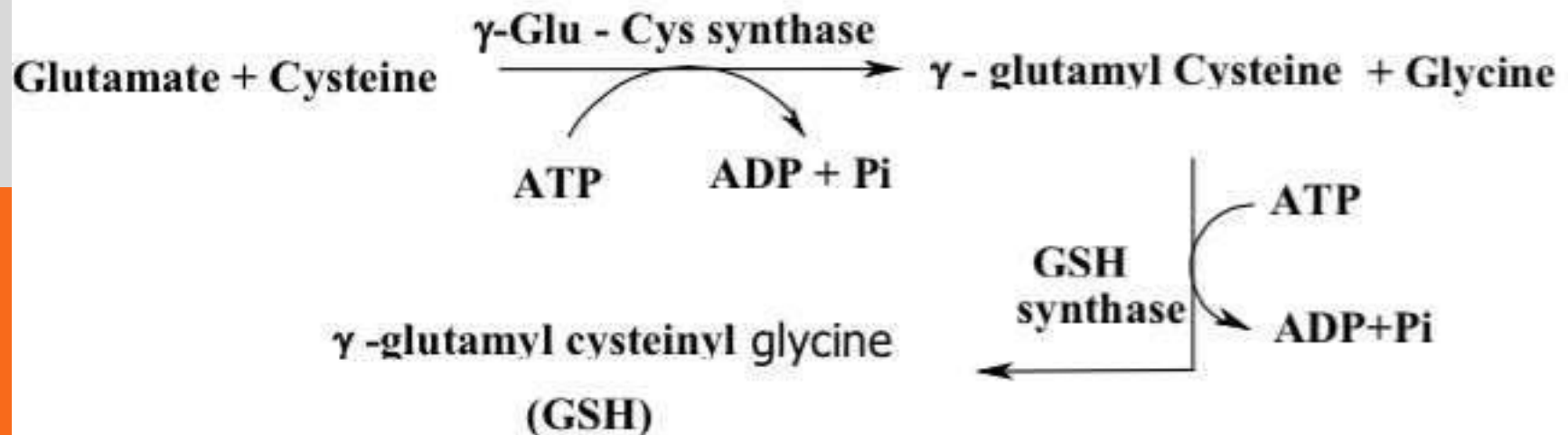
b- Heme c- Purines (C_4, C_5, N_7) d- Creatine

