AMINOACID METABOLISM

- Proteins are the most abundant organic compounds & constitute a major part of the body dry weight (10-12kg in adults).
- Perform a wide variety of structural & dynamic (enzymes, hormones, clotting factors, receptors) functions.
- Proteins are nitrogen containing macromolecules consisting of L-α - amino acids as the repeating units.

- Of the 20 amino acids found in proteins, half can be synthesized by the body & half are supplied through diet.
- The proteins on degradation release individual amino acids.
- Each amino acid undergoes its own metabolism & performs specific functions.

- Some amino acids serve as precursors for the synthesis of many biologically important compounds.
- Certain amino acids may directly act as neurotransmitters (e.g glycine, aspartate, glutamate)

Utilization of amino acids from body pool

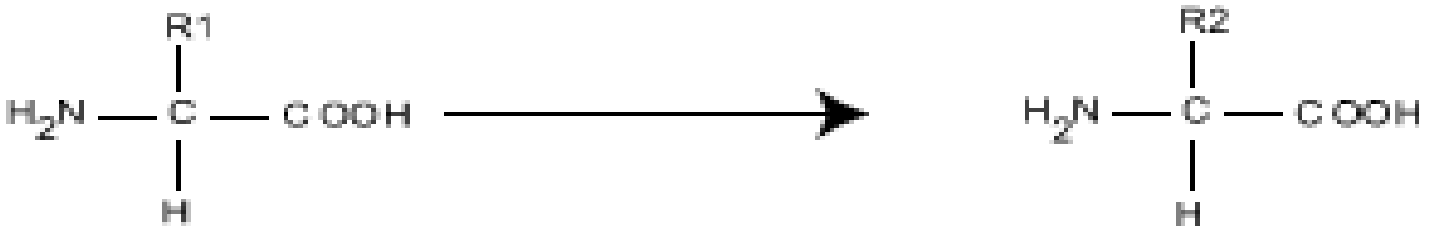
- Proteins function as enzymes, hormones, immunoproteins, contractile proteins etc.
- Many important nitrogenous compounds (porphyrins, purines, pyrimidines, etc) are produced from the amino acids.
- About 10-15% of body energy requirements are met from the amino acids.
- The amino acids are converted into carbohydrates & fats.

Catabolism of amino group occurs in 4 stages

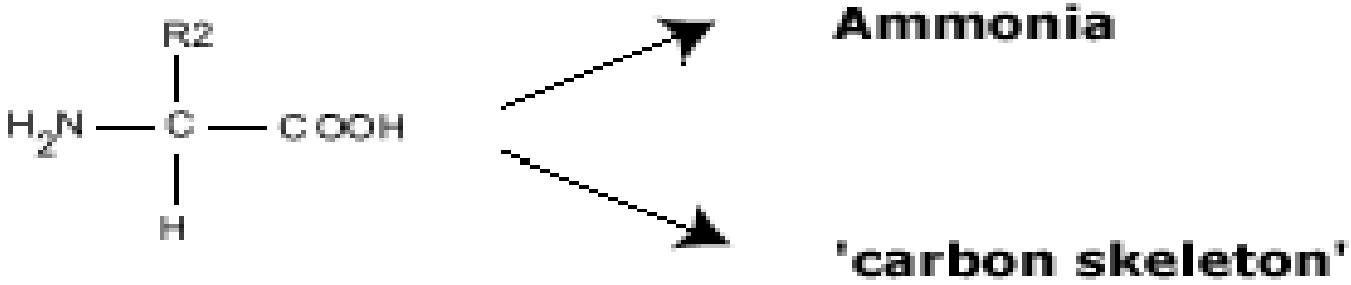
- Transamination
- Oxidative Deamination
- Ammonia Transport
- Urea Cycle

