UNIT-3

(For Internal Circulation only)

METABOLISM of AMINOACIDS

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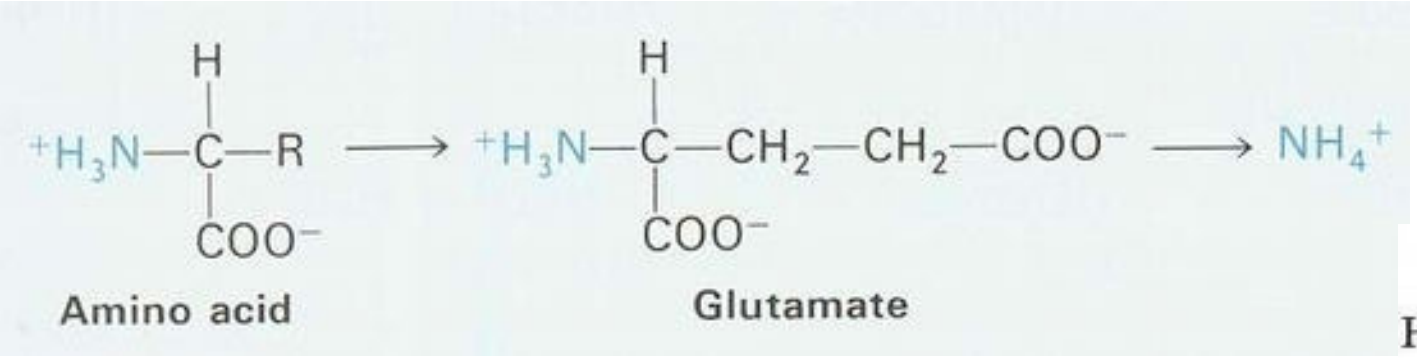
AMINO ACIDS – metabolism (degradation)
Urea Cycle
(Krebs-Henseleit cycle)

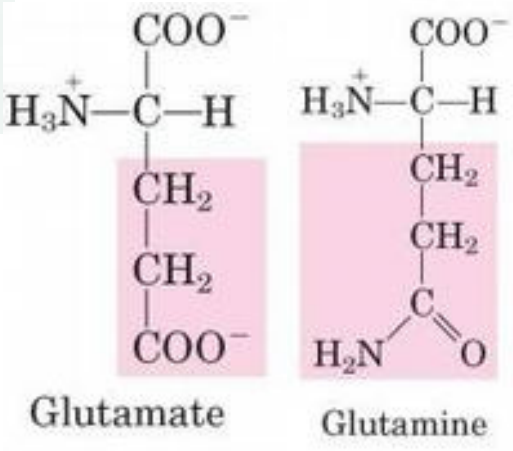
Amino Acid Pool

An adult person has about 100 gram of free amino acids, which represent the amino acid pool of the body.

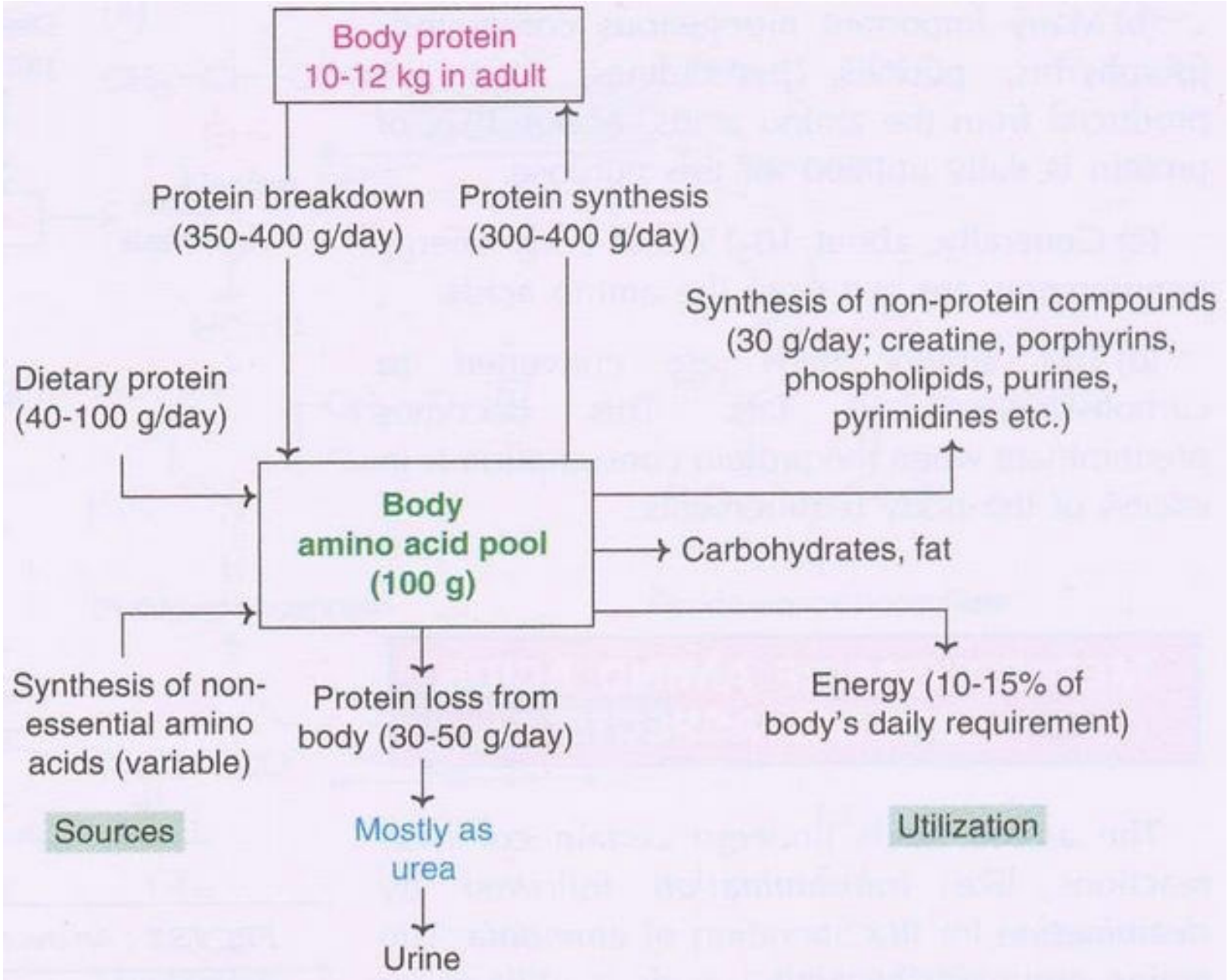
Glutamate and Glutamine together constitute about 50% of body pool,

essential amino acids about – 10%





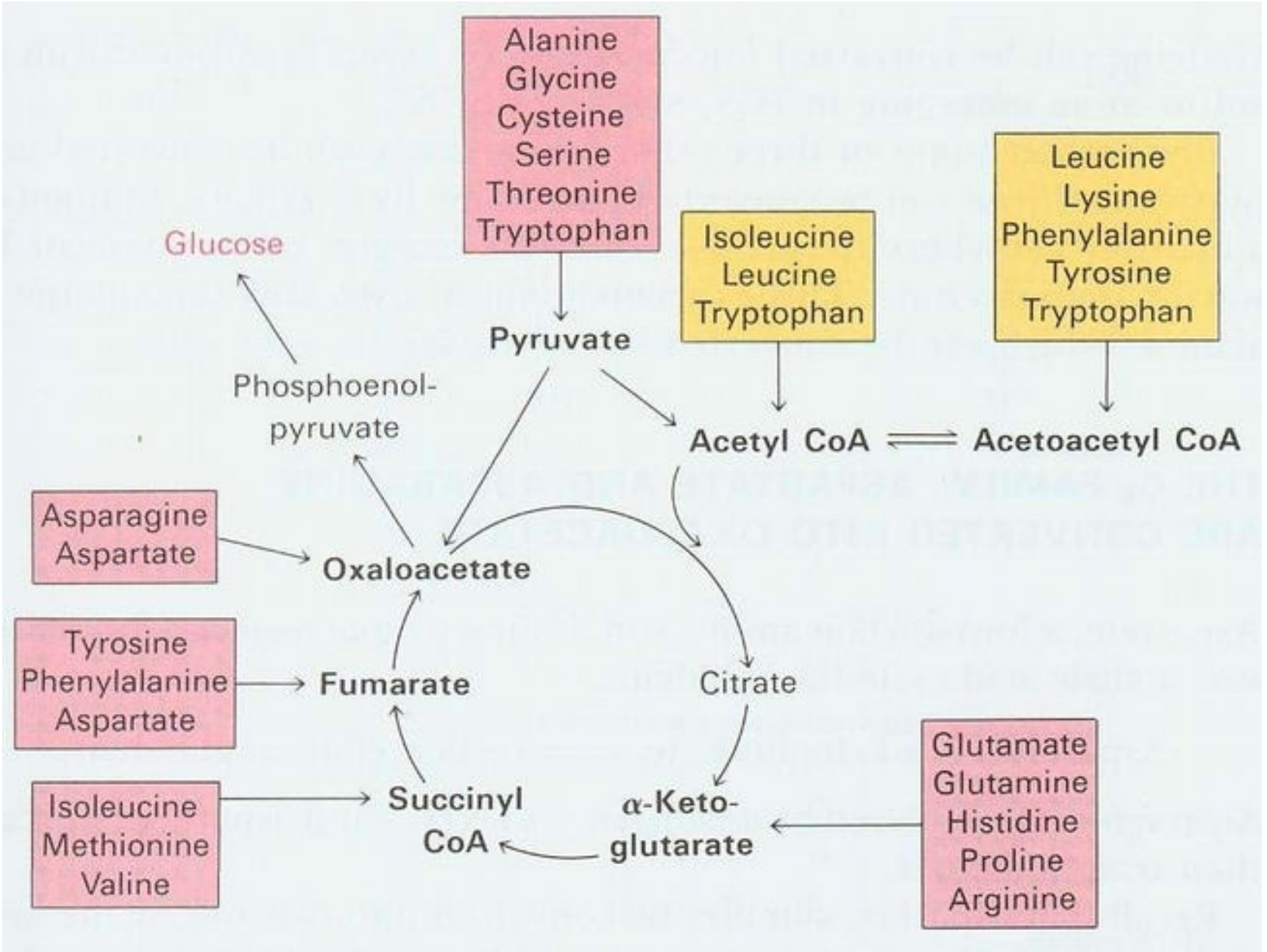
Amino Acid Pool



1.Sources of amino acid [AA] pool
-protein turnover (daily 300-400g of protein degraded to AA)
-dietary protein
-endogenic synthesis of non-essencial AA

2.Utilization of AA from body pool
-AA are converted into carbohydrates and fats
-generally, about 10-15% of body energy requirements are gained from the AA
-many important nitrogenous compounds (porphyrins, purins, pyrimidins) are produced from AA
-most of body proteins (300-400 g/daily) are synthesized from AA pool

Primitive pathway of AA degradation (energy):



General Aspects of Amino Acids Metabolism.

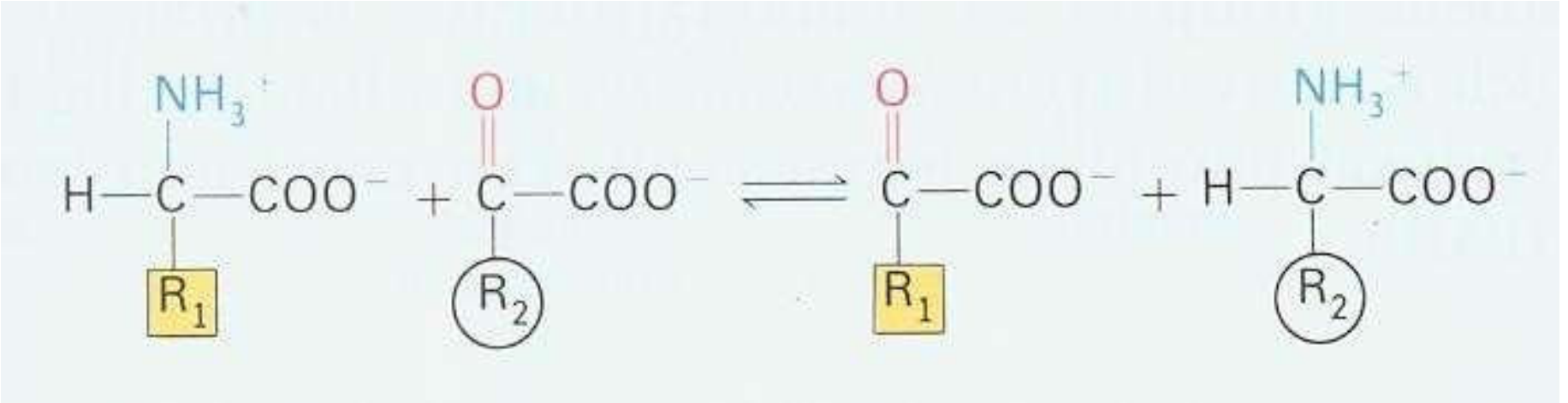
There is a primitive pathways of AA fate degradation:

1.fate of α-amino group is convertation into ammonium ion (by oxidative deamination Glutamate)
2.fate of carbon atoms which mostly turn into energy:
-the C_3 family of AA (Alanine, Serine, and Cysteine) are converted into Pyruvate;
-the C_4 family of AA (Aspartate and Asparagine) are converted into Oxaloacetate;
-the C_5 family of AA (Glutamine, Proline, Arginine, Histidine) into α-ketoglutarate throught Glutamate;

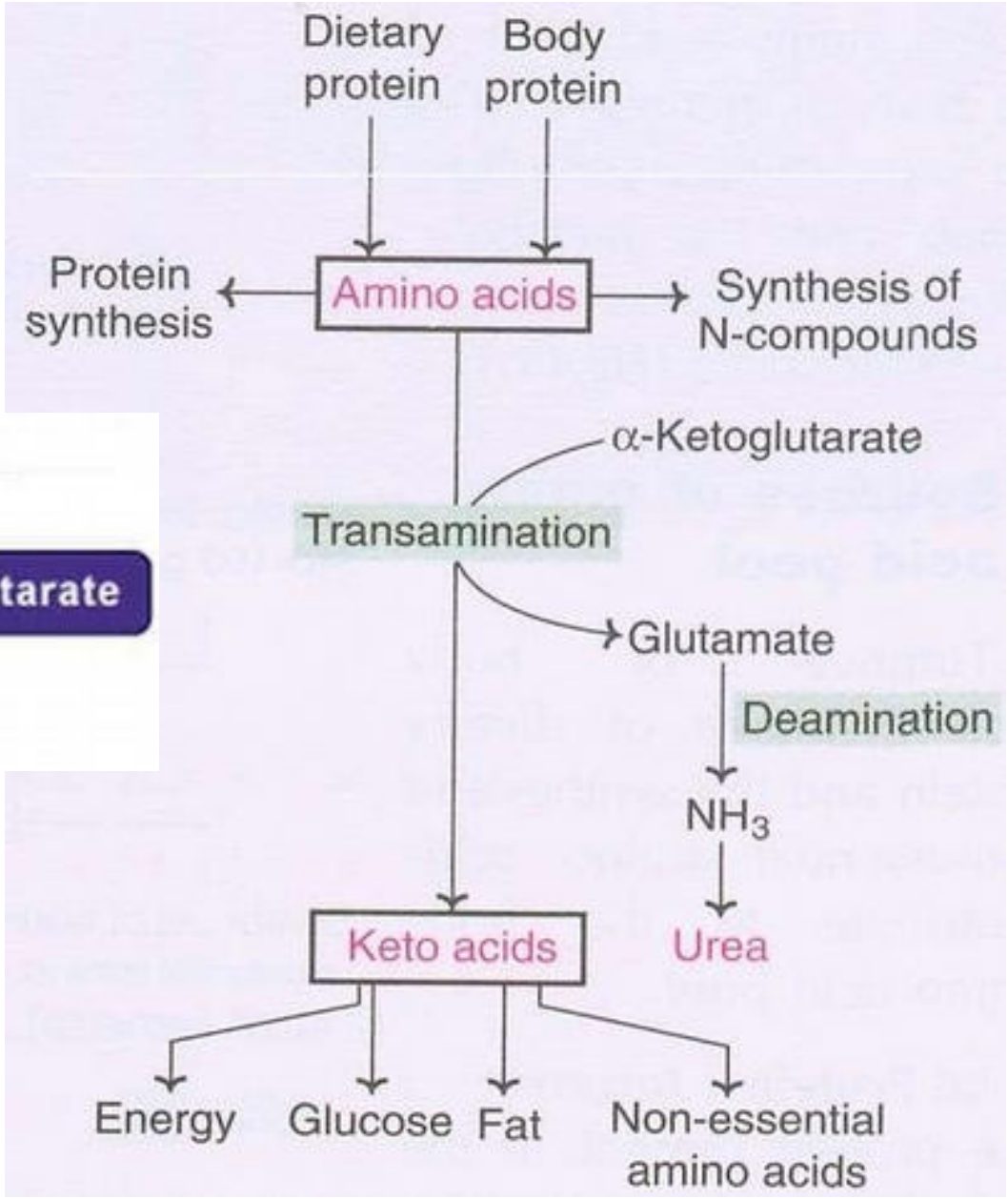
Anyway – the AA undergo certain common reactions:

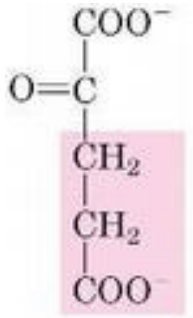
transamination followed by ***deamination*** for the liberation of ammonia.

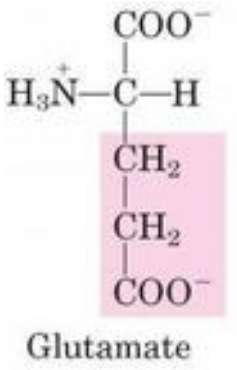
The amino group of the amino acids is utilized for the formation of ***urea*** which is an excretory ***end product***



Ways of Amino Acids convertation.



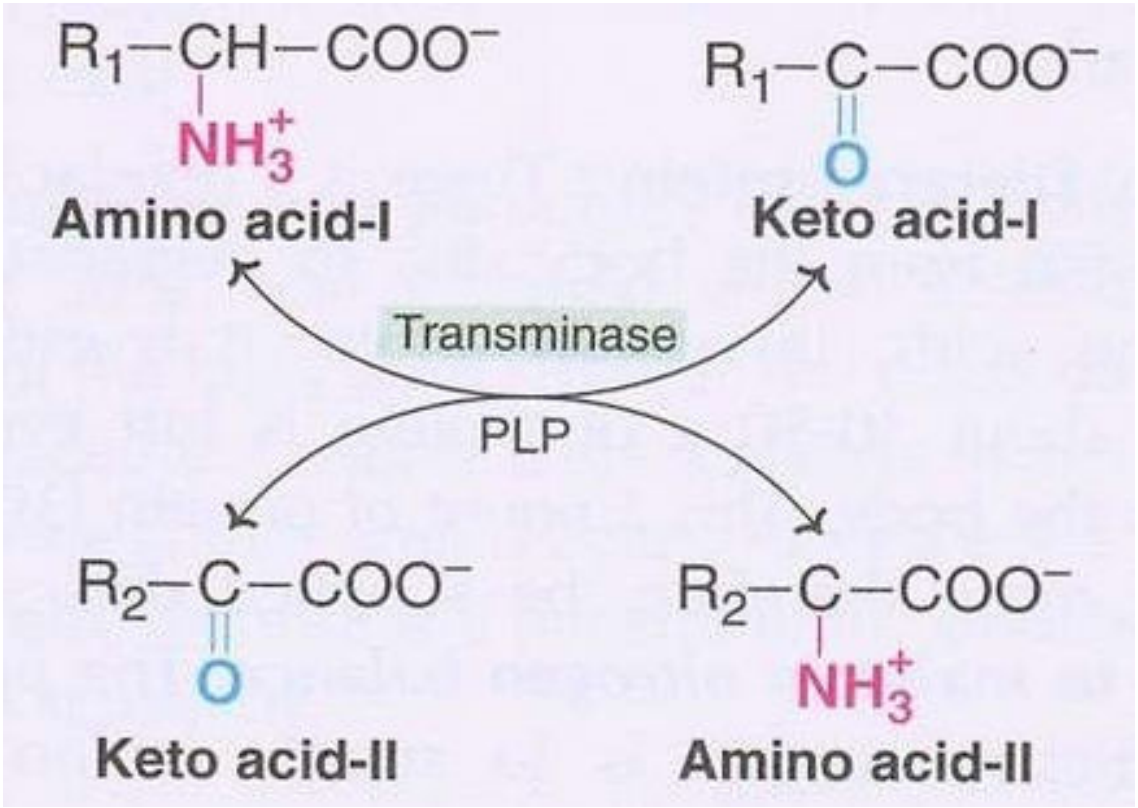


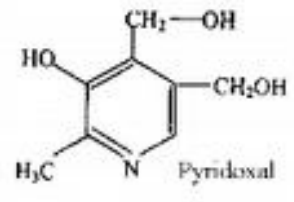


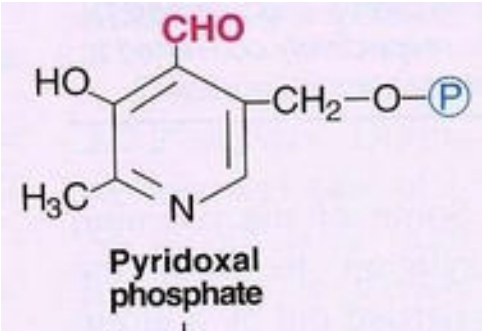
1.Transamination

is a transfer of an amino (-NH_2) group from an amino acid to a keto acid transaminase (recently, aminotransferases)

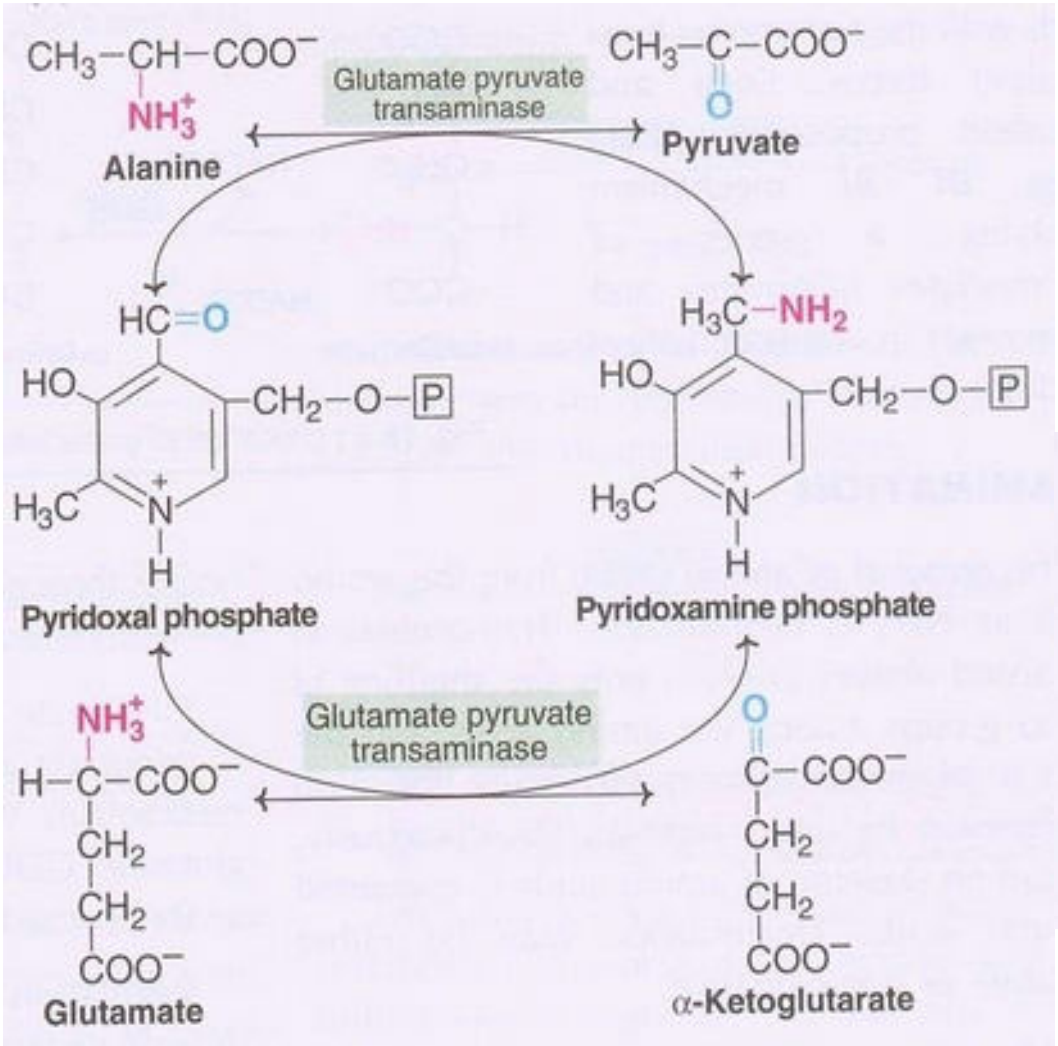
PLP – pyridoxal phosphate [Vitamin B_6 (pyridoxine)]