e- **Glutathione**

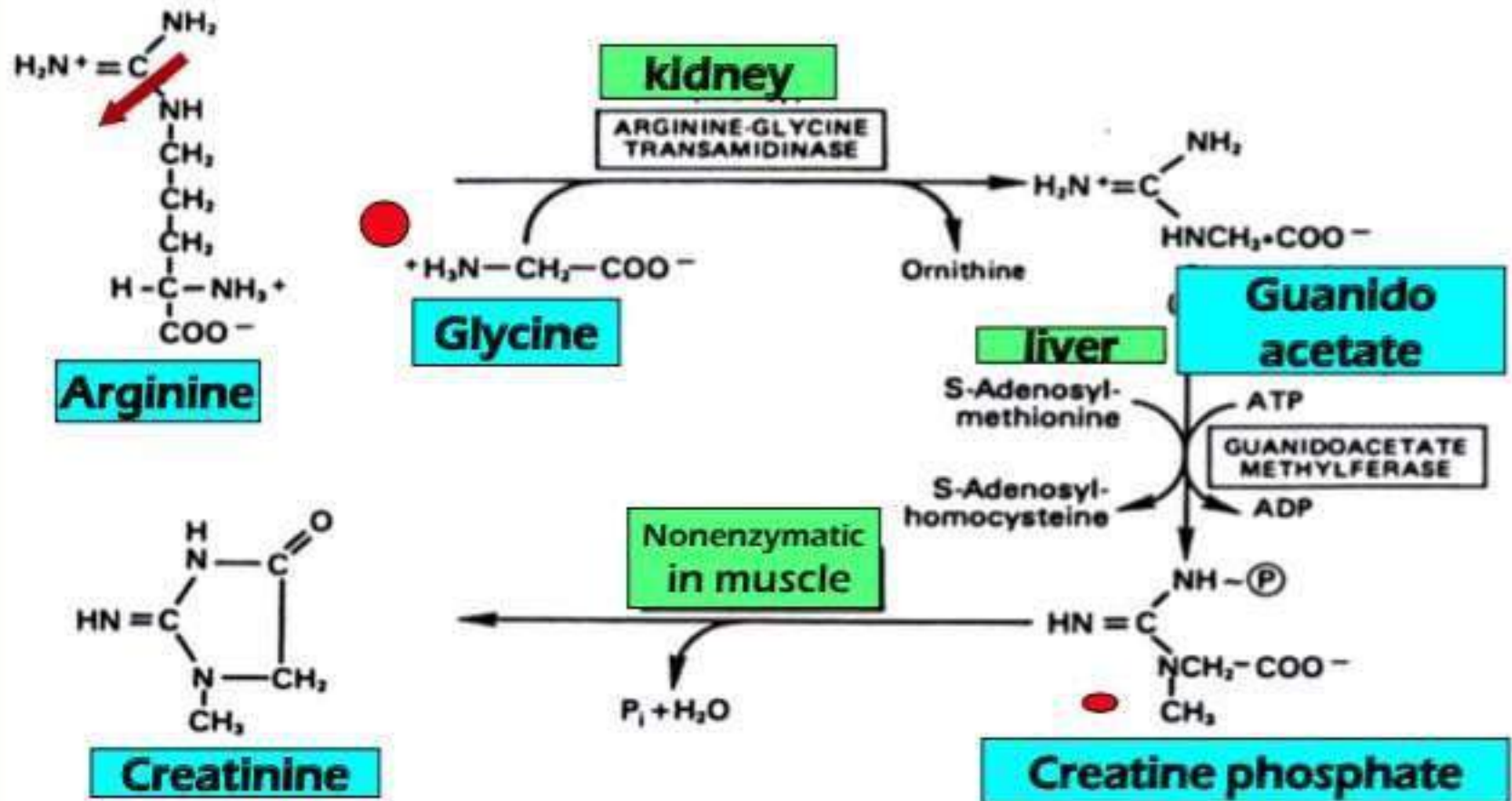
f- **Conjugating reactions:**

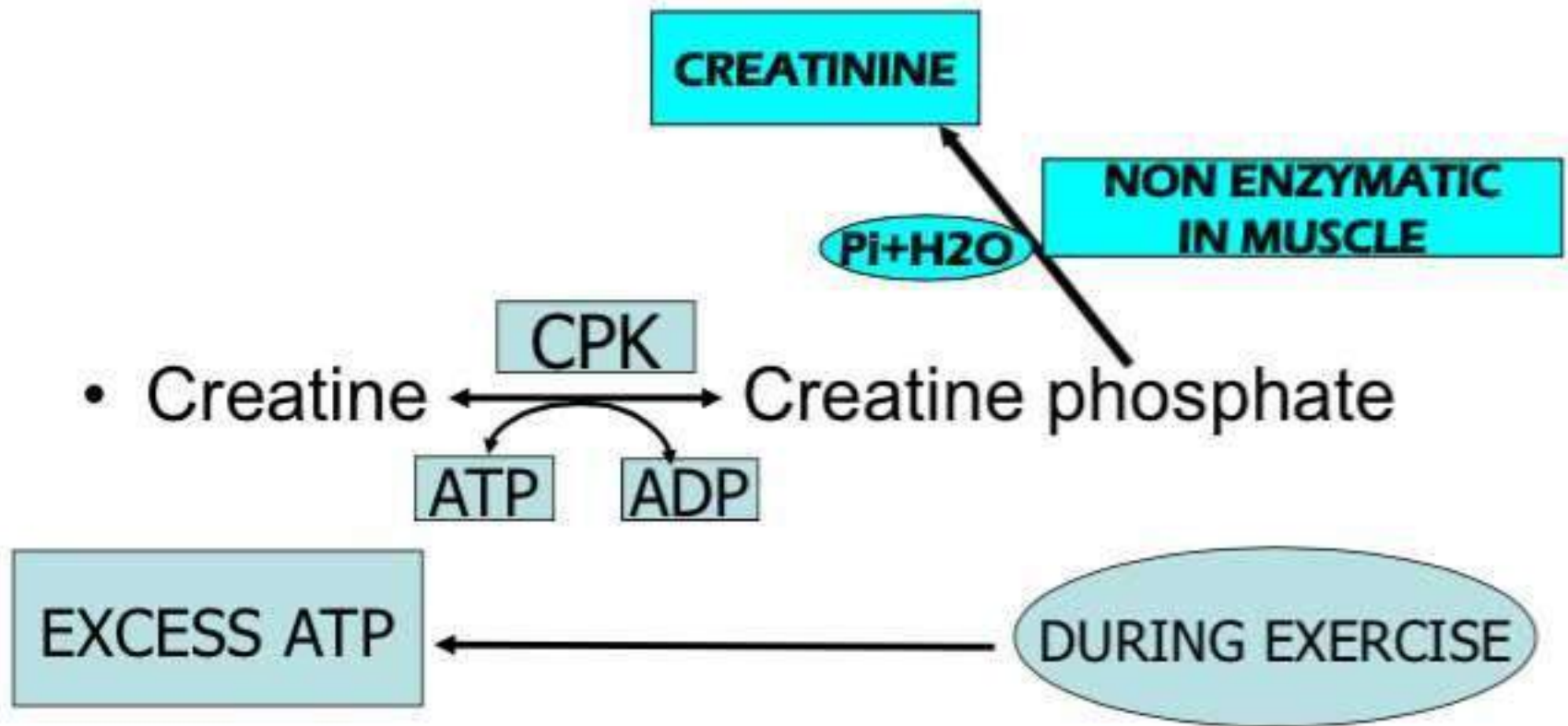
- Glycine + Cholic acid \rightarrow glycocholate.
- Glycine + Benzoic acid \rightarrow Hippuric acid

1. Formation of Glutathione (GSH) Dest.FR & Peroxides



2. Formation of creatine (Methyl guanidoacetate)

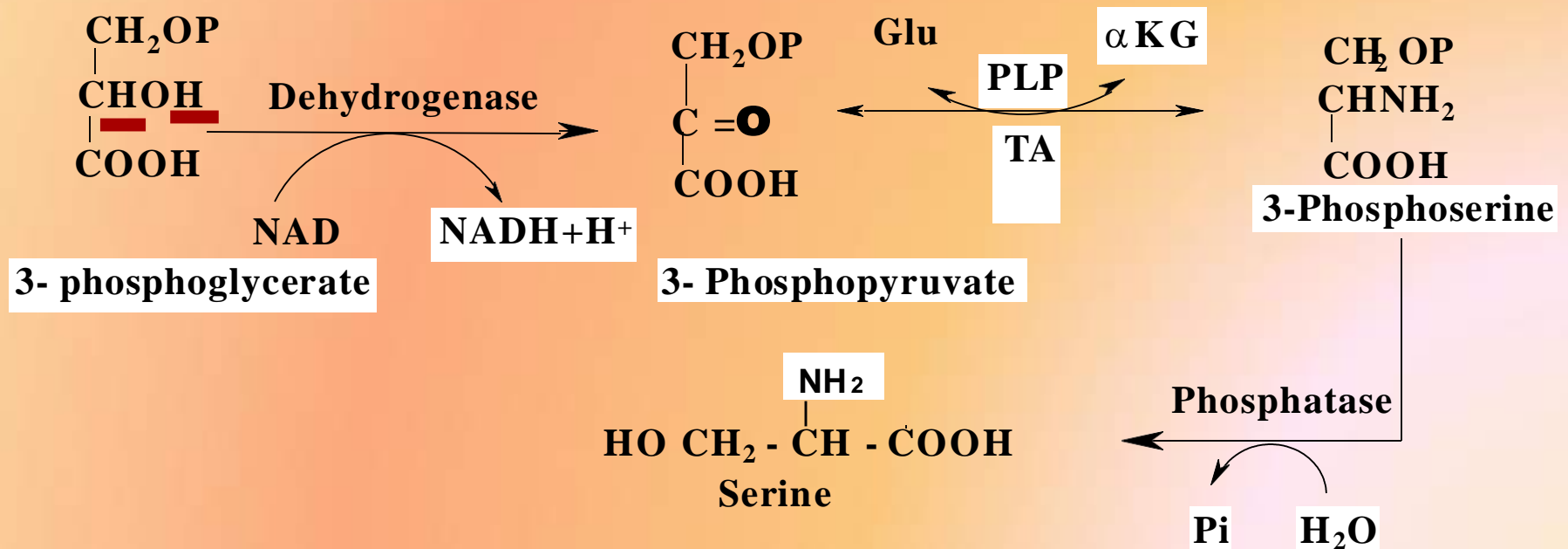




- Cr-P is the storage form of high energy phosphate in muscle
- Creatinine is excreted in urine & increases on kidney failure due to its filtration is decreased.
Its level is constant per 24 hrs
& is proportional to muscle mass in human.

2. Metabolism of Serine: nonessential & glucogenic

- It is synthesized from glycine or
- intermediate of glycolysis,
- all enzymes are activated by testosterone in liver, kidney & prostate.



Degradative Pathways of Serine:

1. **Serine** \longleftrightarrow **Glycine** \longleftrightarrow **CO₂+NH₃** (major)



Serine is important in synthesis of:

- a. **Phosphoprotein**
- b. **Purines & pyrimidine**
- c. **Sphingosine**
- d. **Choline**
- e. **Cysteine**