Amino Acid metabolism

(a) Tansamination



(b) Deamination



(c) Detoxification

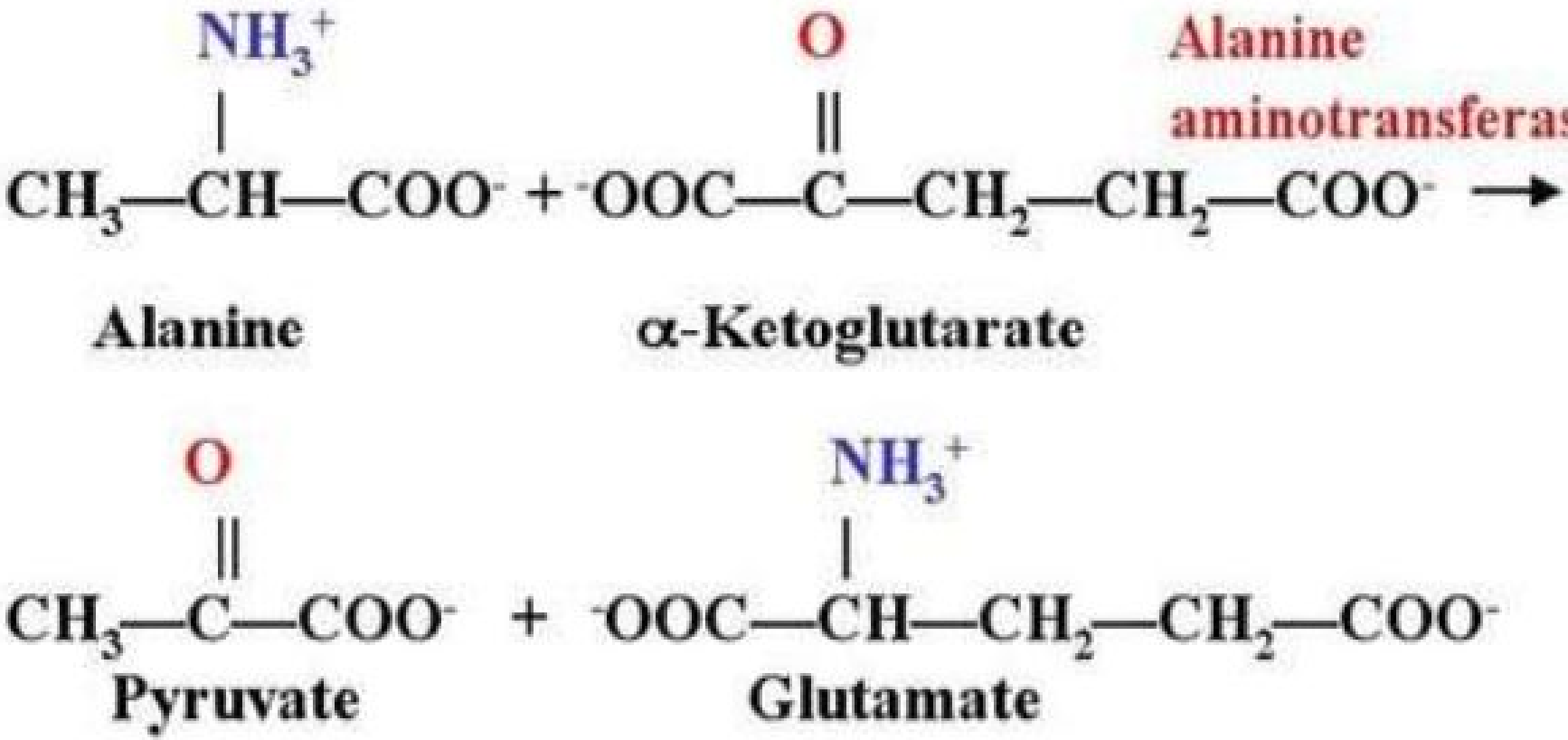
Ammonia → Urea + Water

(Urine)

Transamination

- The transfer of an amino (-NH_2) group from an amino acid to a ketoacid, with the formation of a new amino acid & a new keto acid.
- Catalysed by a group of enzymes called transaminases (aminotransferases)
- Pyridoxalphosphate (PLP)– Co-factor.
- Liver, Kidney, Heart, Brain - adequate amount of these enzymes.

A Transamination Reaction



Salient features of transamination

- All transaminases require PLP.
- No free NH_3 liberated, only the transfer of amino group.
- Transamination is reversible.
- There are multiple transaminase enzymes which vary in substrate specificity.
- AST & ALT make a significant contribution for transamination.

PLP – pyridoxylphosphate, AST- aspertate transaminase, ALT – alanine transaminase

- Transamination is important for redistribution of amino groups & production of non-essential amino acids.
- It diverts excess amino acids towards the energy generation.
- Amino acids undergo transamination to finally concentrate nitrogen in glutamate.

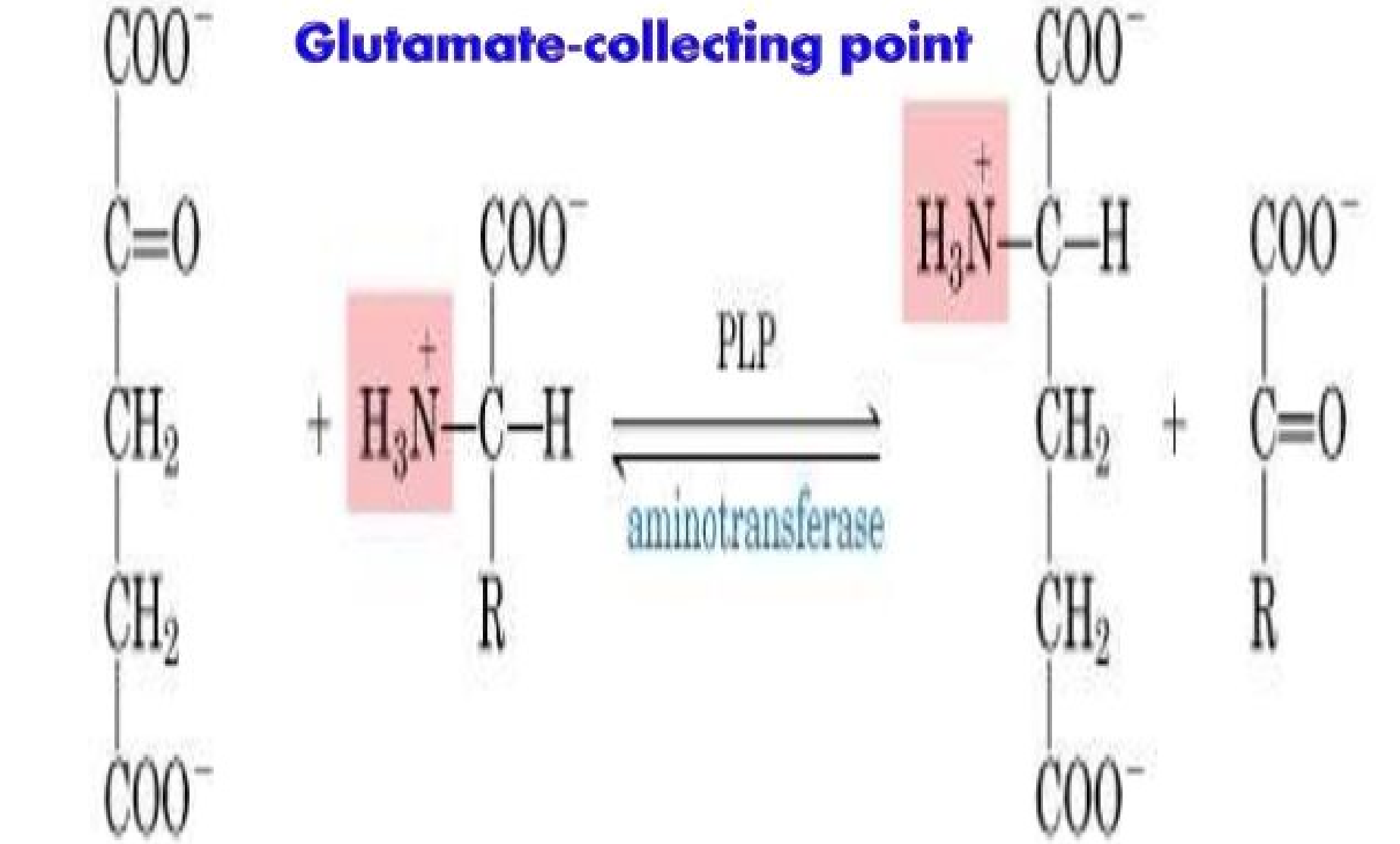
- Glutamate undergoes oxidative deamination to liberate free NH_3 for urea synthesis.
- All amino acids except, lysine, threonine, proline & hydroxyproline participate in transamination.
- It involves both anabolism & catabolism, since – reversible.