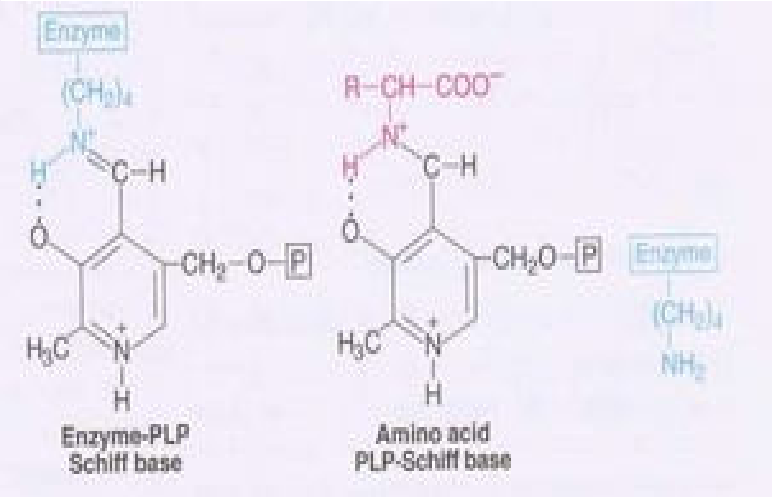






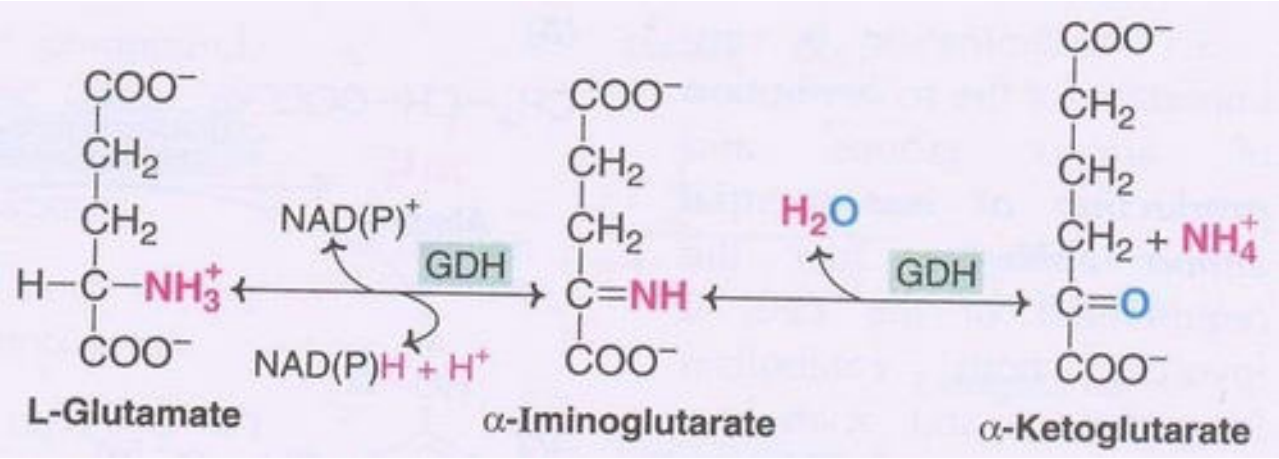
1.Transamination
involvement of pyridoxal phosphat (PLP) and formation of enzyme-PLP-Schiff base

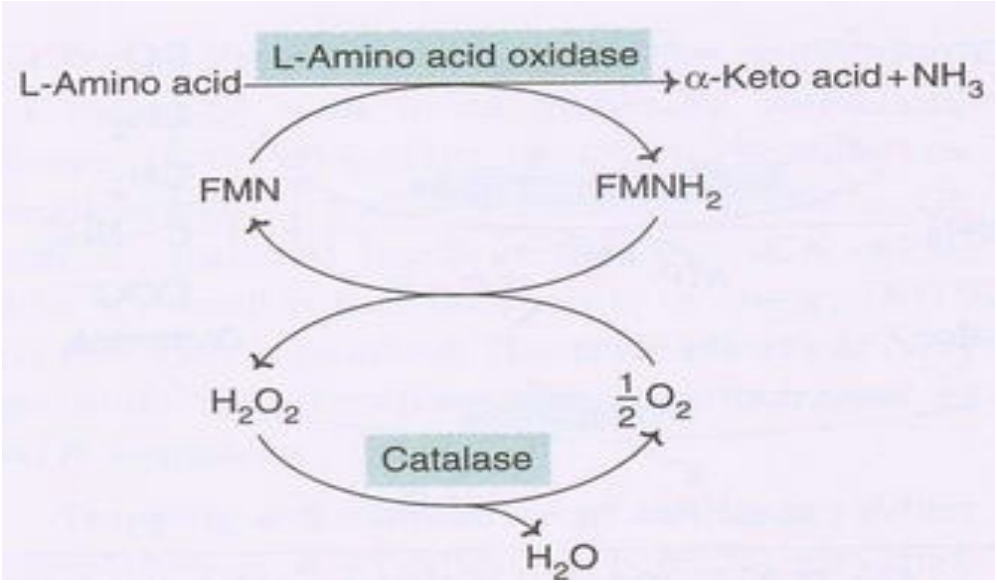




2.Deamination (oxidative and non- oxidative)

-oxidative deamination

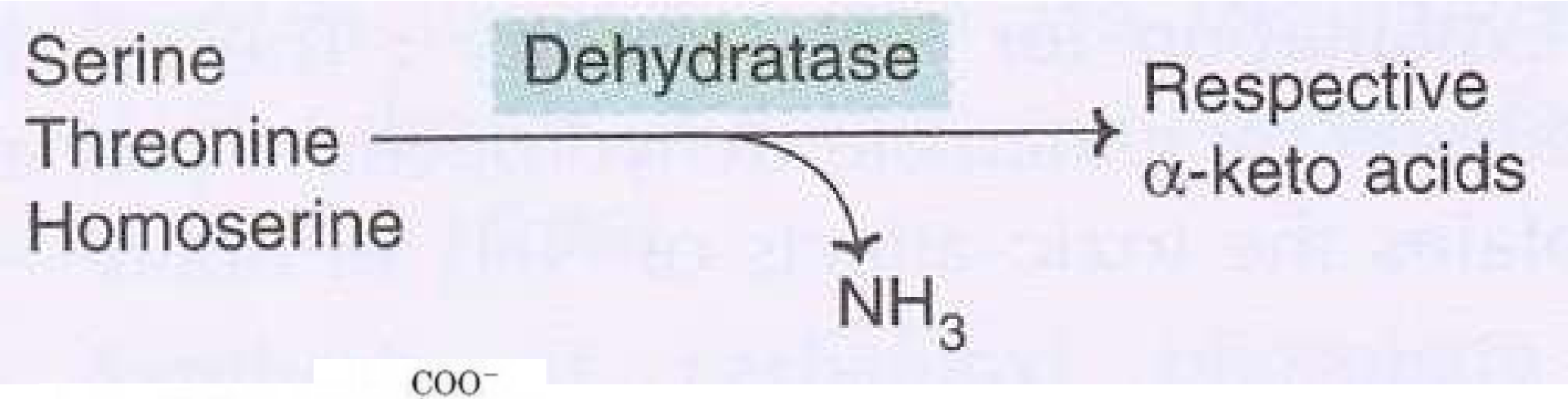


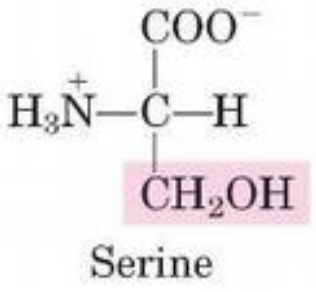


2.Deamination (1/3)

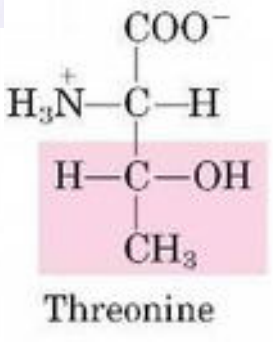
- non-oxidative deamination

a.amino acids dehydrases (serine, threonine and homoserine – are hydroxy AA deamination of which is catalysed by pyridoxal phosphate [PLP])

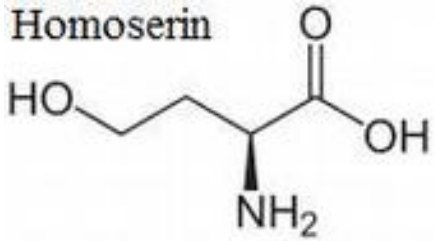




Serine



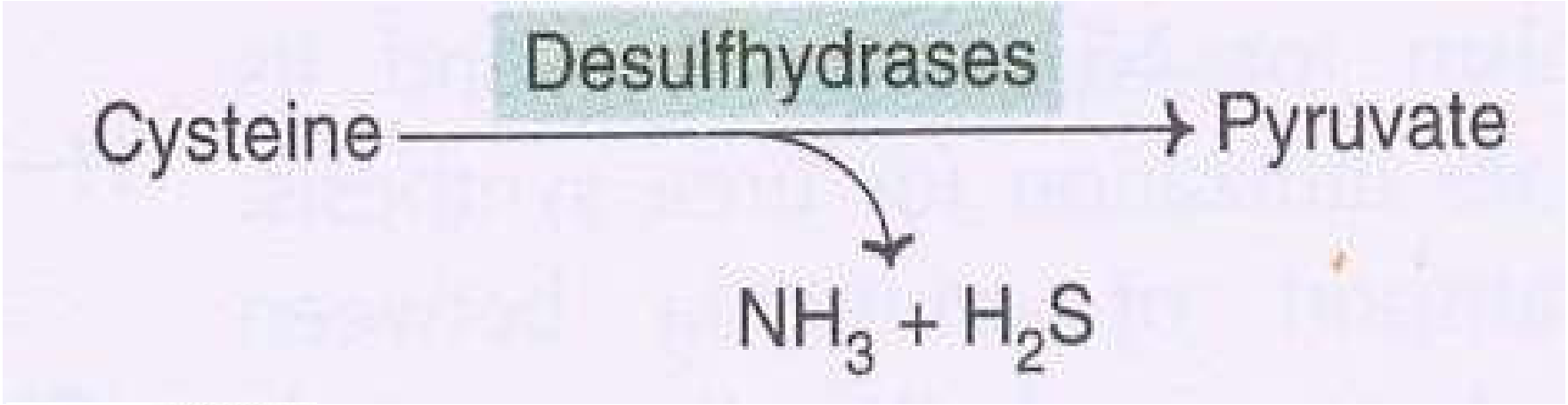
Threonine

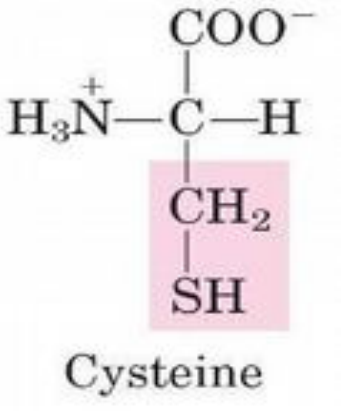


2.Deamination (2/3)

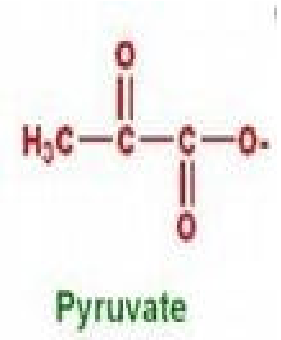
- non-oxidative deamination

b.sulfur amino acids (cystein, homocystein) undergo deamination coupled with desulfhydrases



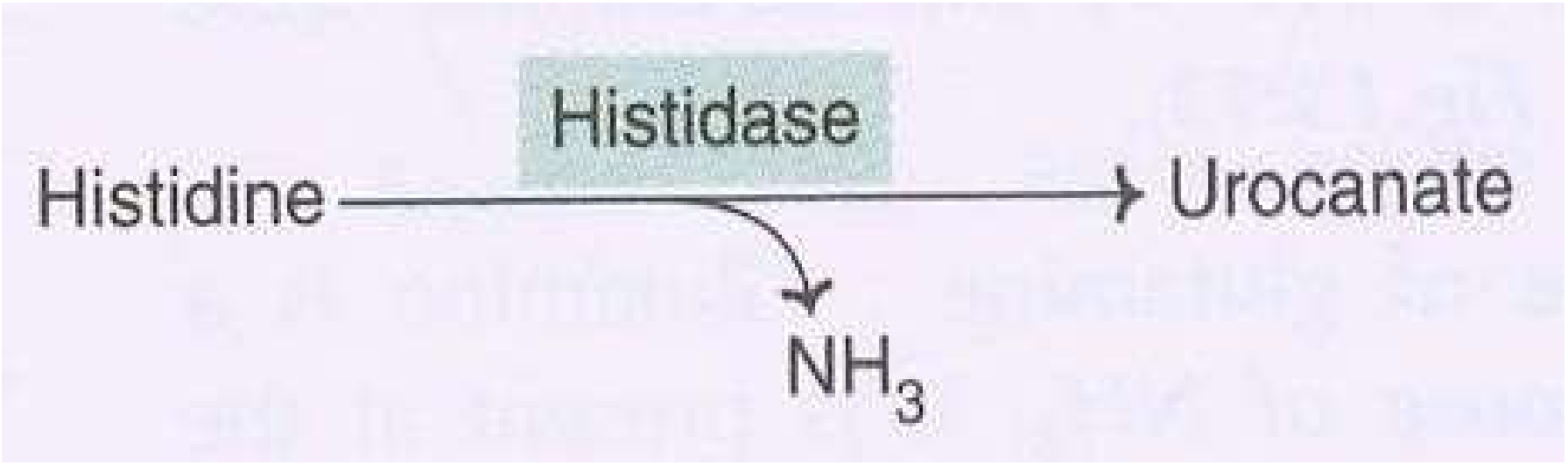


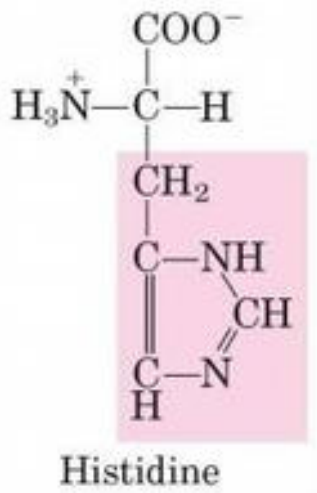
Cysteine



Pyruvate

2.Deamination (3/3)
- non-oxidative deamination
c.dehydratation of histidine is catalised by histidase





Histidine

Urocanic acid (Urocanate) is an intermediate in the catabolism of L-histidine. It is formed from L-histidine through the action of histidine ammonilyase (also known as histidase or histidinase) by elimination of ammonium. In the liver, urocanic acid is transformed by urocanate hydratase (or urocanase) to 4-imidazolone-5-propionic acid and subsequently to glutamic acid.