3. Metabolism of Sulfur-Containing amino acids (Methionine, cyteine & Cystine):

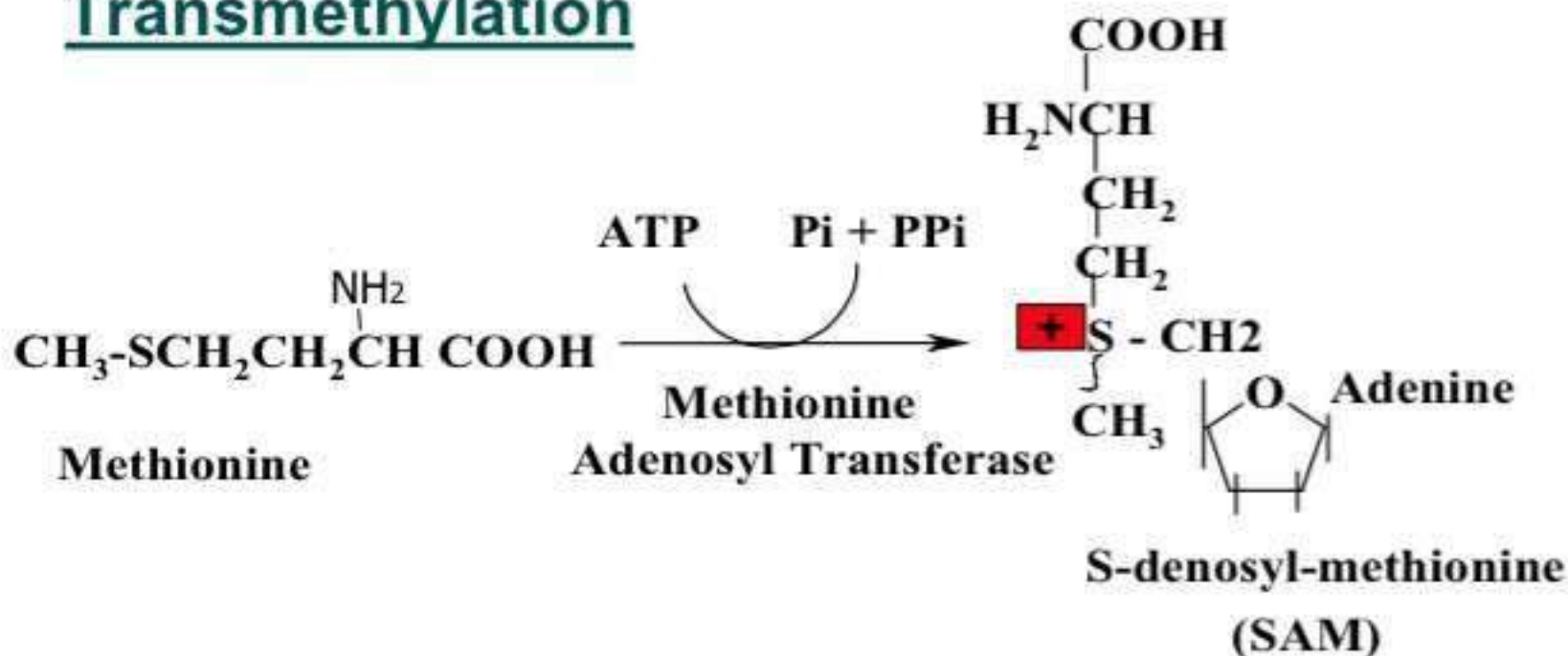
a) Metabolism of methionine: (essential)

Met. \longrightarrow Cysteine (diet.pr.)

- 2 principal metabolic pathways:

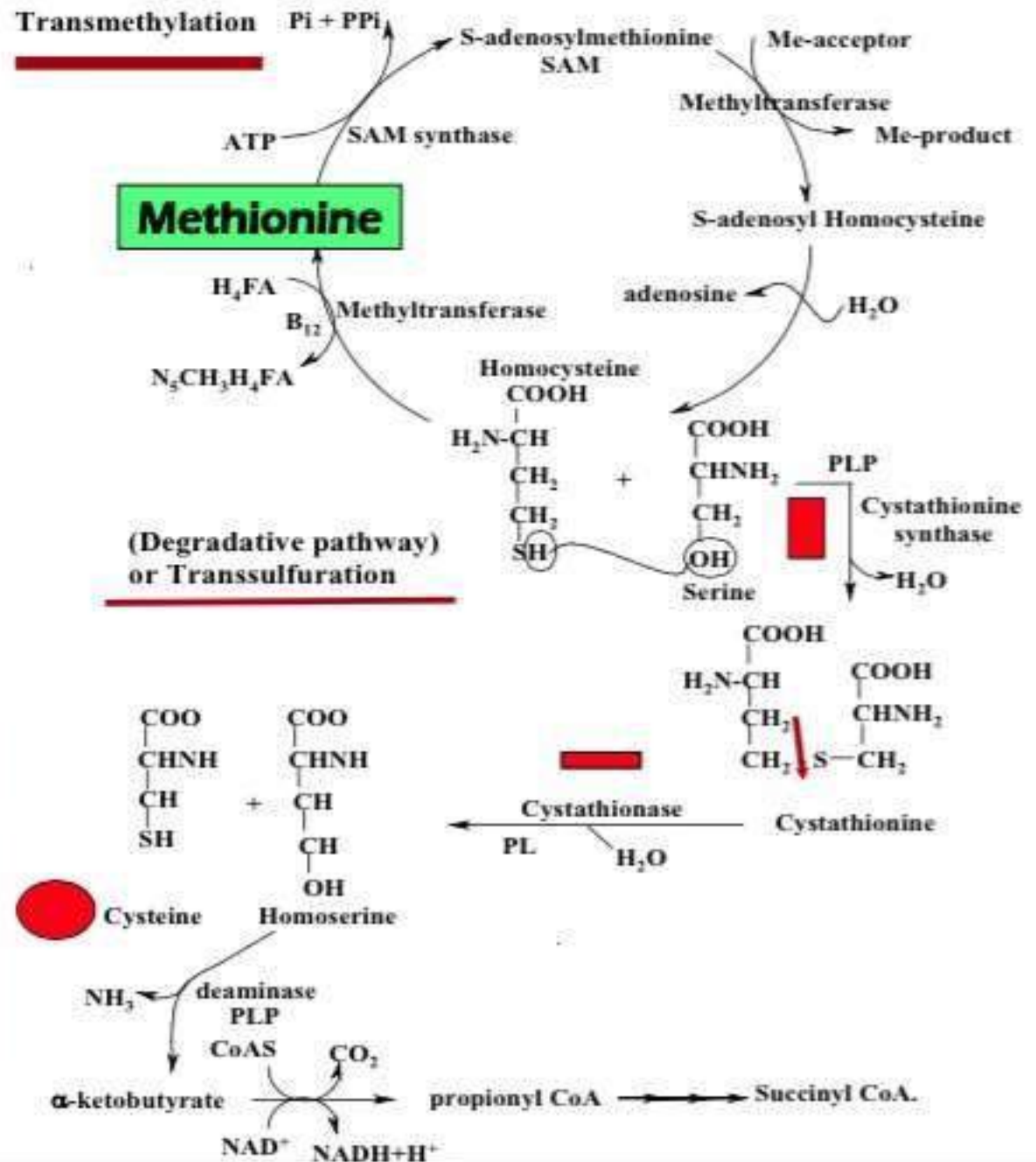
Transmethylation and transsulfuration

- Transmethylation

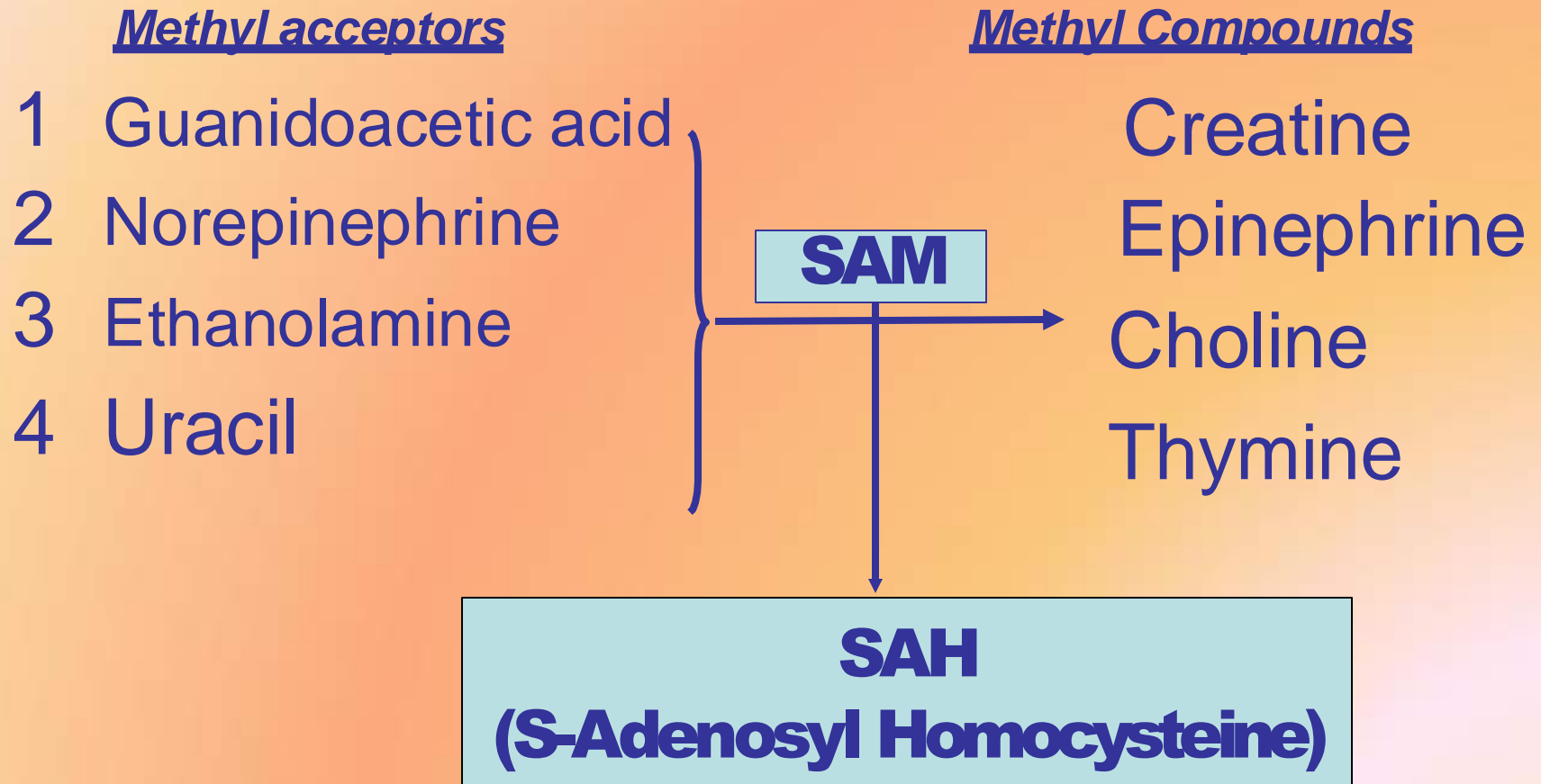


Homocystinuria
Lack of
Cystathionine
synthase

C-skeleton of cysteine
From serine &
S from methionine

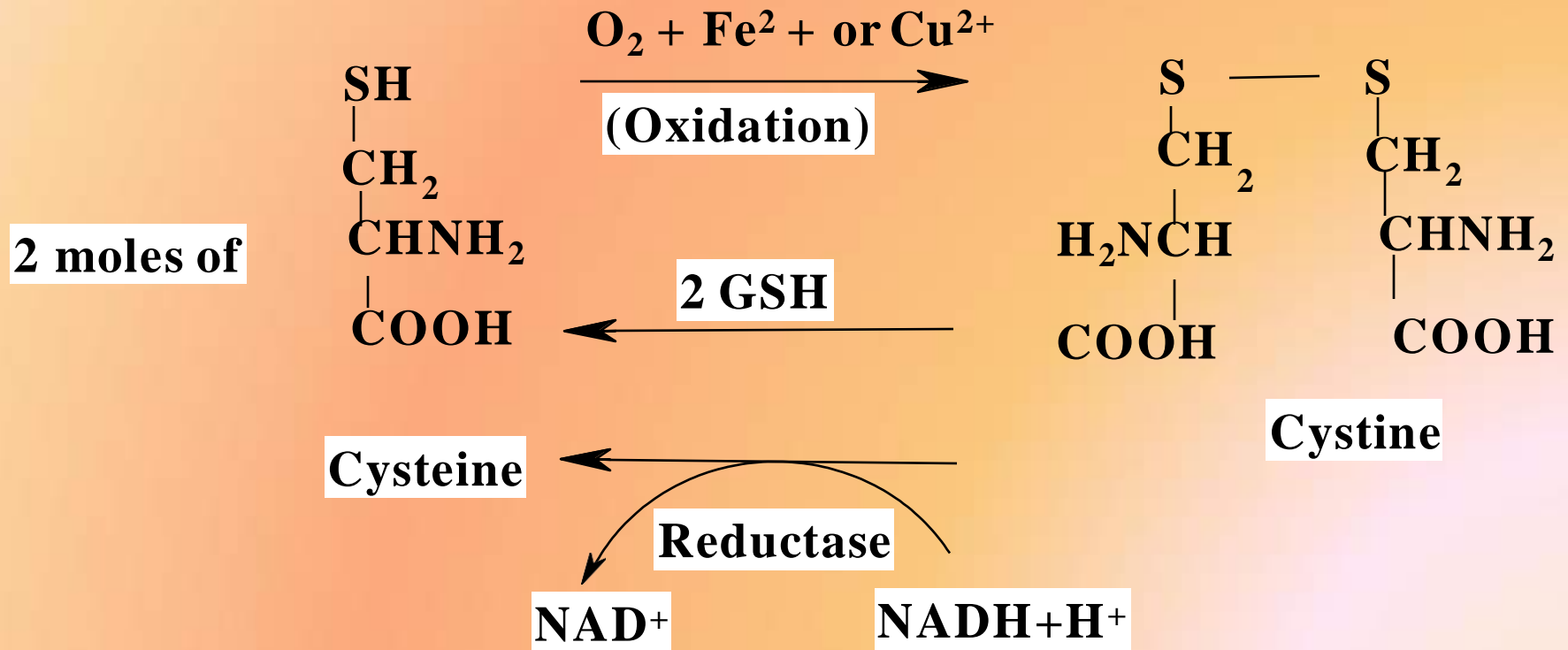


In transmethylation there are:

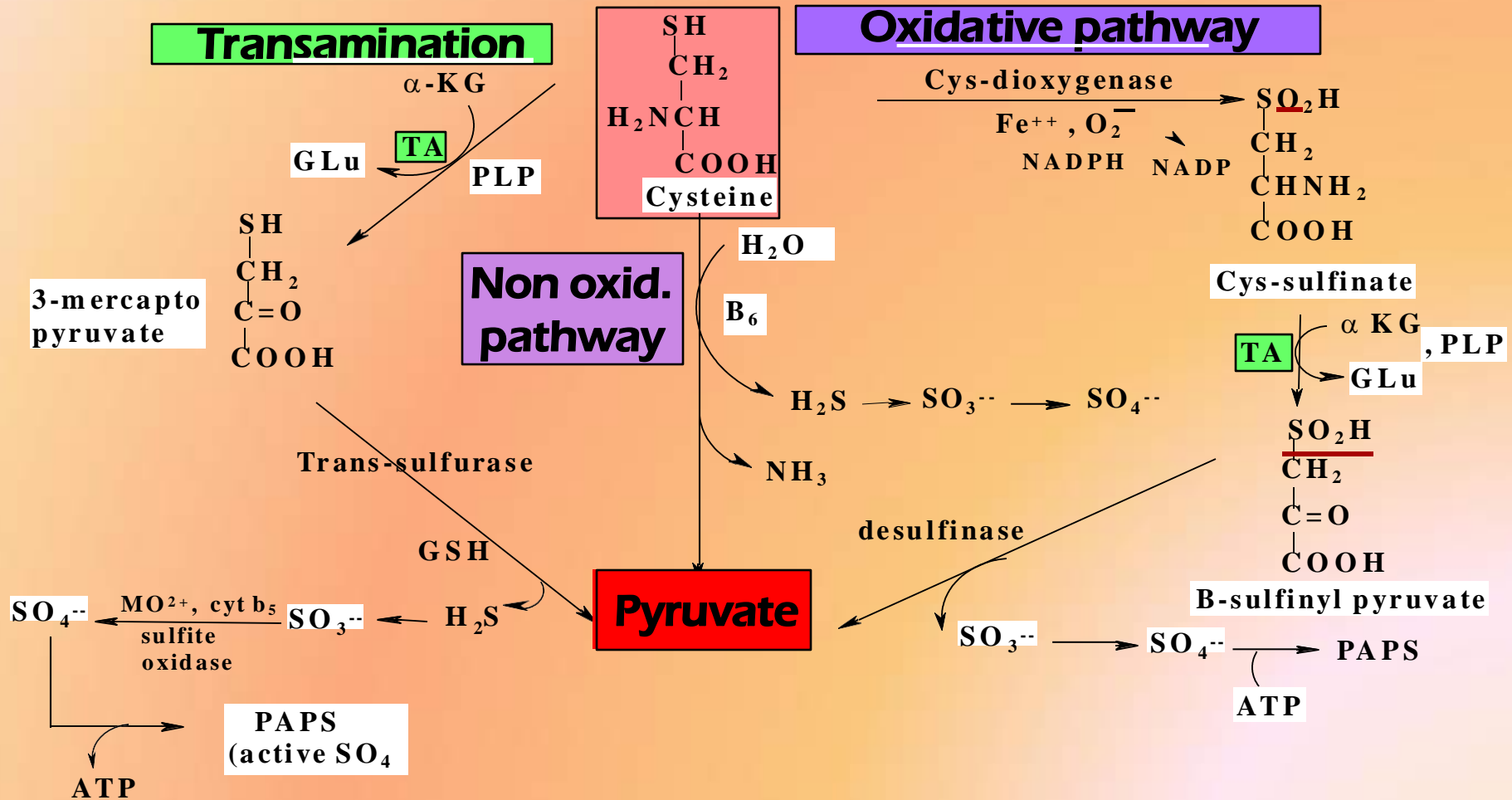


Metabolism of Cysteine & Cystine:

- They are interconvertible & They are not essential
- can be synthesized from Met & Ser

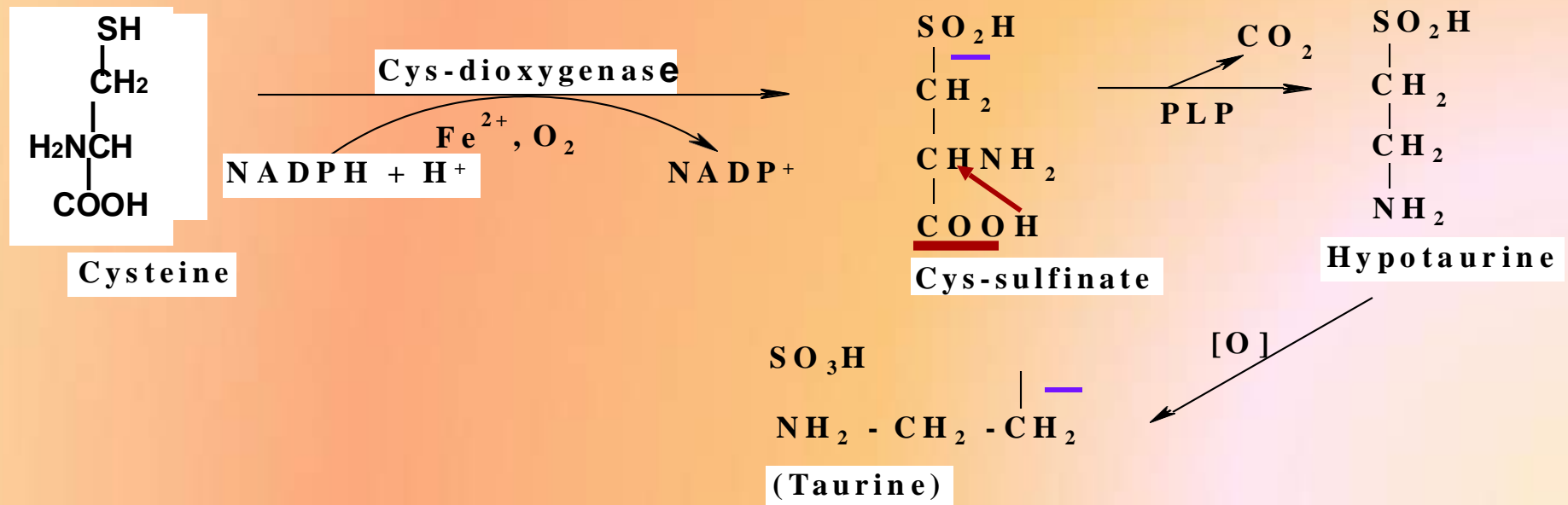


Degredative pathway of cysteine:



Biochemical functions of cysteine

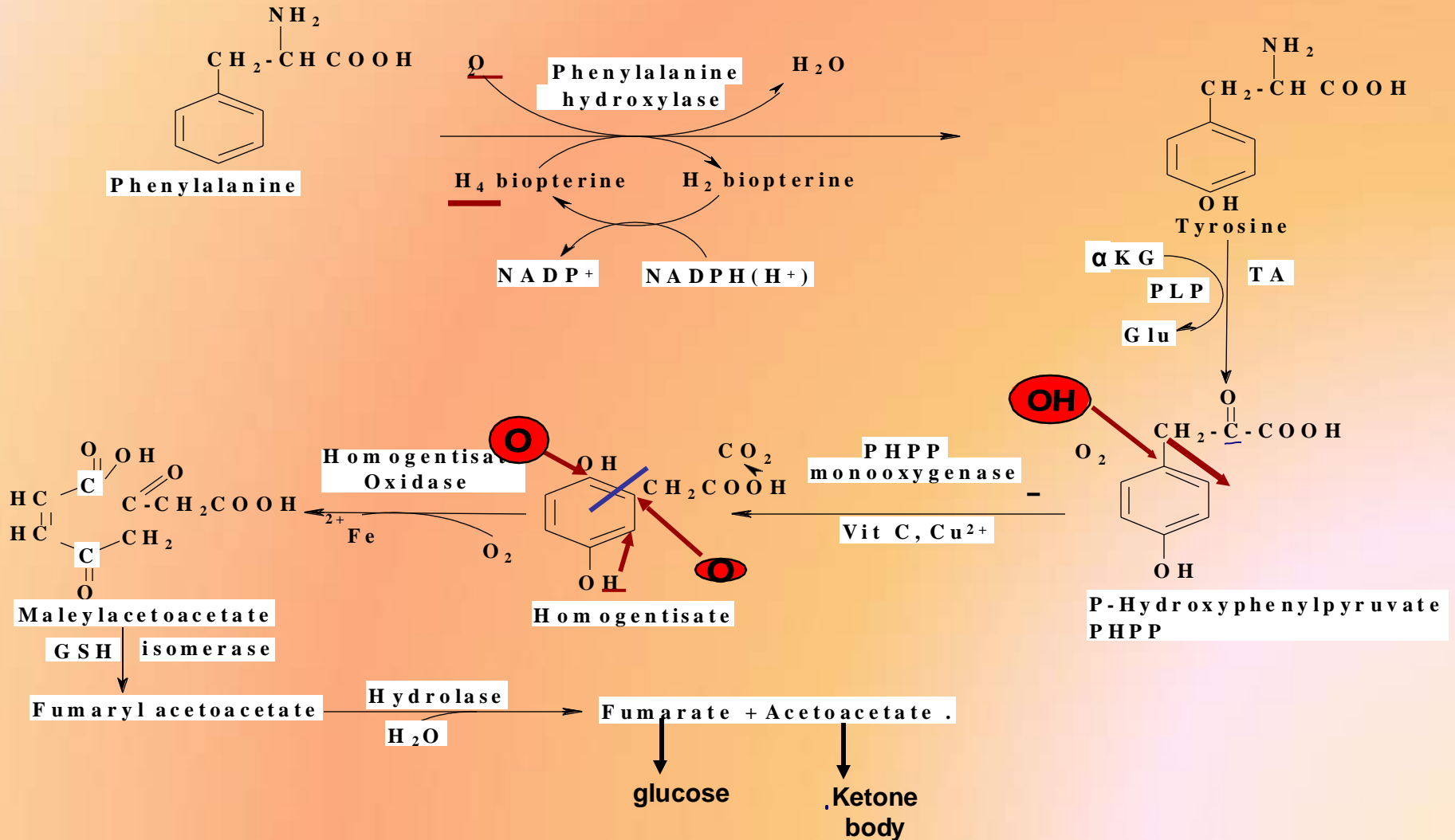
- PAPS Formation: (3'-phosphoadenosine,5'-phosphosulphate)** active sulphate used in formation of sulfate esters of steroids, alcohol, phenol, some lipids, proteins and mucopolysaccharides
- Sulfur of COASH, GSH, vasopressin, insulin**
- Detoxication reaction** of bromo, chloro, iodobenzene, naphthalene and anthracene & of phenol, cresol, indol and skatol that is formed by the action of intestinal bacteria on some amino acids in large intestine with formation of **ethereal sulfates** which is water soluble and rapidly removed by the kidney
- Taurine Formation** (with bile acids form taurocholate)