$AA_1 + \alpha\text{-}KG \longleftrightarrow ketoacid_1 + Glutamate$

$Alanine + \alpha\text{-}KG \longleftrightarrow Pyruvate + Glutamate$

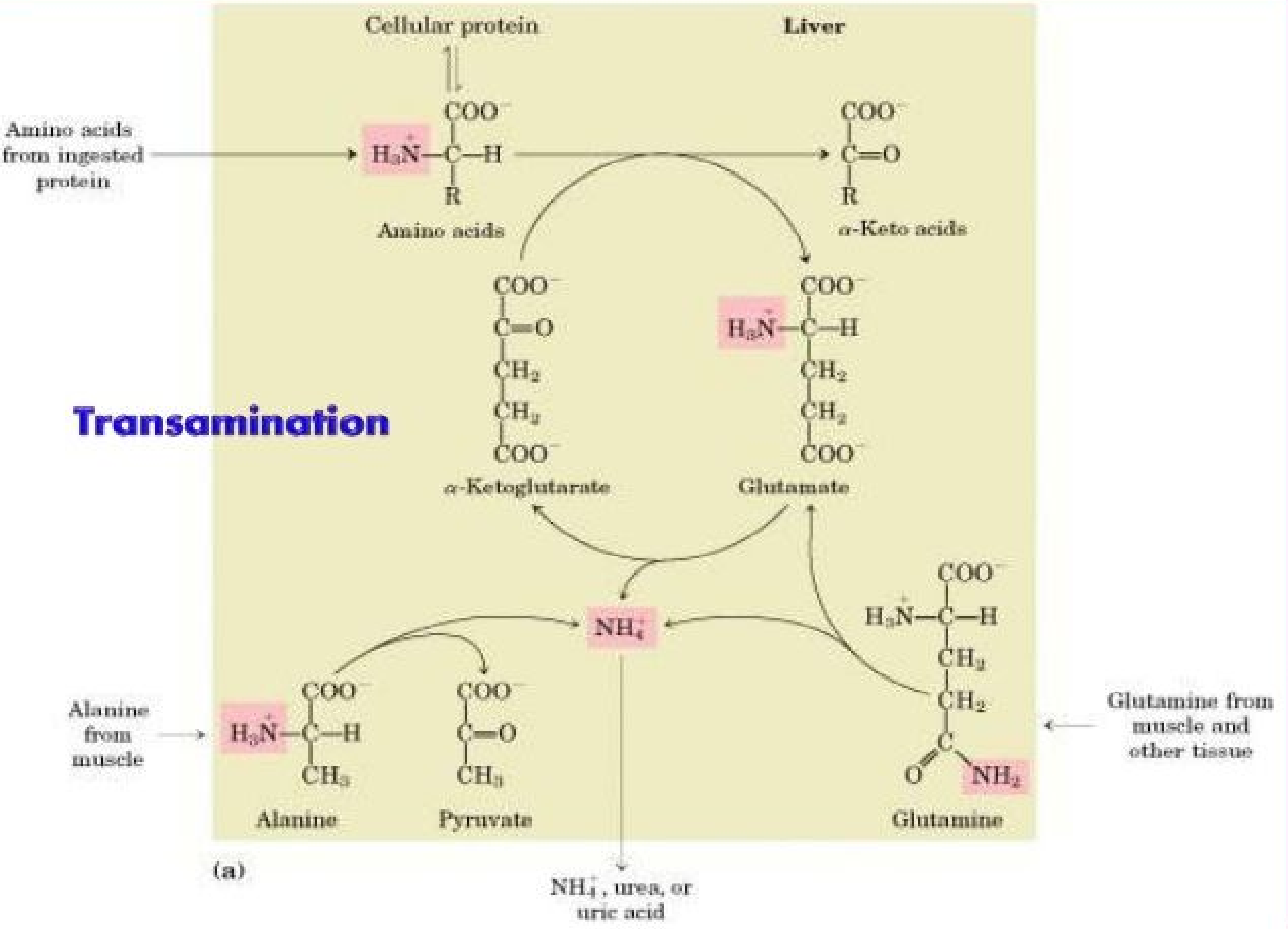
$Aspartate + \alpha\text{-}KG \longleftrightarrow Oxaloacetetae + Glutamate$