Metabolism of ammonia

-formation of ammonia (occurs during transamination and deamination)

-transport and storage of NH_3

(mainly provided by glutamine [is a storehouse of ammonia] or alanine) concentration of NH_3 is surprisingly low [normal plasma 10-20 mg/dl]

-functions of ammonia (directly or via glutamine NH_3 involved into synthesis of non-essencial AA, purines, pyrimidines, amino sugars, aspsrsgine) ammonia forms the acid-base balance

-disposal of ammonia (during course of evolution the organisms have developed different mechanisms for the disposal of ammonia from the body)

a.ammoniotelic – aquatic animals dispose off NH_3 into the surrounding water

b.uricotelic – in reptiles and birds – ammonia is converted mostly into uric acid

c.ureotelic – mammals – convert ammonia into urea

-toxicity of ammonia – all disorders of ammonia disposal leads to hyperammonemia and cause hepatic coma and mental retardation

The molecular weight of urea (NH_2–CO–NH_2) is 60 [14+2+12+16+14+2] – and about half of it (28) – is contributed by the two nitrogen atoms.

Thus, if blood urea concentration is 60 mg, then about half of it – 28 – is **blood urea nitrogen** (BUN).

Therefore,

BUN = ½ NPN (non protein nitrogen)

NPN = 2 BUN

Estimation of BUN or NPN are used rather than blood urea for assessing kidney function. The normal range for ***ratio*** of ***BUN*** to serum ***creatinine*** is 10:1 to 15:1.

Urea Cycle – Krebs-Henseleit cycle

[Hans] Krebs - [Kurt] Henseleit (1932)

$$NH_4^+ + CO_2 + \text{Aspartate} + 3ATP \rightarrow$$
$$\text{Urea} + \text{Fumarate} + 2ADP + 2P_i + AMP + PP_i$$

-synthesis of carbomoyl phosphate

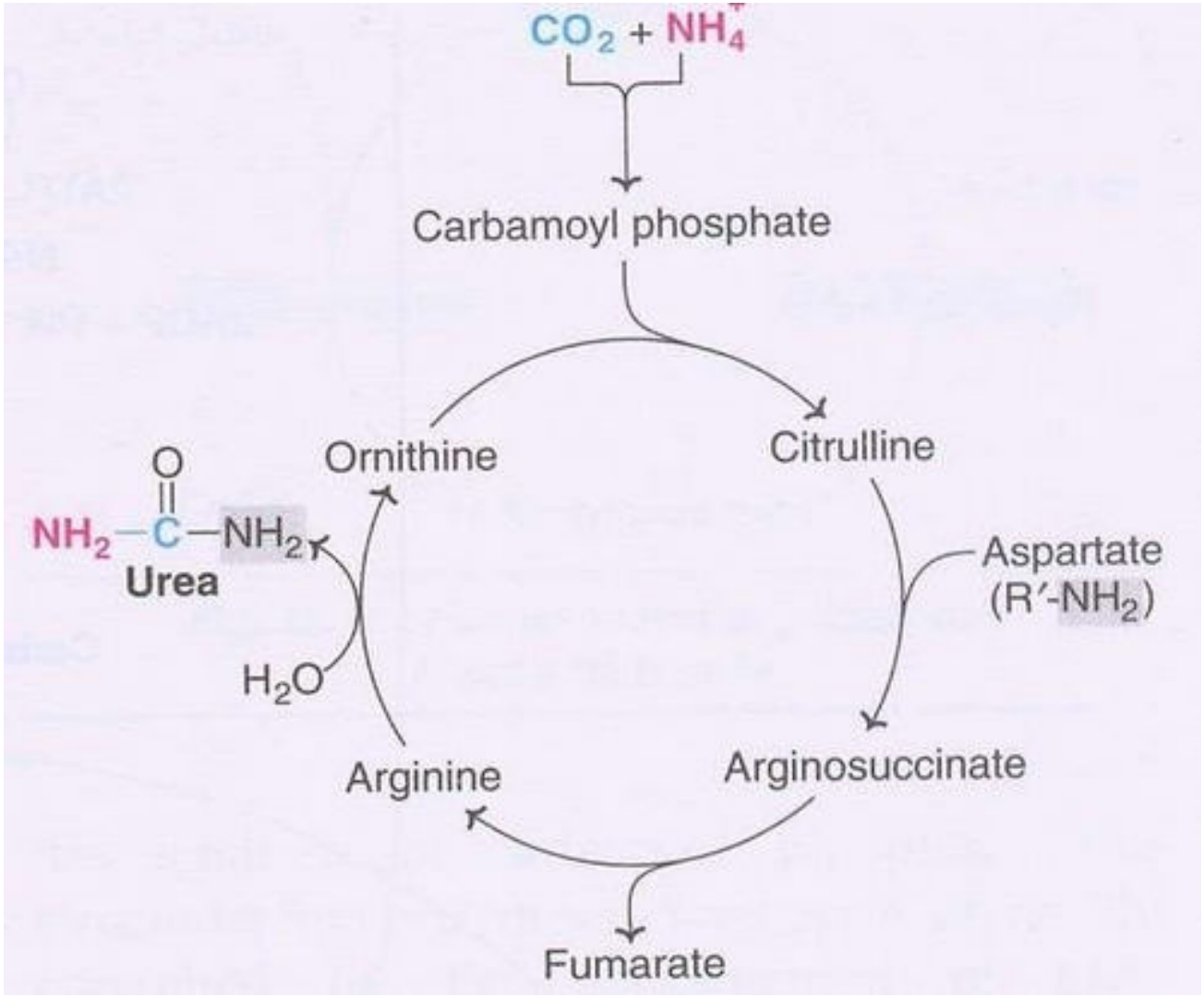
-formation of citrulline

-synthesis of arginisuccinate

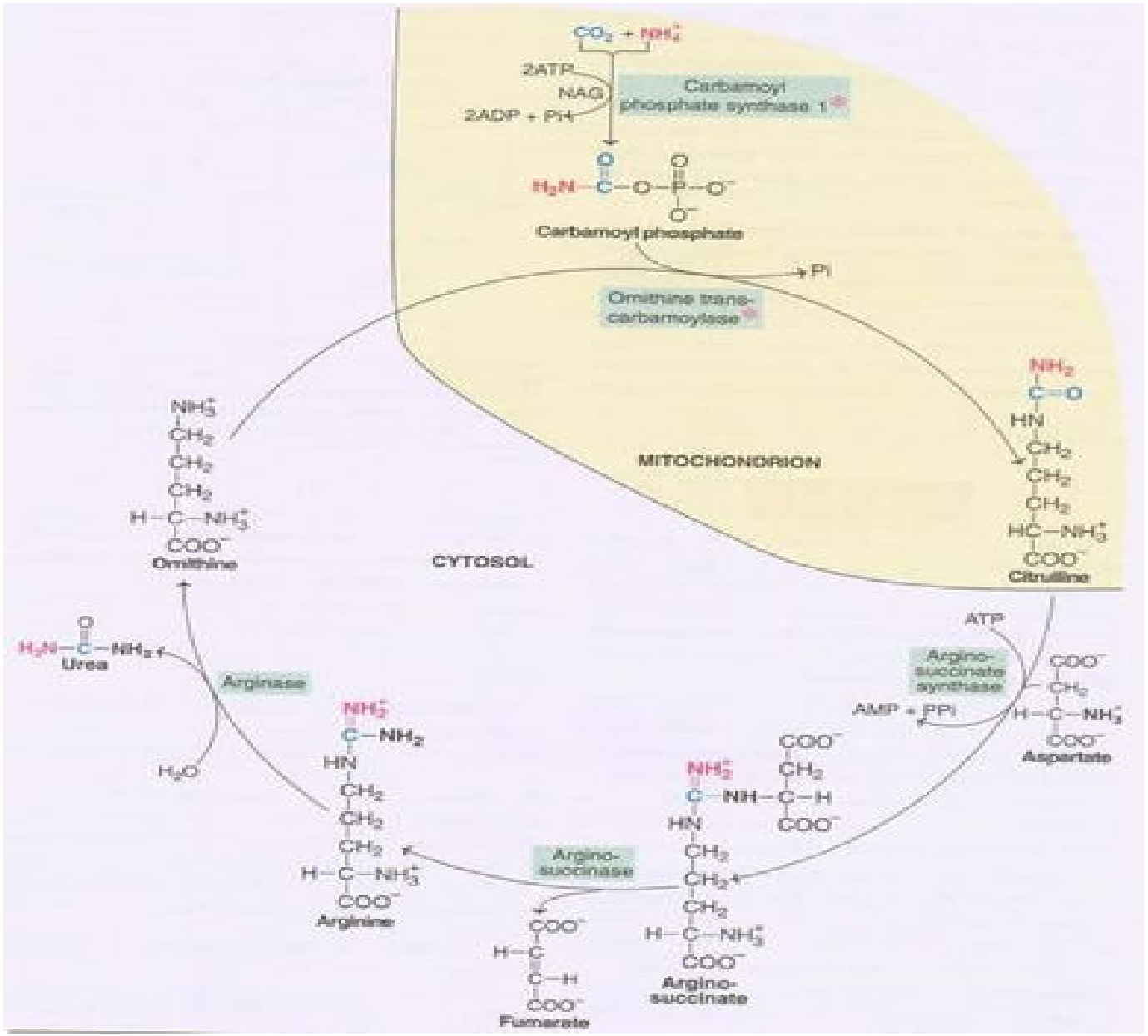
-cleavage of arginisuccinate

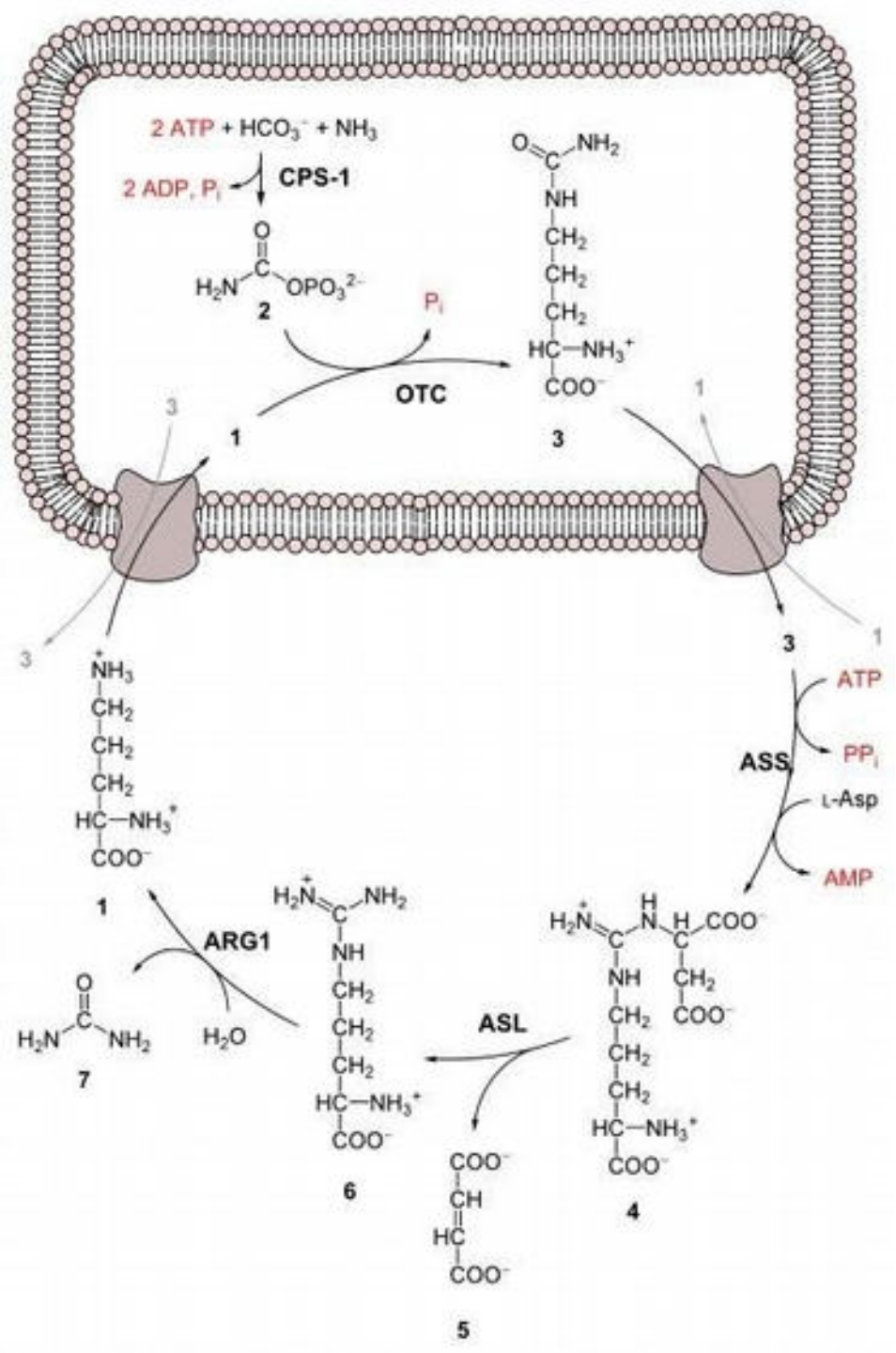
-formation of urea

Urea Cycle – Krebs-Henseleit cycle (General view)