4. Aromatic amino acids

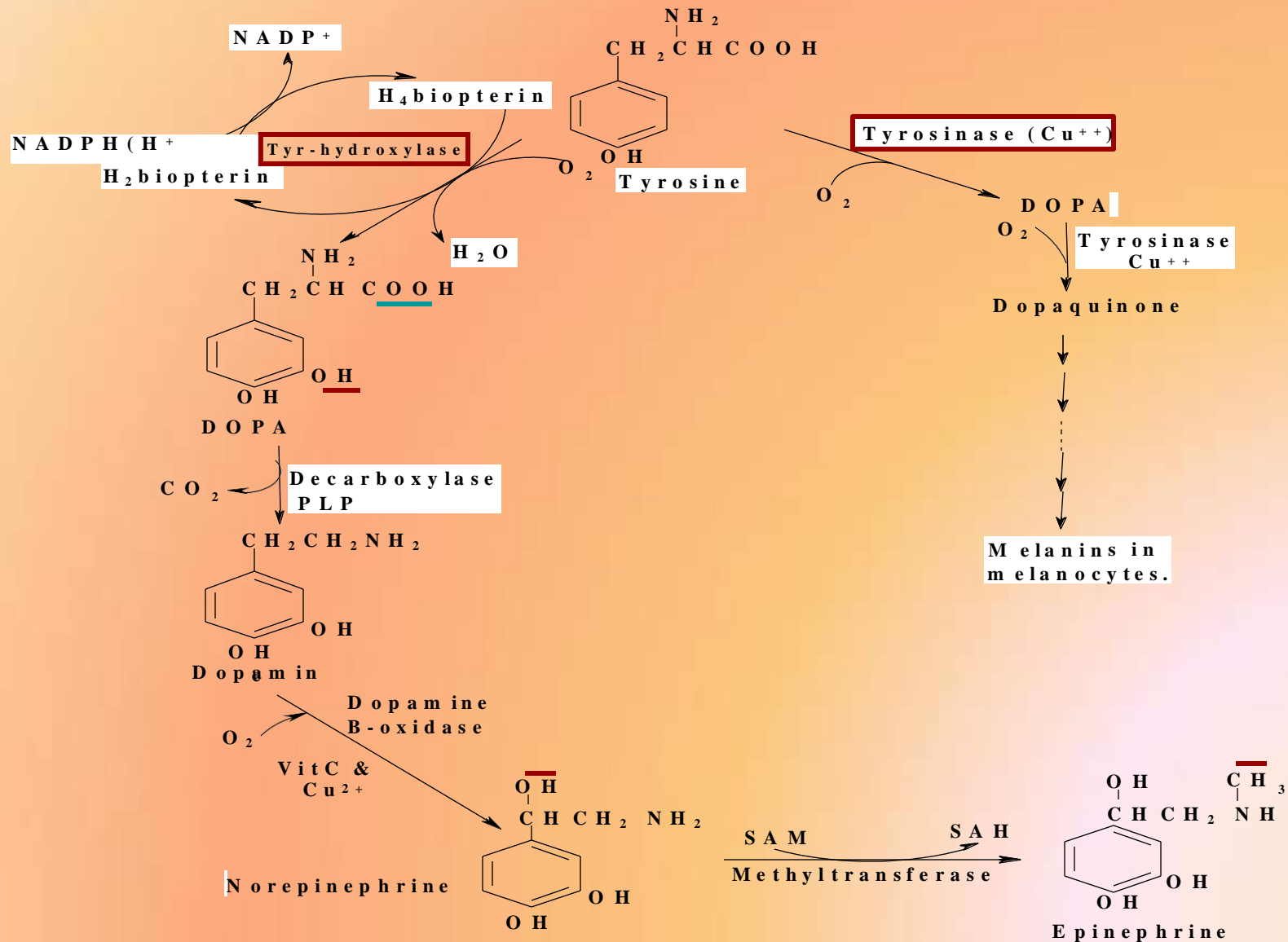
a) Metabolism of Phenylalanine

ketogenic)&(glucogenic



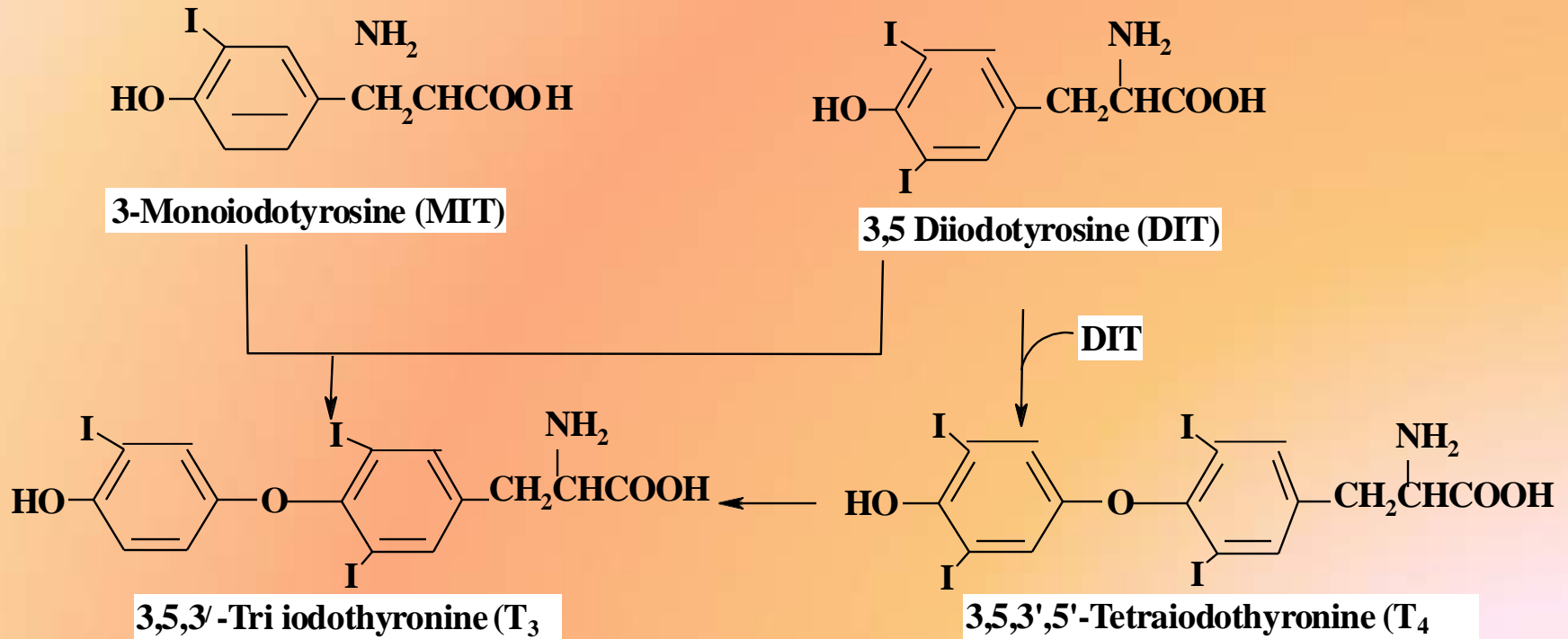
b) Tyrosine is a precursor of:

-1 DOPA (3,4 dihydroxy phenylalanine)

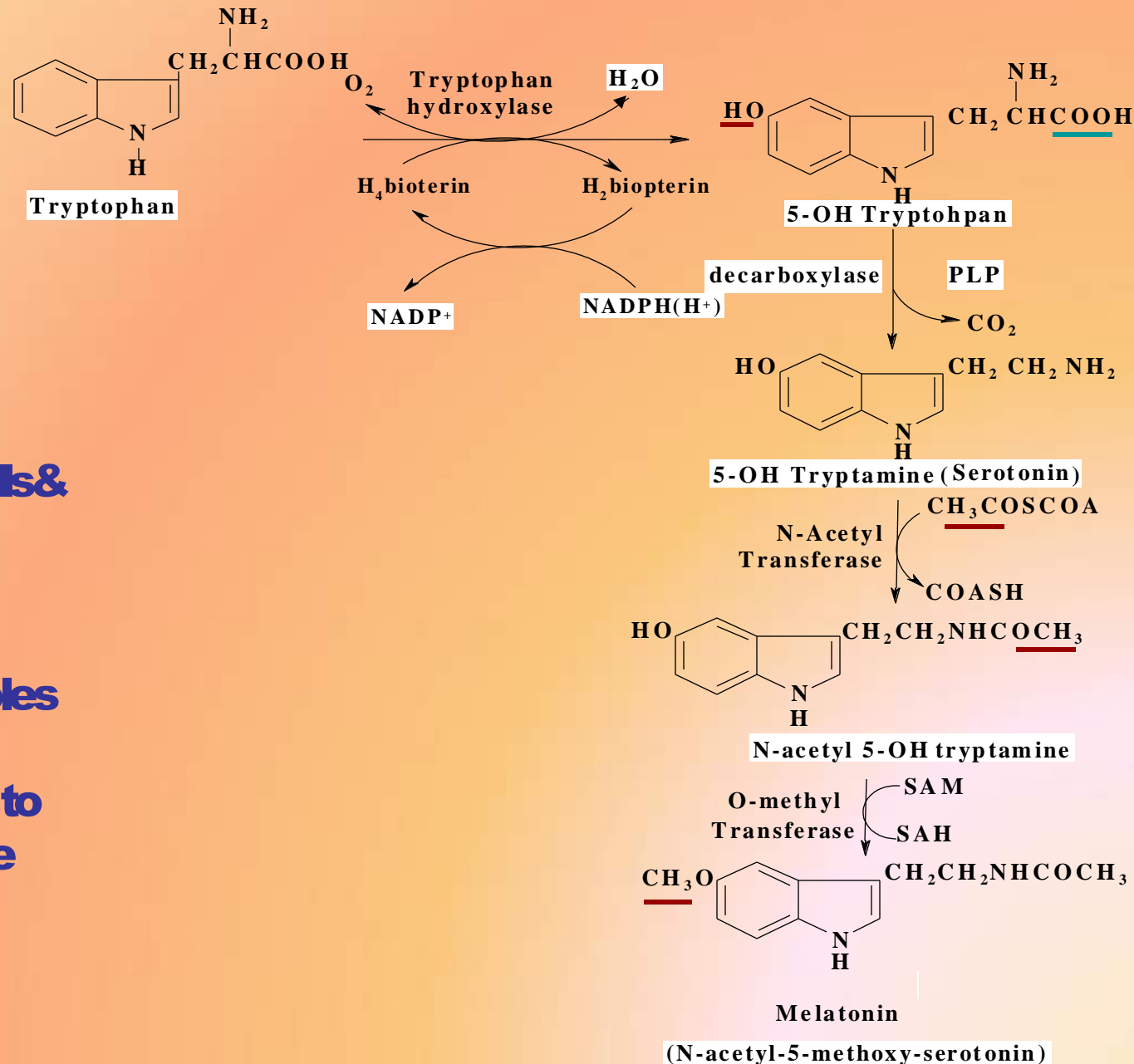


-2Thyroid hormones:

Thyroxine Formation:



II] Serotonin Pathway:



* **Neurotransmitter**

* **Founds in mast cells& platelets.**

* **Vasoconstrictor for B.V.& bronchioles**

* **Transmitter in GIT to release the peptide hormones.**

III] Melatonin formation pathway

- It is the hormone of **pineal body** in brain of man.
Formed by the acetylation and methylation of serotonin.
- It has effects on **hypothalamic-pituitary** system.
It **blocks** the action of **MSH & ACTH**.
- It is important in regulation of **gonad & adrenal functions**.
- It has a **circadian rhythm** due to its formation occurs only **in dark**, due to high activity of **N-acetyl transferase enzyme** so it is a **biological clock**.
- It keeps the **integrity of cells** during aging due to it has an antioxidant property
- It enhances the body defense against infection in AIDS patients by increasing the number of immune cells.
- **It reduces the risk of cancer&heart diseases**

5. Branched Chain Amino Acids:

- **Leucine, isoleucine and valine** are taken up by striated muscles after protein meal and oxidized in sk. muscle.
- They are used by **the brain**.
- *Summary of their degradation:*

Nitrogen : Transferred from all of them forming glutamate

Carbons :	Leucine	Acetyl CoA & acetoacetate
	Isoleucine	Succinyl CoA & Acetyl CoA
	Valine	Succinyl CoA & CO ₂

6. Basic Amino Acids:

1) Histidine (glucogenic amino acid):

a) Together with B-alanine , It forms **carnosine** (B-alanyl histidine) and **anserine** (methyl carnosine):

1. They are buffer the pH of anerobically contracting skeletal muscle

2.They **activate myosin ATP-ase**

3.They **chelate copper and enhance Cu^{2+} uptake.**

b) Histidine is a source of one-carbon atom.