Glutamate-collecting point



α-Ketoglutarate L-Amino acid L-Glutamate α-Keto acid

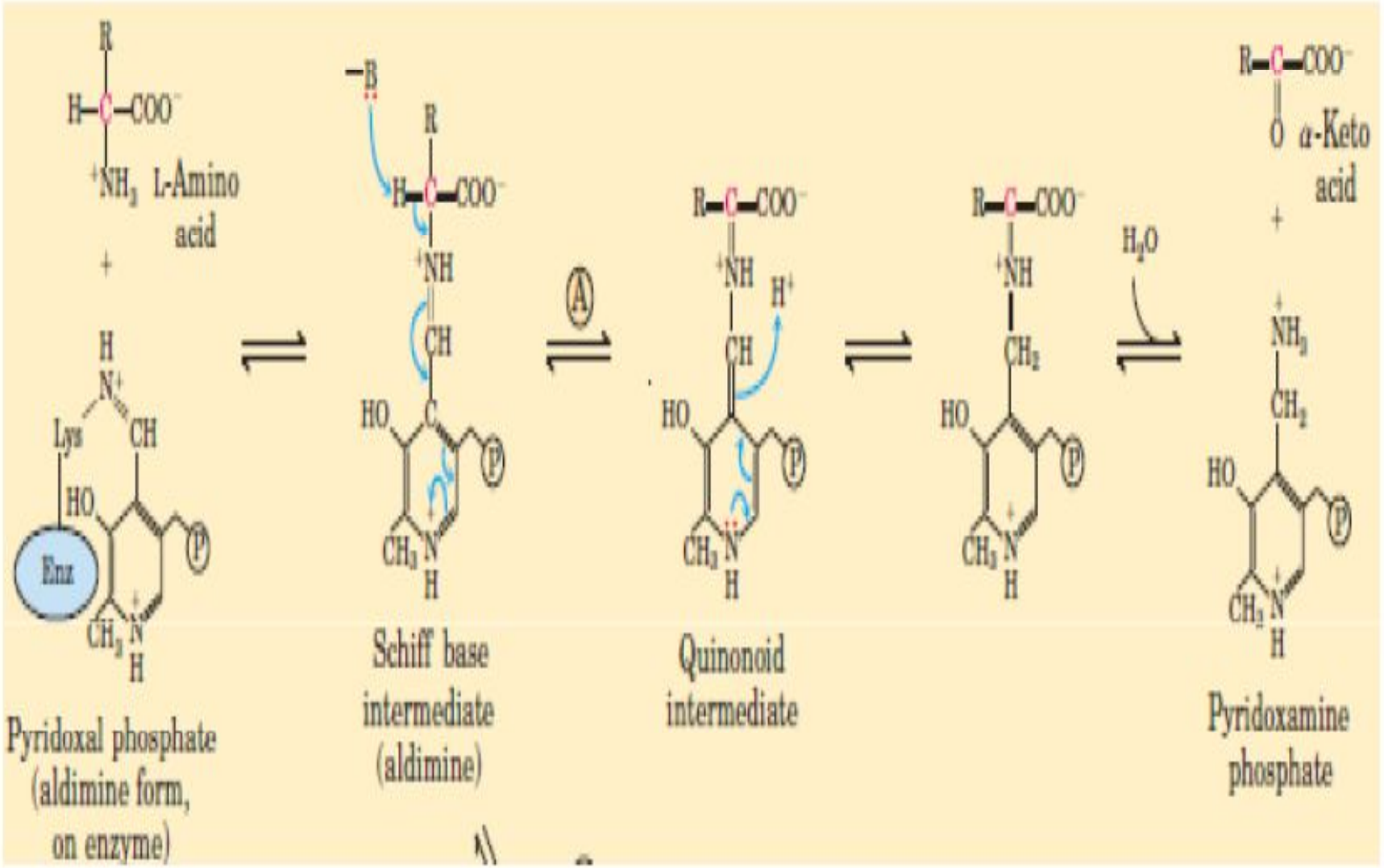
Transamination

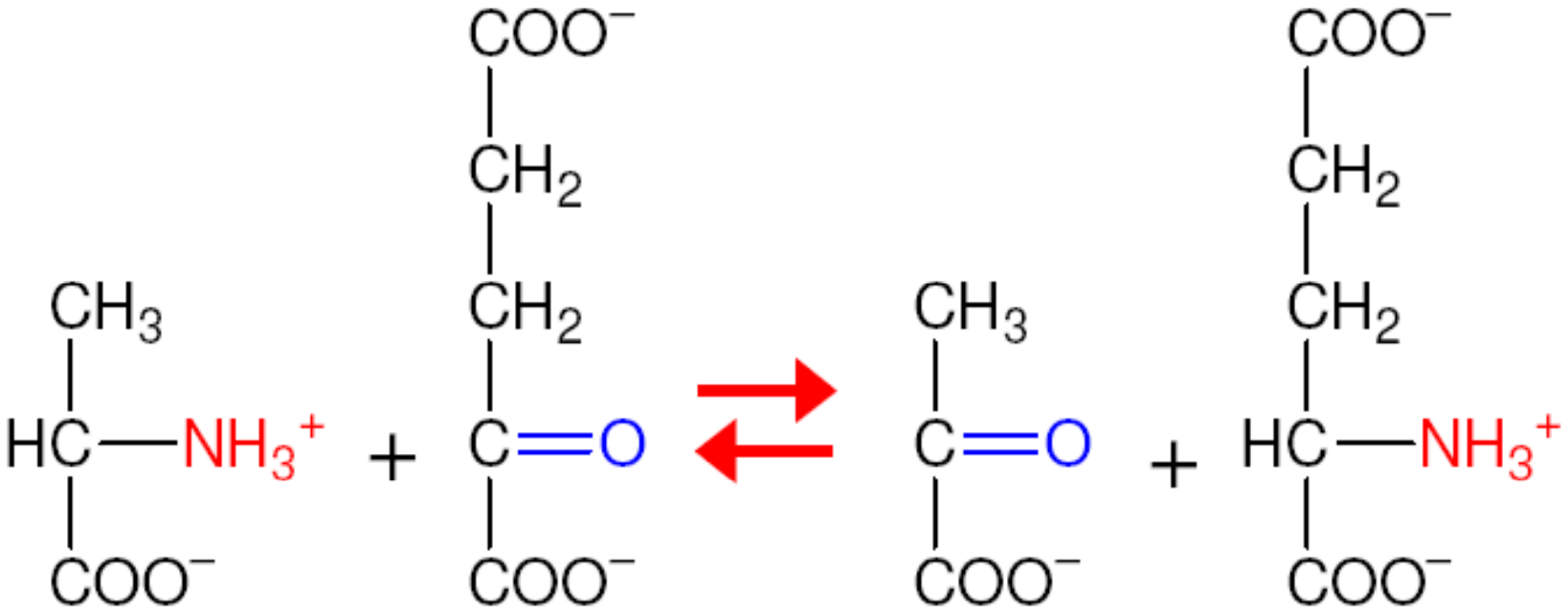


Mechanism of transamination

- **Step: 1**
- Transfer of amino group from AA_1 to the coenzyme PLP to form pyridoxamine phosphate.
- Amino acid1 is converted to Keto acid2.
- **Step: 2**
- Amino group of pyridoxamine phosphate is then transferred to a keto $acid_1$ to produce a new AA_2 & enzyme with PLP is regenerated.

Mechanism of Transamination reaction: role of PLP





In another example, alanine becomes pyruvate as the amino group is transferred to α-ketoglutarate.

Trans-deamination

- The amino group of most of the amino acids is released by a coupled reaction, trans-deamination.
- Transamination followed by oxidative deamination.
- Transamination takes place in the cytoplasm.

- The amino group is transported to liver as glutamic acid, which is finally oxidatively deaminated in the mitochondria of hepatocytes.

Deamination

- The removal of amino group from the amino acids as NH_3 is deamination.
- Deamination results in the liberation of ammonia for urea synthesis.
- The carbon skeleton of amino acids is converted to keto acids.
- Deamination may be either oxidative or non-oxidative

- Only liver mitochondria contain glutamate dehydrogenase (GDH) which deaminates glutamate to α-ketoglutarate & ammonia.
- It needs NAD^+ as co-enzyme.
- It is an allosteric enzyme.
- It is activated by ADP & inhibited by GTP.

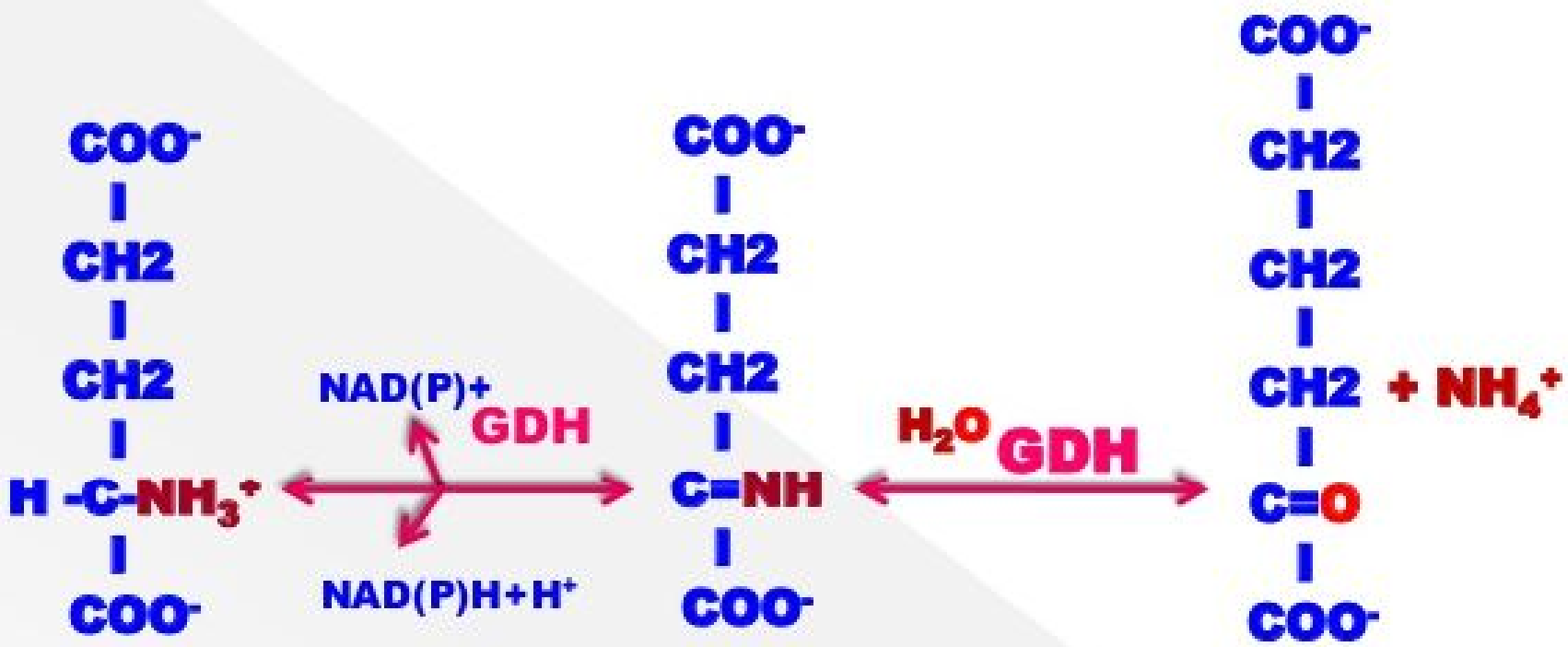
Oxidative Deamination

- **Oxidative deamination** is the liberation of free ammonia from the amino group of amino acids coupled with oxidation.
- **Site**: Mostly in liver & kidney.
- Oxidative deamination is to provide NH_3 for urea synthesis & α-keto acids for a variety of reactions, including energy generation.

Role of glutamate dehydrogenase

- Glutamate is a 'collection centre' for amino groups.
- Glutamate rapidly undergoes oxidative deamination.
- Catalysed by GDH to liberate ammonia.
- It can utilize either NAD^+ or $NADP^+$.
- This conversion occurs through the formation of an α-iminoglutarate

Oxidation of glutamate by glutamate by GDH



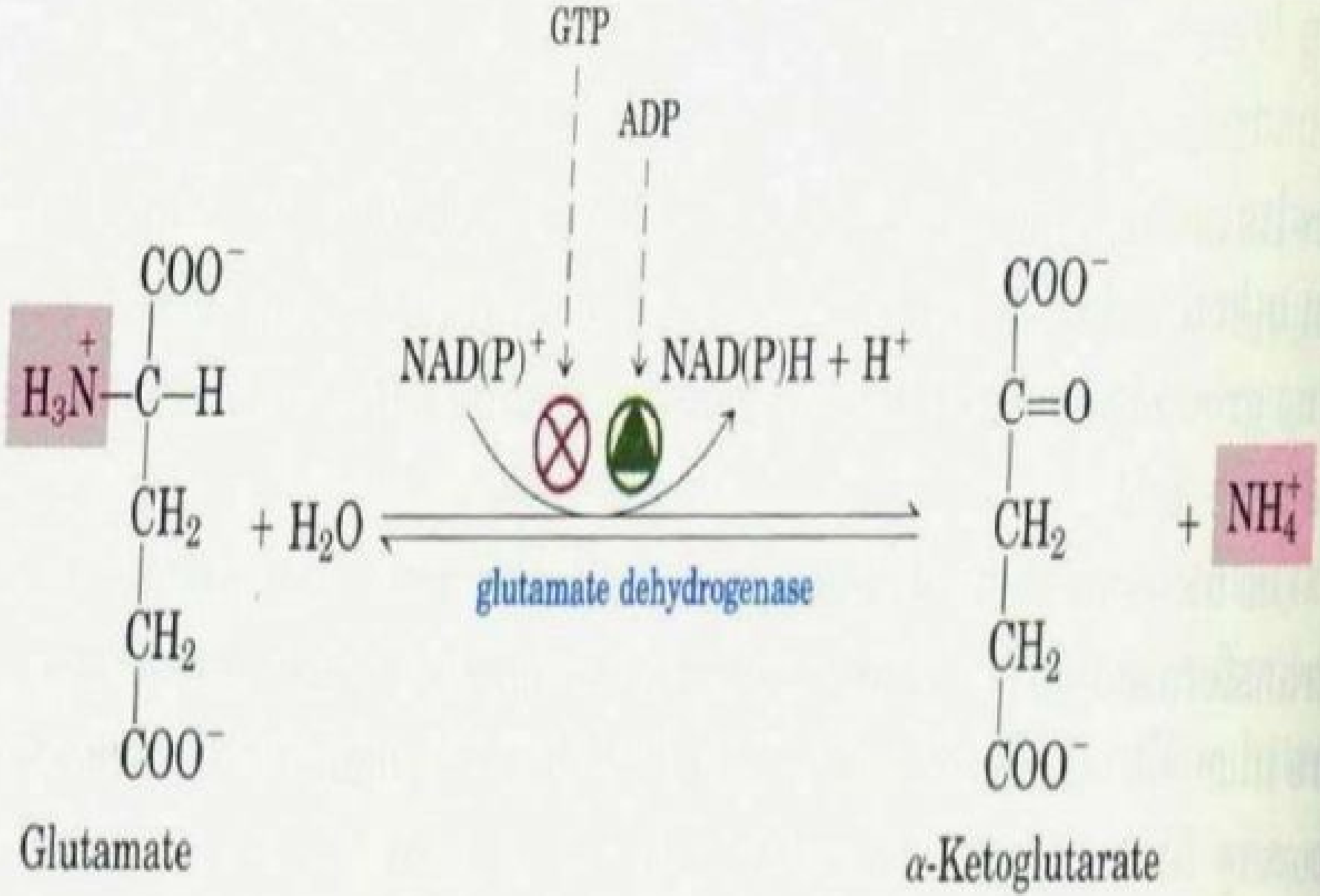
L-Glutamate

α- Iminoglutarate

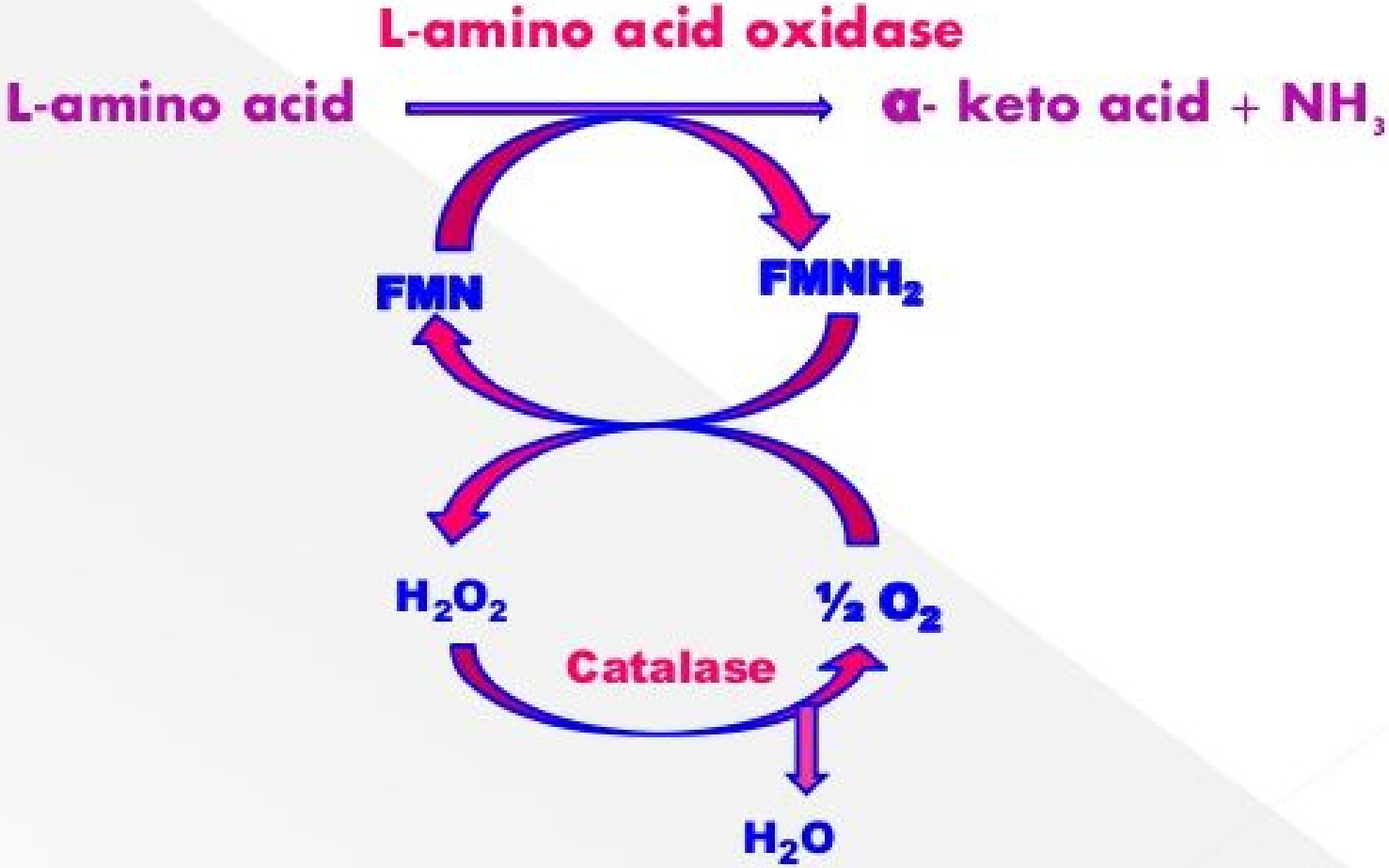
α- ketoglutarate

Metabolic Significance

- Reversible Reaction
- Both Anabolic & Catabolic.
- Regulation of GDH activity:
- Zinc containing mitochondrial, allosteric enzyme.
- Consists of 6 identical subunits.
- Molecular weight is 56,000.


GTP
ADP
NAD(P)+
NAD(P)H + H+
COO−
H3N+–C–H
CH2
CH2
COO−
+ H2O
glutamate dehydrogenase
COO−
C=O
CH2
CH2
COO−
+ NH4+
Glutamate
α-Ketoglutarate

Oxidative deamination of amino acids

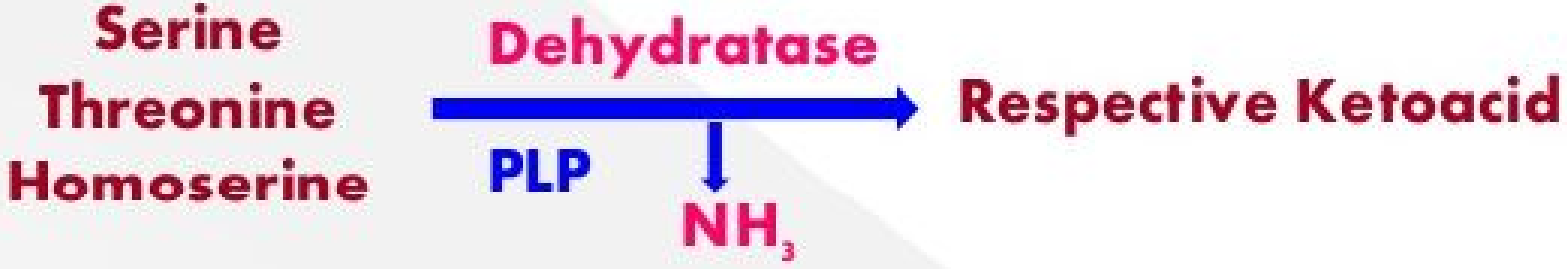


- L-Amino acid Oxidase acts on all Amino acids, except glycine & dicarboxylic acids.
- Activity of D-Amino oxidase is high than that of L-Amino acid oxidase
- D-Amino oxidase degrades D-Amino acids in bacterial cell wall.

Non-Oxidative deamination

- Direct deamination, without oxidation.
- Amino acid Dehydratases:
- Serine, threonine & homoserine are the hydroxy amino acids.
- They undergo non-oxidative deamination catalyzed by PLP-dependent dehydratases

Non-Oxidative deamination



Amino acid Desulfhydrases

- **Cysteine & homocysteine undergo deamination coupled with desulfhydration to give keto acids.**

- **Deamination of histidine:**

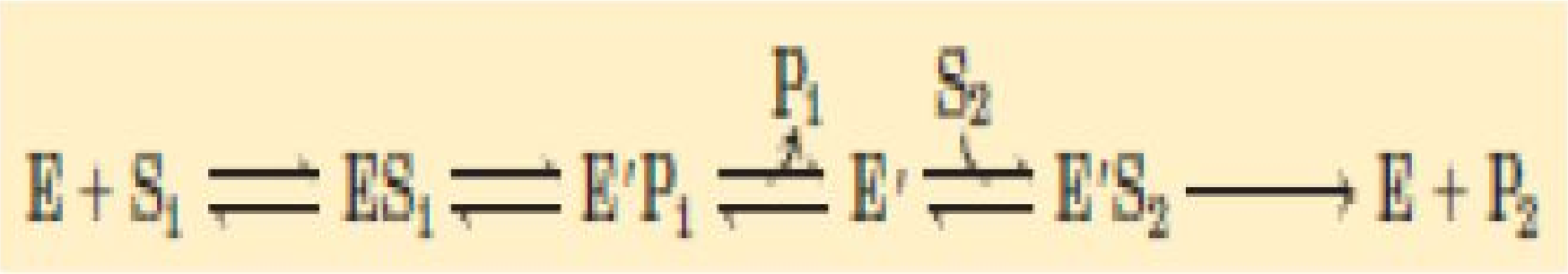
Ping-Pong reaction of aminotransferases

- Amino transferases are examples of enzymes catalyzing bimolecular Ping-Pong reactions in which the first substrate reacts before the second substrate can bind.

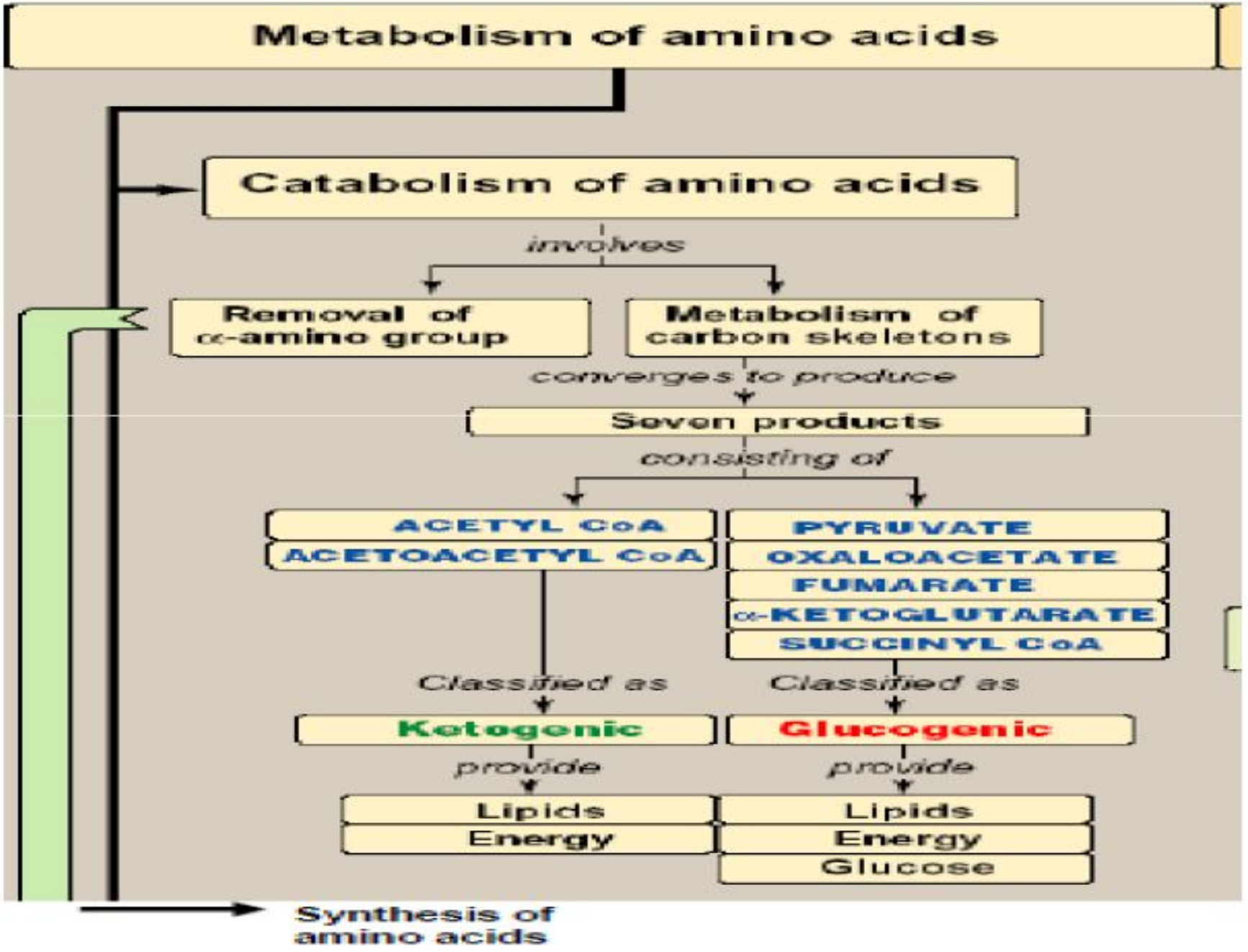
- Thus the incoming amino acid donates its amino group to pyridoxal phosphate, and departs in the form of an -ketoacid.

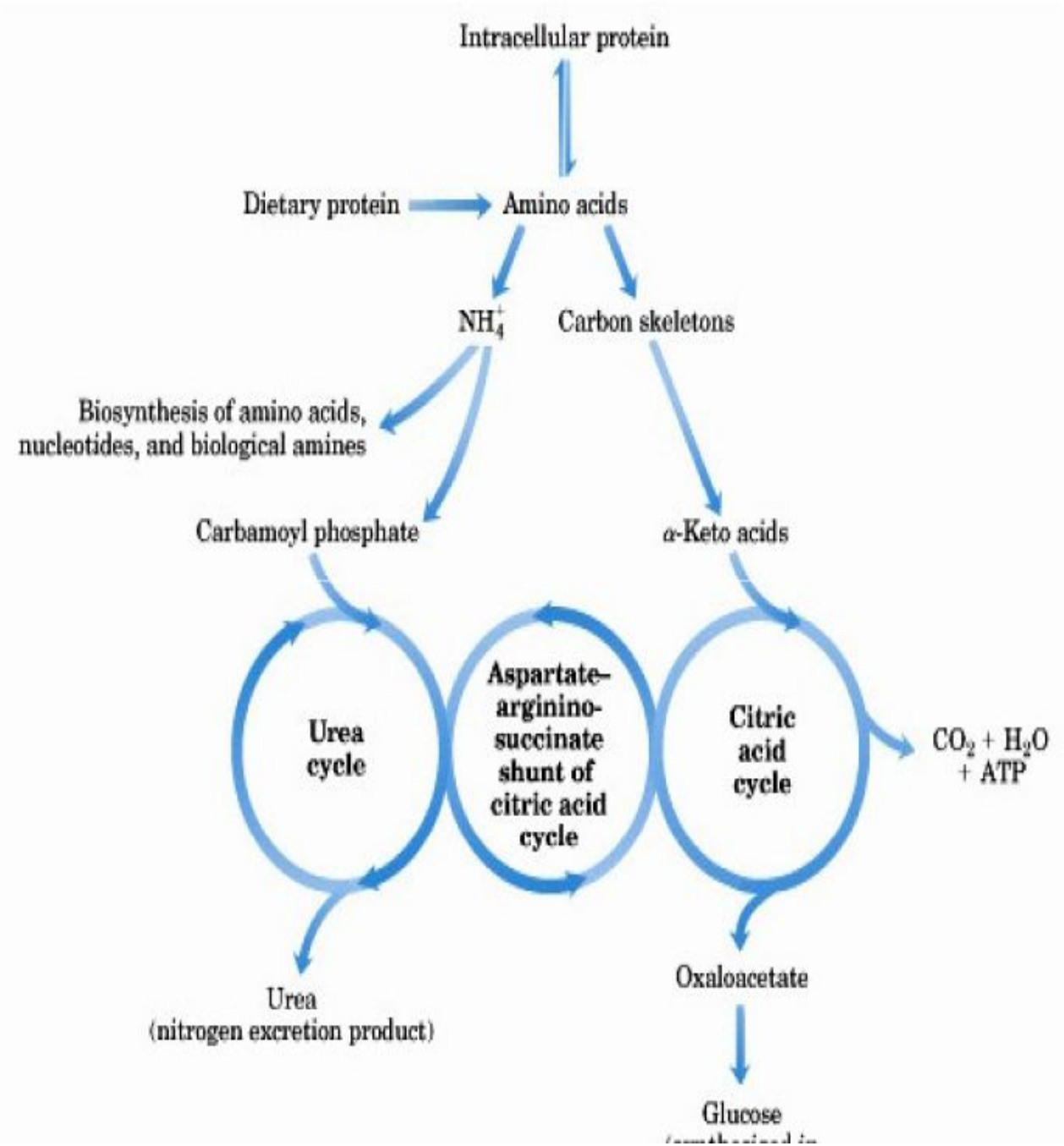
- The incoming -keto acid then binds, accepts the amino group from pyridoxamine phosphate, and departs in the form of an amino acid.

- Measurement of the alanine amino transferase and aspartate aminotransferase levels in blood serum is important in some medical diagnoses.



Key concepts of amino acid metabolism




Intracellular protein
Dietary protein
Amino acids
NH_4^+
Carbon skeletons
Biosynthesis of amino acids, nucleotides, and biological amines
Carbamoyl phosphate
α-Keto acids
Urea cycle
Aspartate–arginino-succinate shunt of citric acid cycle
Citric acid cycle
$CO_2 + H_2O$ + ATP
Urea (nitrogen excretion product)
Oxaloacetate
Glucose