Urea Cycle – Krebs-Henseleit cycle (all steps)

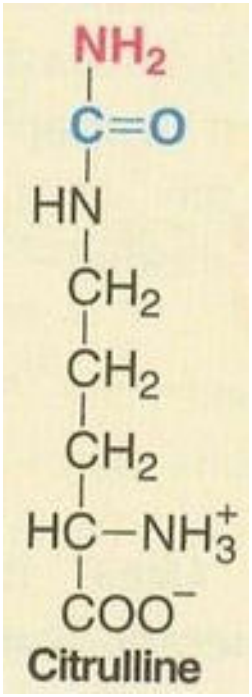




Urea Cycle (Krebs-Henseleit cycle)

1 L-ornithine
2 carbamoyl phosphate
3 L-citrulline
4 argininosuccinate
5 fumarate
6 L-arginine
7 urea
L-Asp L-aspartate
CPS-1 carbamoyl phosphat synthetase I
OTC Ornithine transcarbamoylase
ASS argininosuccinate synthetase
ASL argininosuccinate lyase
ARG1 arginase 1

Urea Cycle – Krebs-Henseleit 1
argino-succinate synthase
(cytosomal enzym in cytosol)



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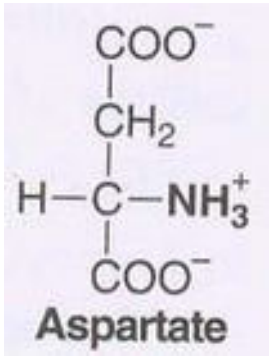

ATP

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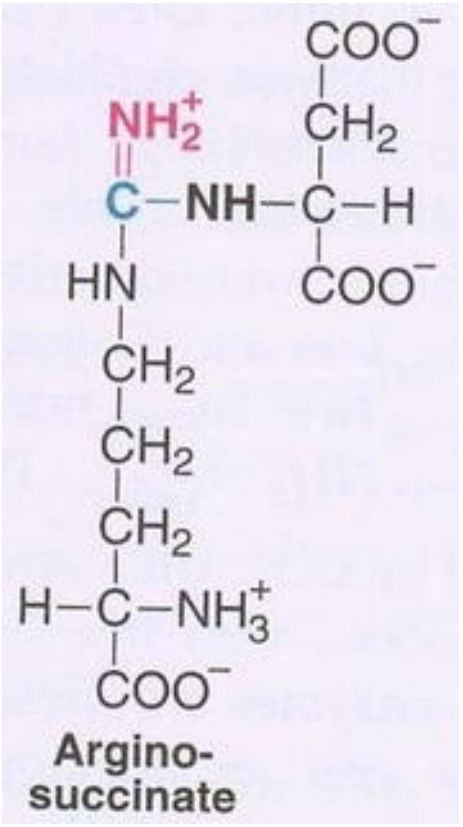
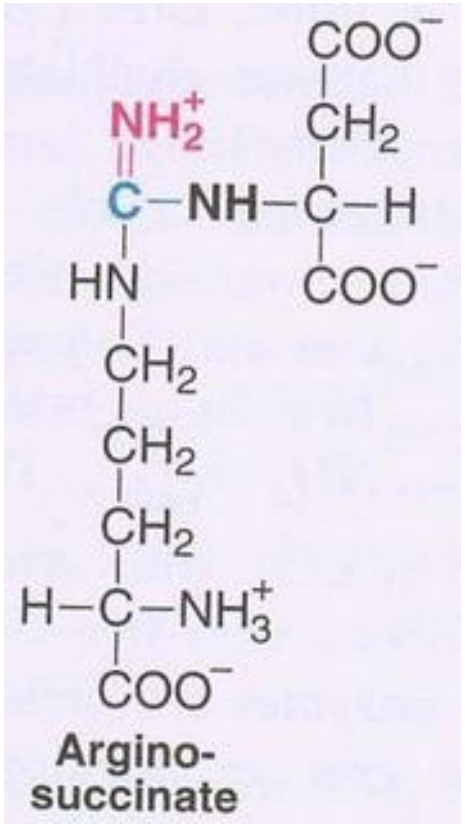
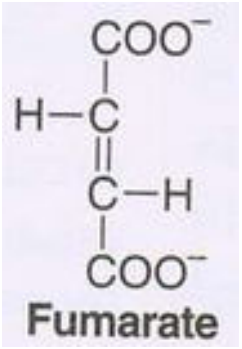
– AMP + PP_i

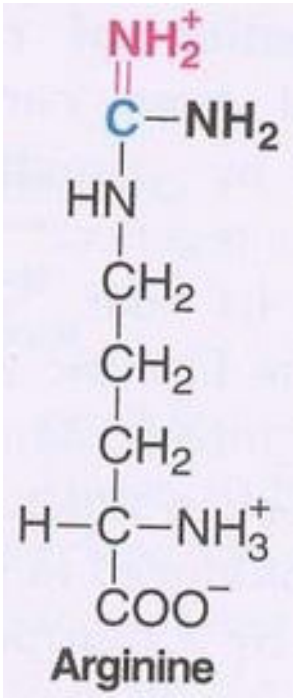


Urea Cycle – Krebs-Henseleit 2
argino succininase (cytosomal enzym)

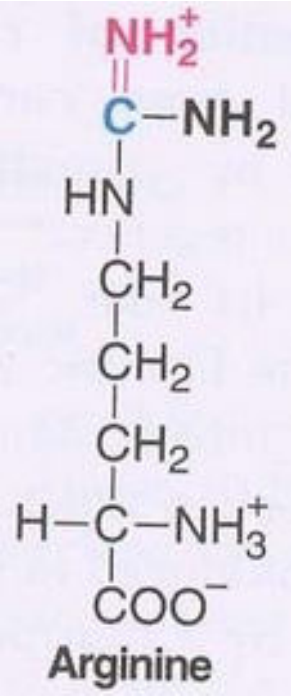


argino
succininase
→





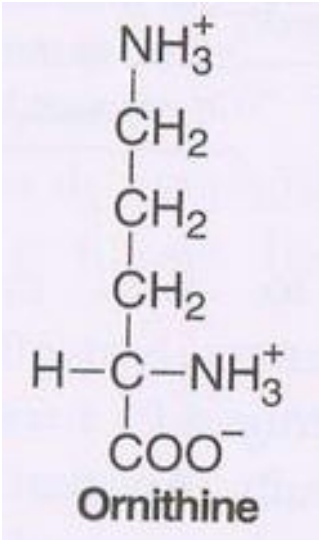
Urea Cycle – Krebs-Henseleit 3
arginase (cytosomal enzym)



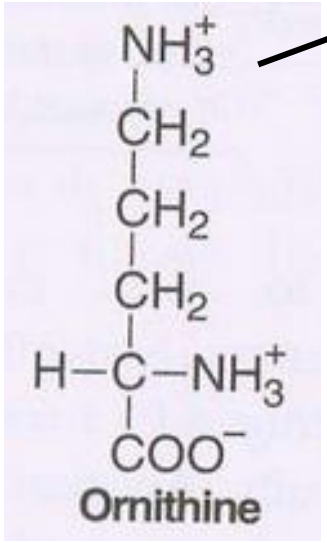
+ H_2O

arginase

→



Urea Cycle – Krebs-Henseleit 4
ornithine transcarbamoylase (mitochondrial enzym)



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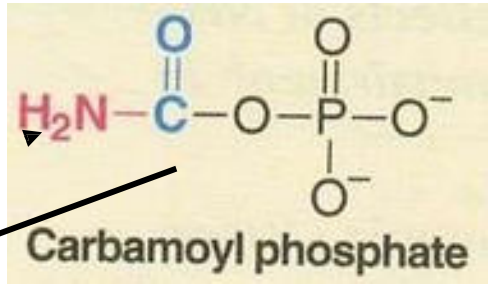
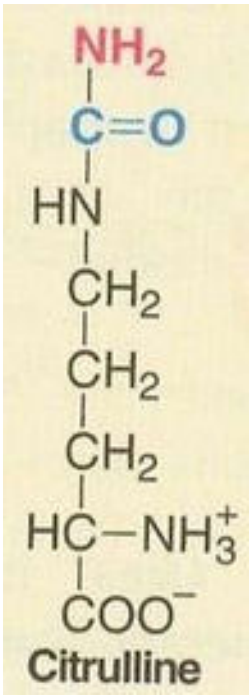


ornithine
transcarbamoylase

→

$- P_i$



Urea Cycle – Krebs-Henseleit “pre 1st ” step

[NAG – N-acetylglutamate]

carbamoylphosphat synthase (mitochondrial enzym)

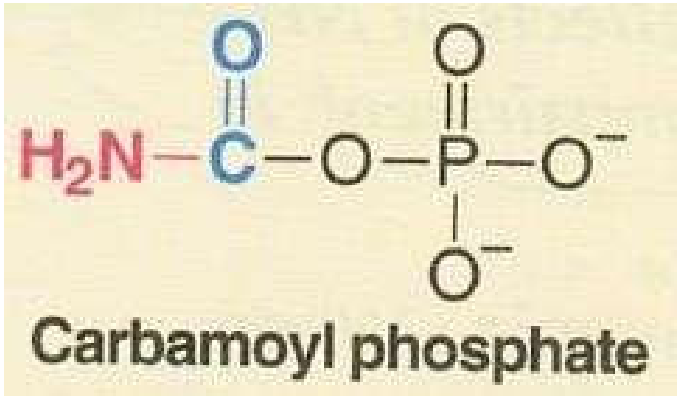
$CO_2 + NH_4^+$ + 2ATP

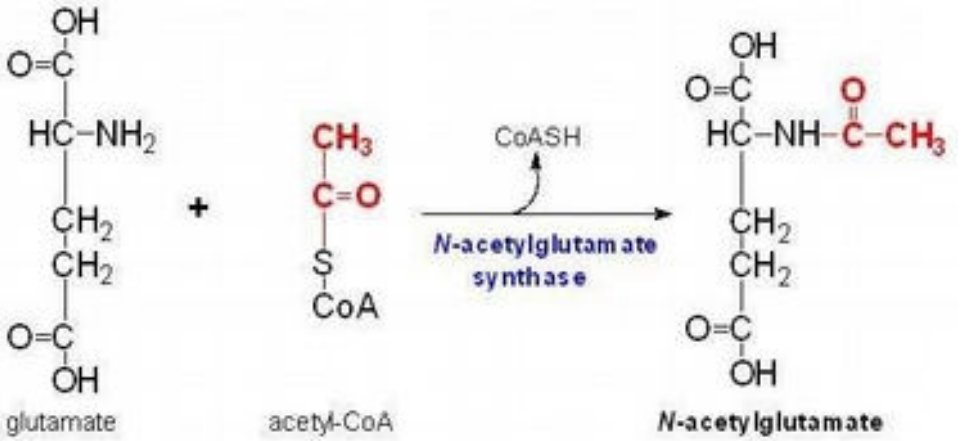
[NAG]

carbamoylphosphat synthase

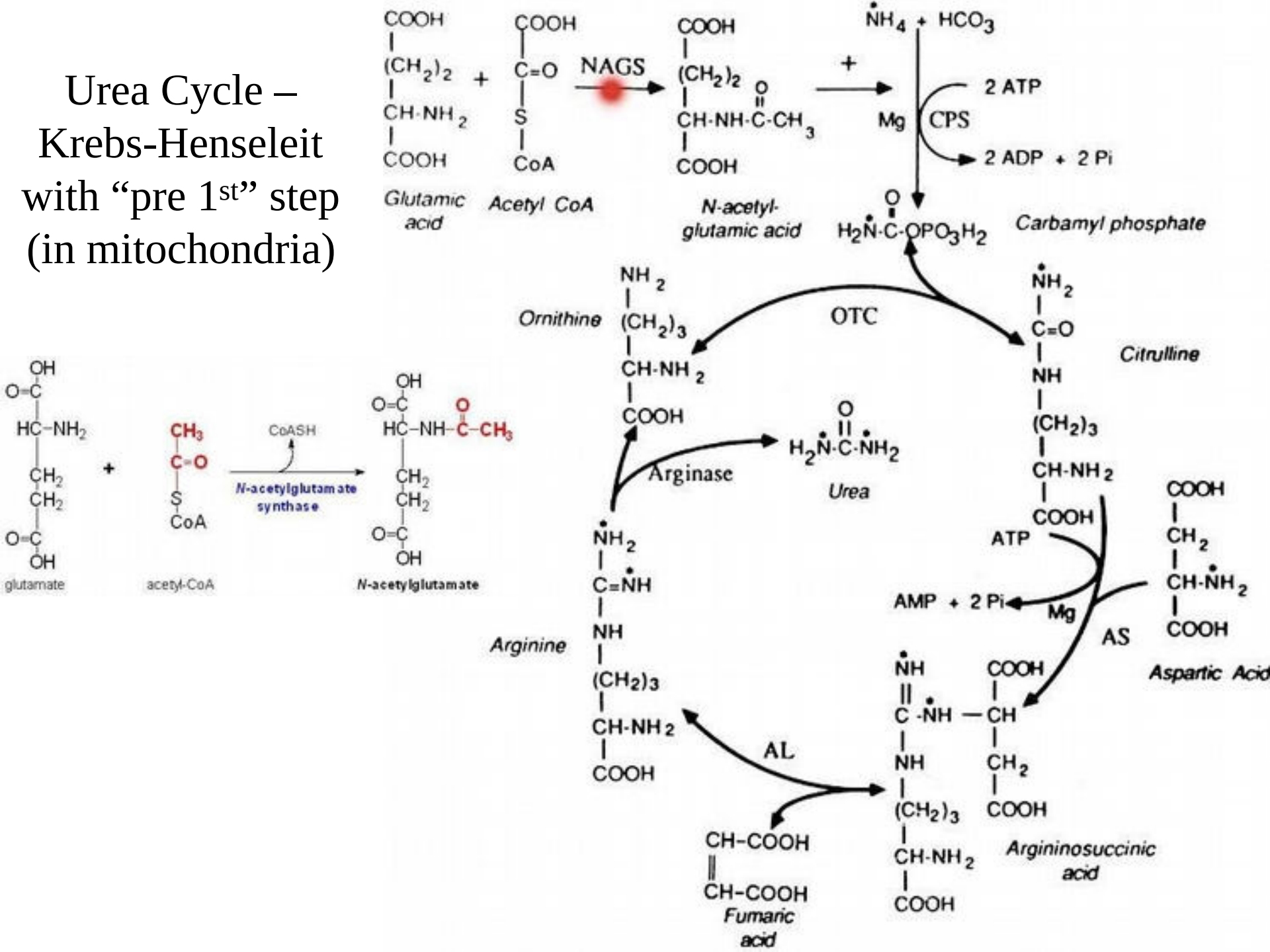
→

– 2ADP+P_i

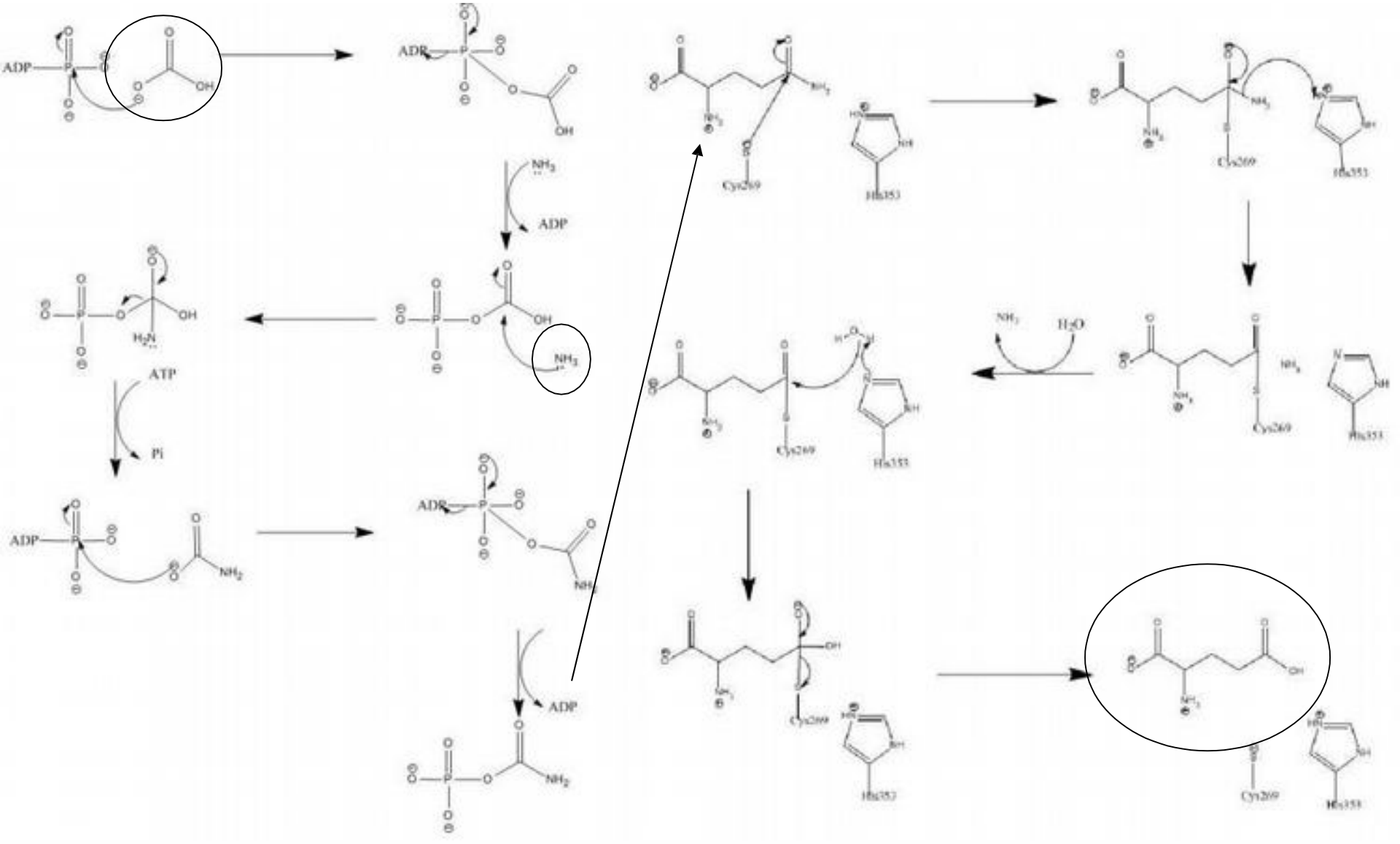




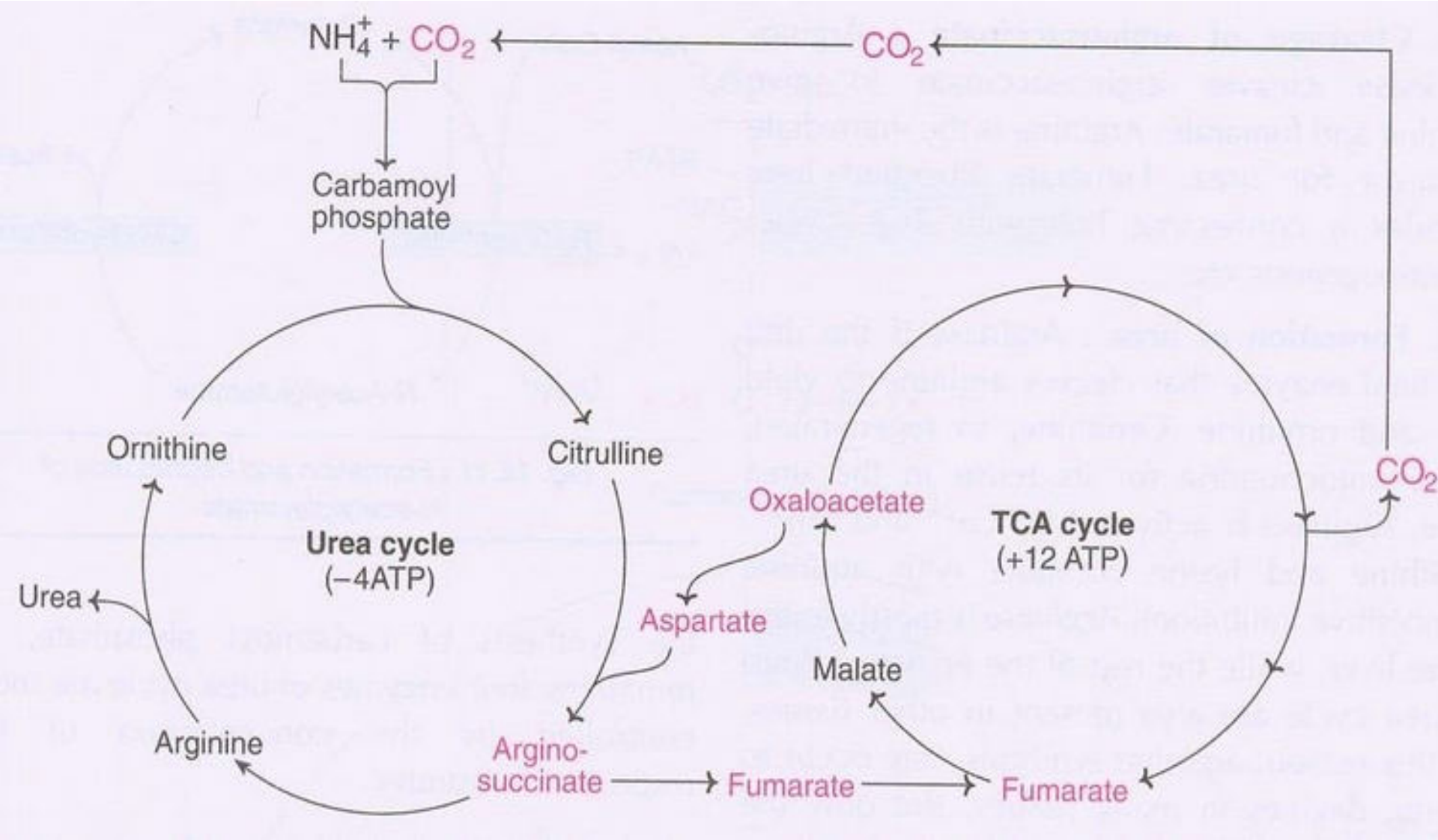
Urea Cycle – Krebs-Henseleit with "pre 1st" step (in mitochondria)



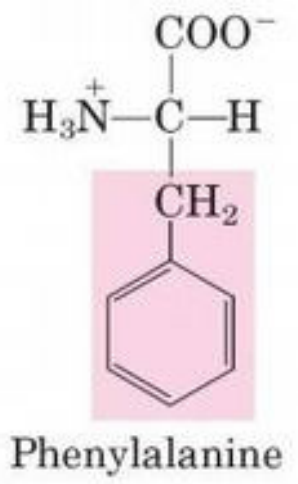
Substeps of “pre 1st” step
[carbamoylphosphat synthase carbamoyl phosphate formation]



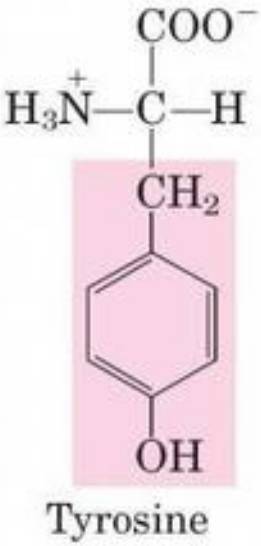
Integration between Urea cycle and TriCarboxylic Acid (TCA) cycle



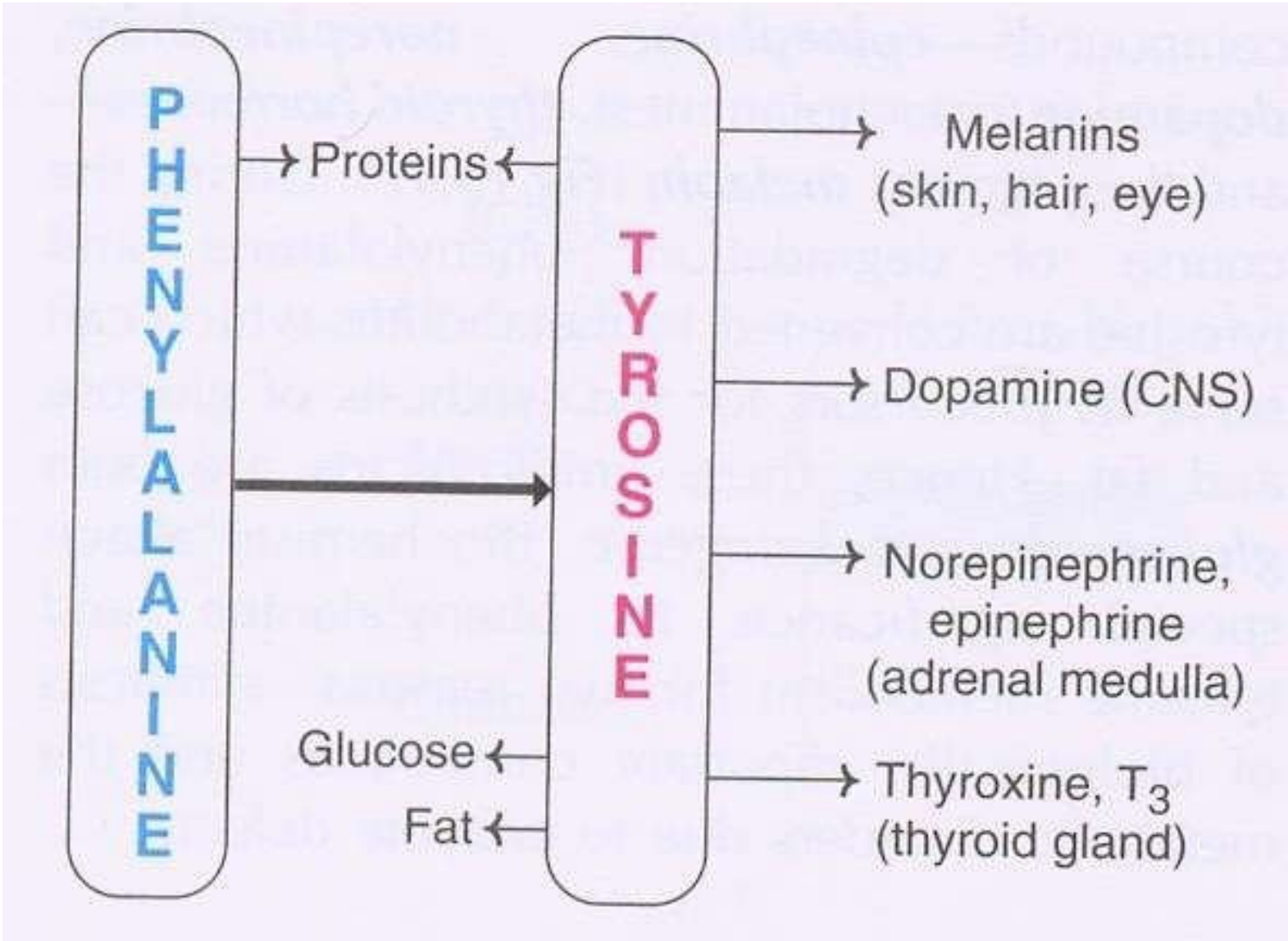
Metabolism of individual Amino Acids
Phenylalanine and Tyrosine



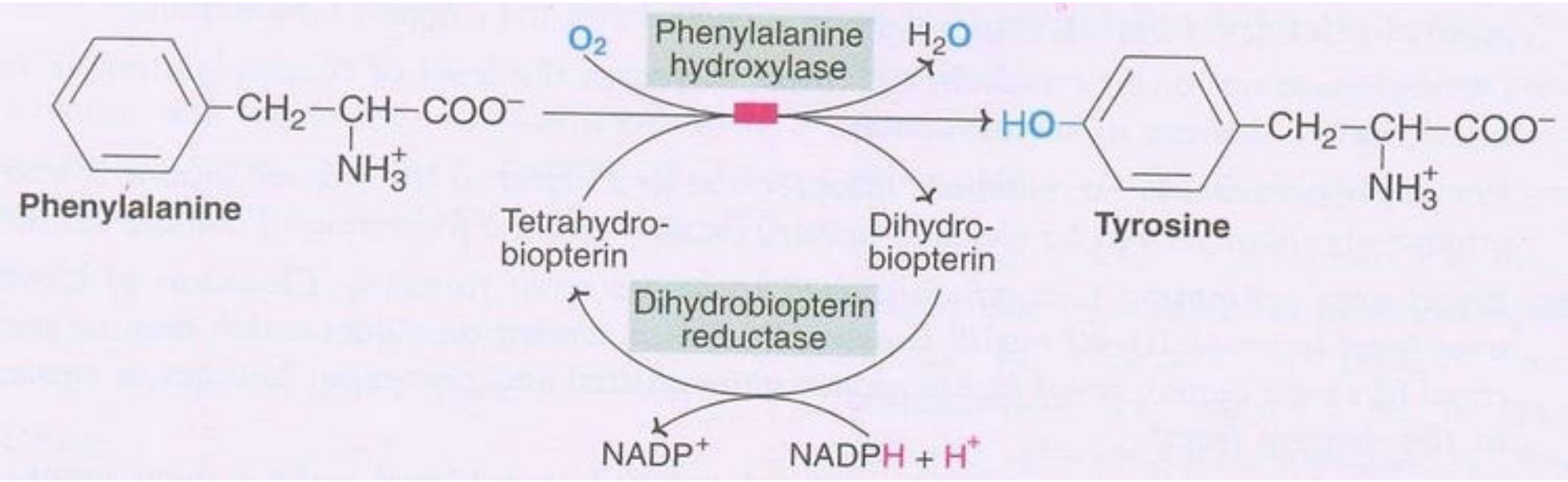
Phenylalanine



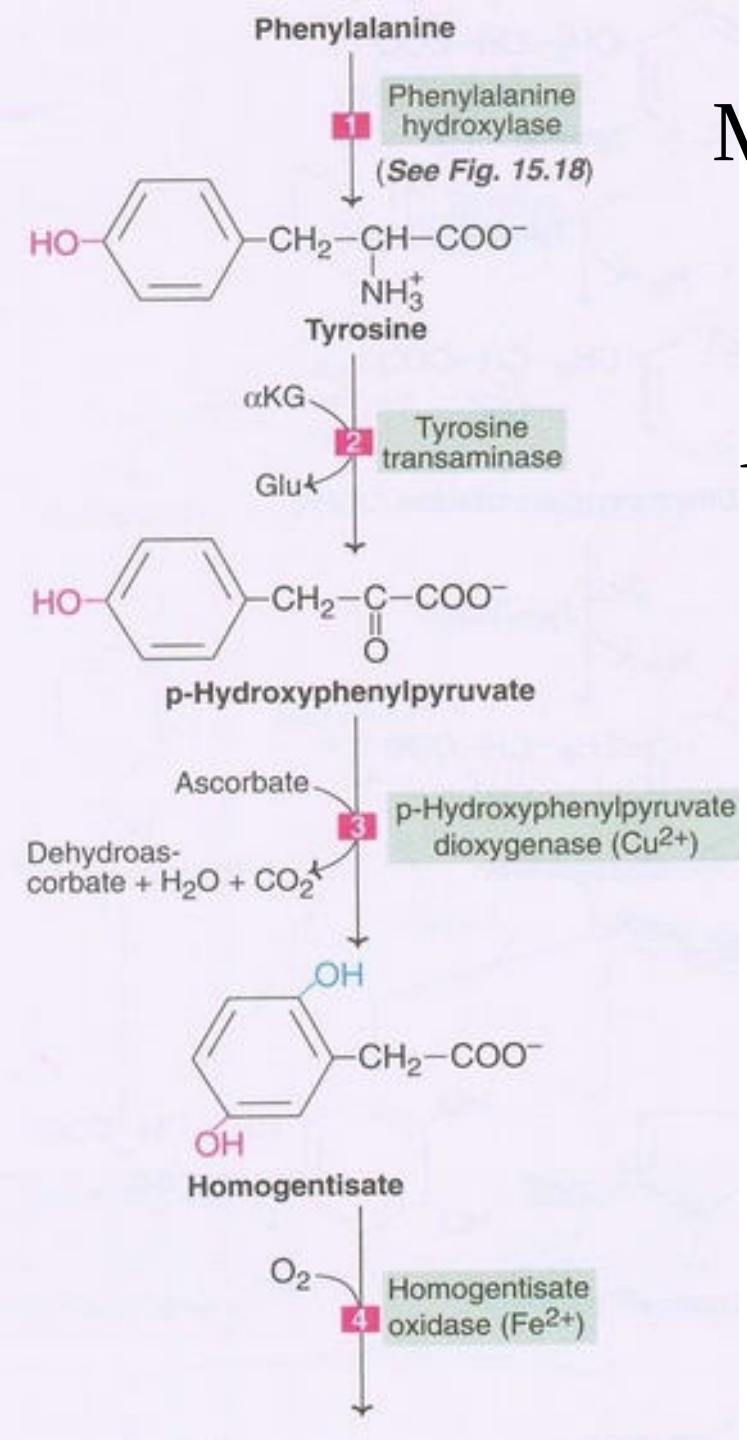
Tyrosine

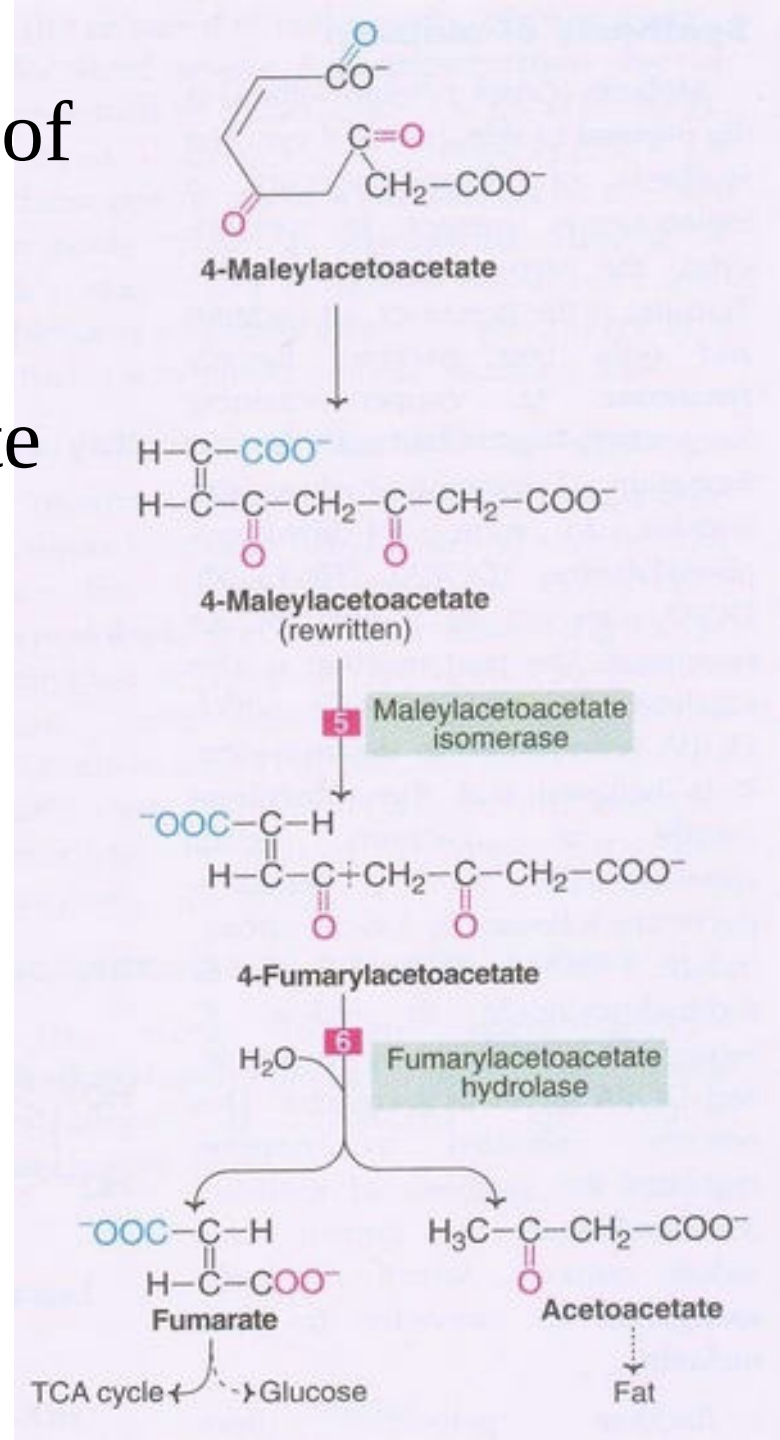


Synthesis of Tyrosine from Phenylalanine

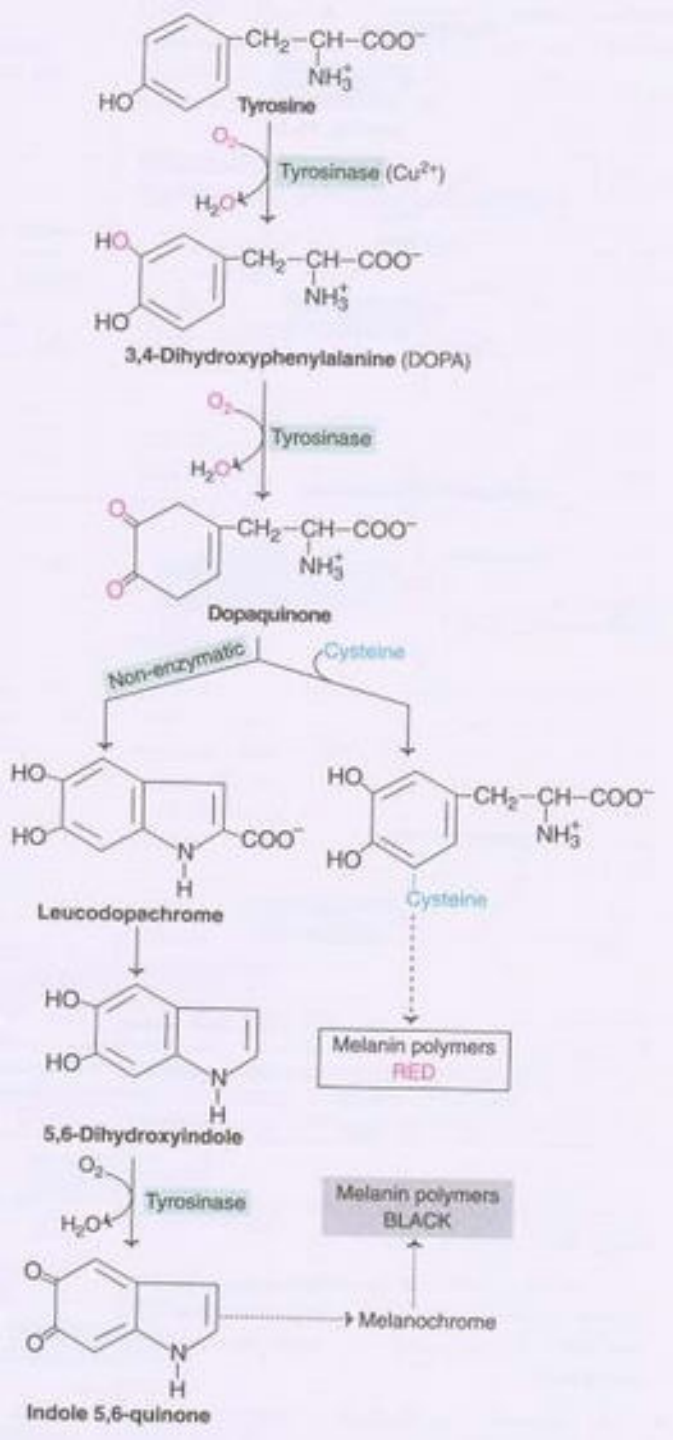


Metabolism of Tyrosine forming Acetoacetate and Fat

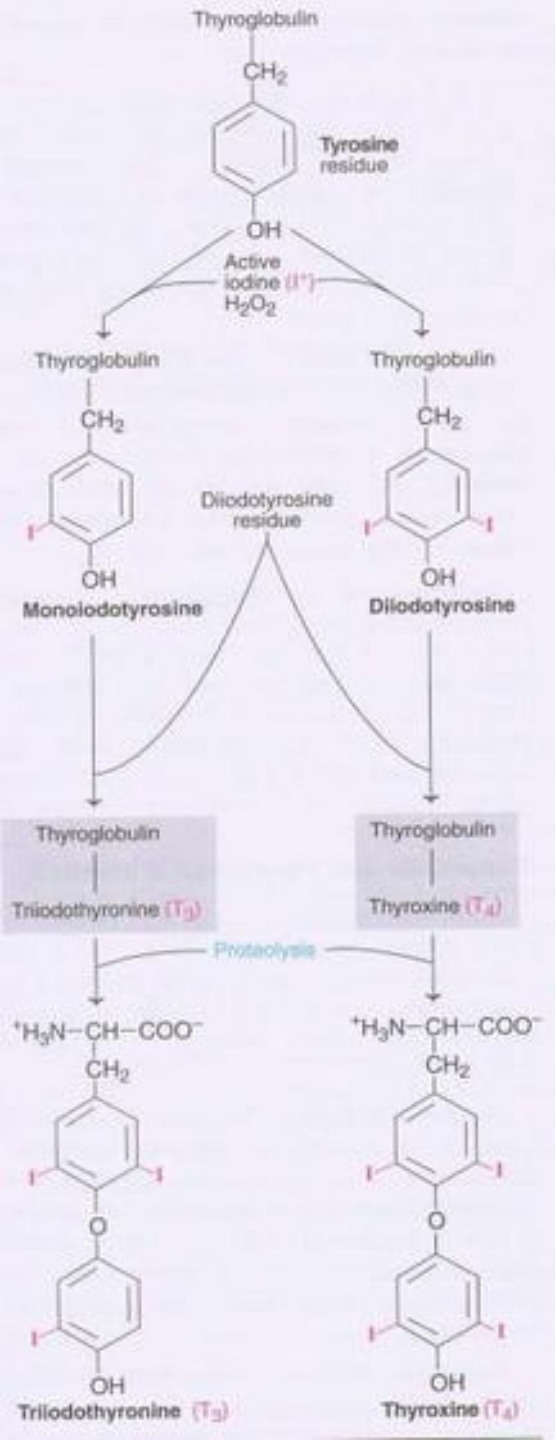


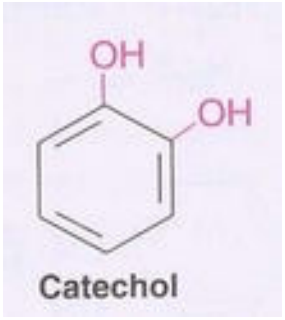


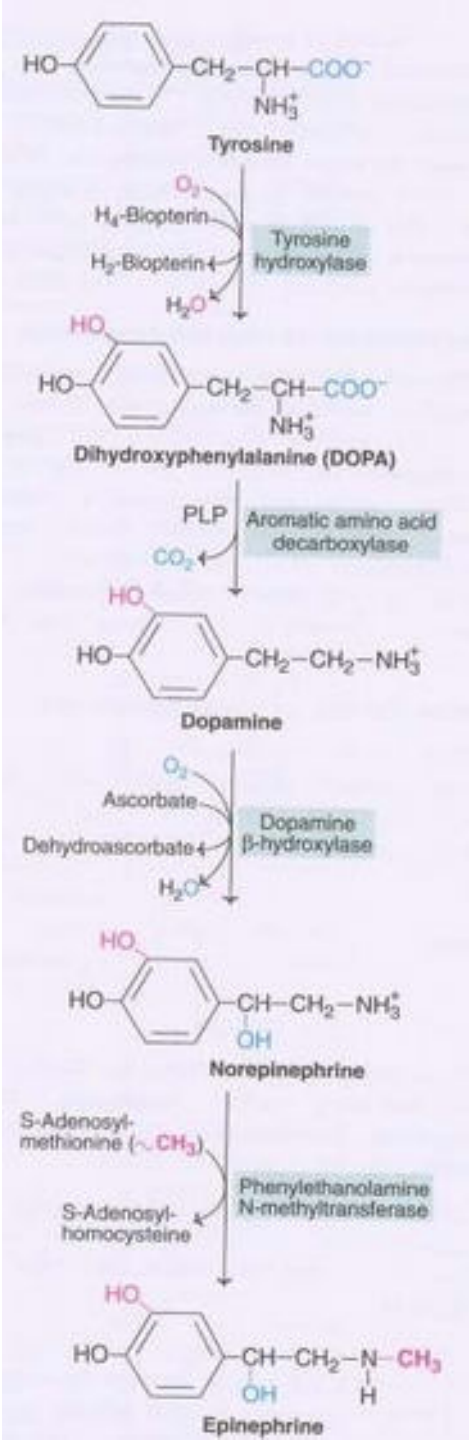
Metabolism of Tyrosine – biosynthesis of Melanin



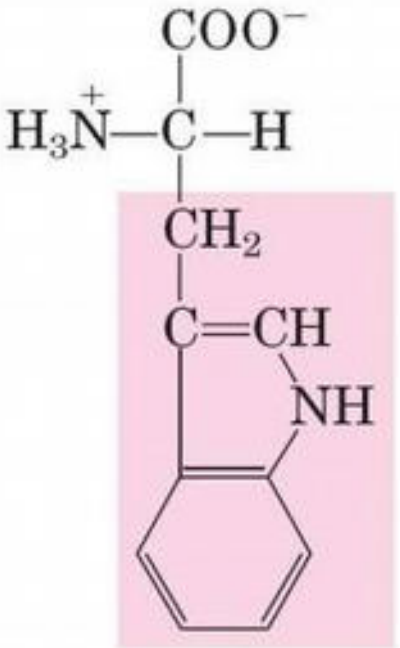
Metabolism of Tyrosine – synthesis of thyroid hormones and catecholamines: Norepinephrine and Epinephrine



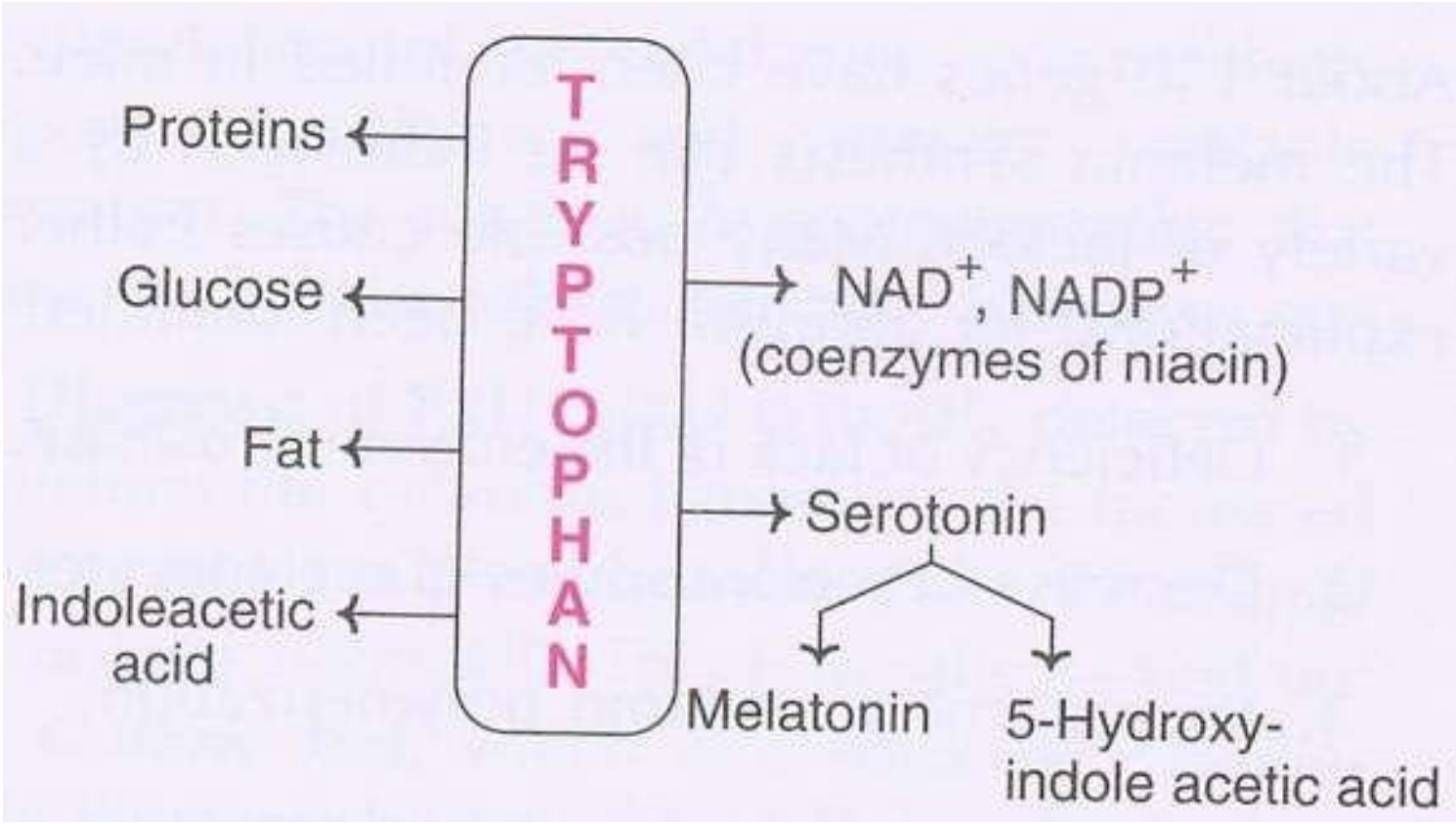




Metabolism of Tryptophan (Trp, W essencial AA)



Tryptophan



Metabolism of individual AA and TCA