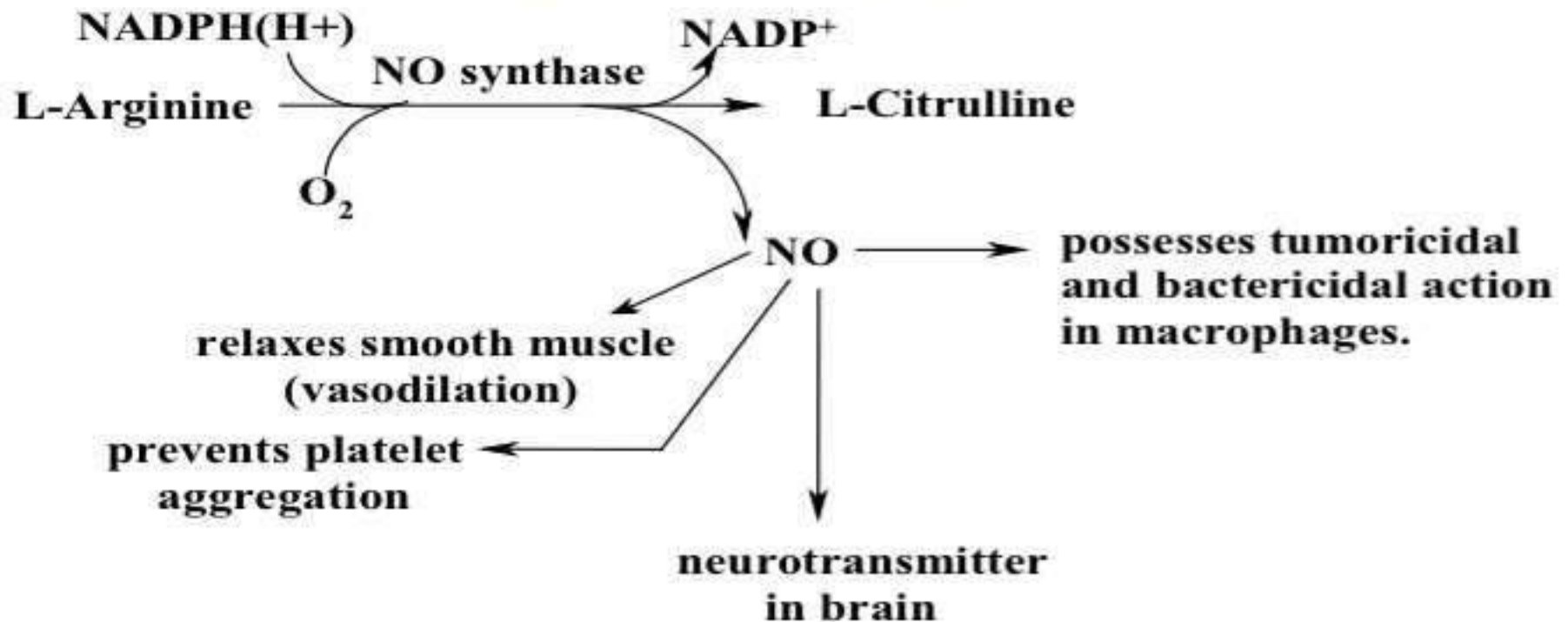
c) Histidine  \longrightarrow Histamine

Histamine is a chemical messenger that mediates **allergic and inflammatory reactions, gastric acid secretion and neurotransmission in the brain.**

(2) Arginine: (nonessential & glucogenic amino acid):

It participates in formation of:

- a) Creatine
- b) Polyamines
- C) Nitric oxide NO (Free radical gas).

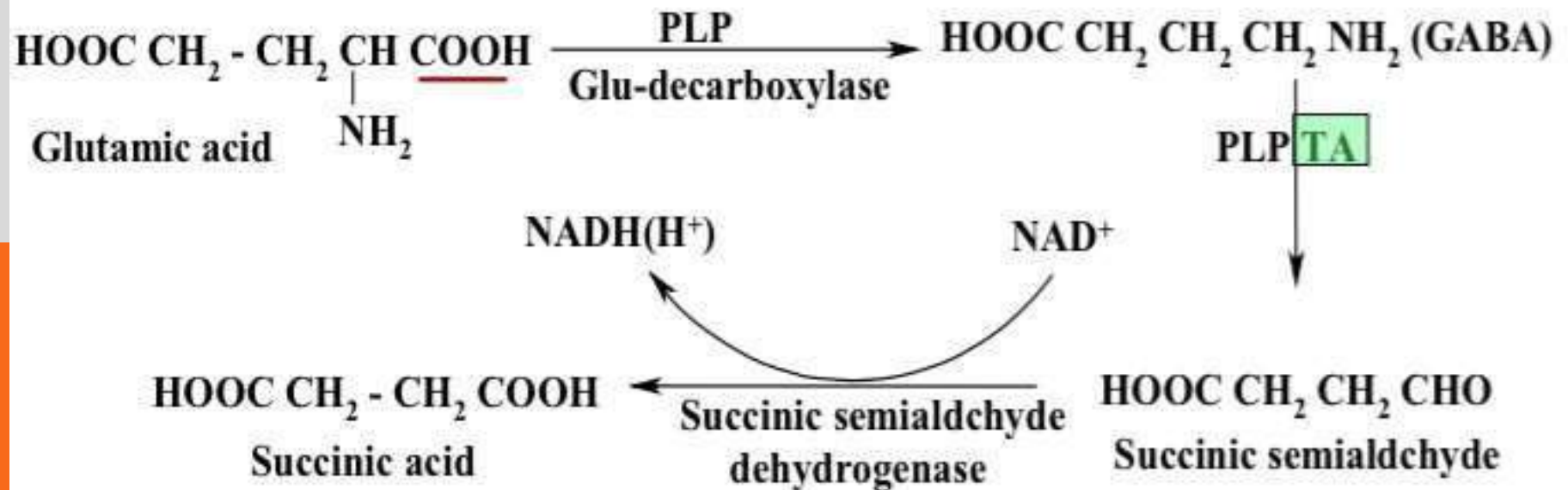


7. Acidic Amino Acids :

1. Glutamic acid : (nonessential & glucogenic amino acid).

It participates in formation of:

- 1- GSH.
- 2- Proline
- 3- Glutamine: as storage and transporter form of ammonia
- 4- GABA (δ -aminobutyric acid) neurotransmitter in brain.



2. Aspartic acid

- Acidic, non essential & glucogenic
- It is important in formation of:
 1. Asparagine with NH_3 .
 2. Purine & pyrimidine.
 3. Argininosuccinate in urea cycle.
 4. Alanine by decarboxylation.
 5. Oxalate & glucose by T.A.

Amino acids as precursors of neurotransmitters

1. Serine Choline --- Acetyl choline.
2. Arginine -----NO
3. Tryptophan-----Serotonin
4. Histidine-----Histamine
5. Phenyl alanine-----dopa, dopamine, NE&E
6. Glutamic acid-----GABA

Errors Of Amino Acid Metabolism And Clinical Significance--



TABLE 18-2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

<i>Medical condition</i>	<i>Approximate incidence (per 100,000 births)</i>	<i>Defective process</i>	<i>Defective enzyme</i>	<i>Symptoms and effects</i>
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation: white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β -synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α -keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation