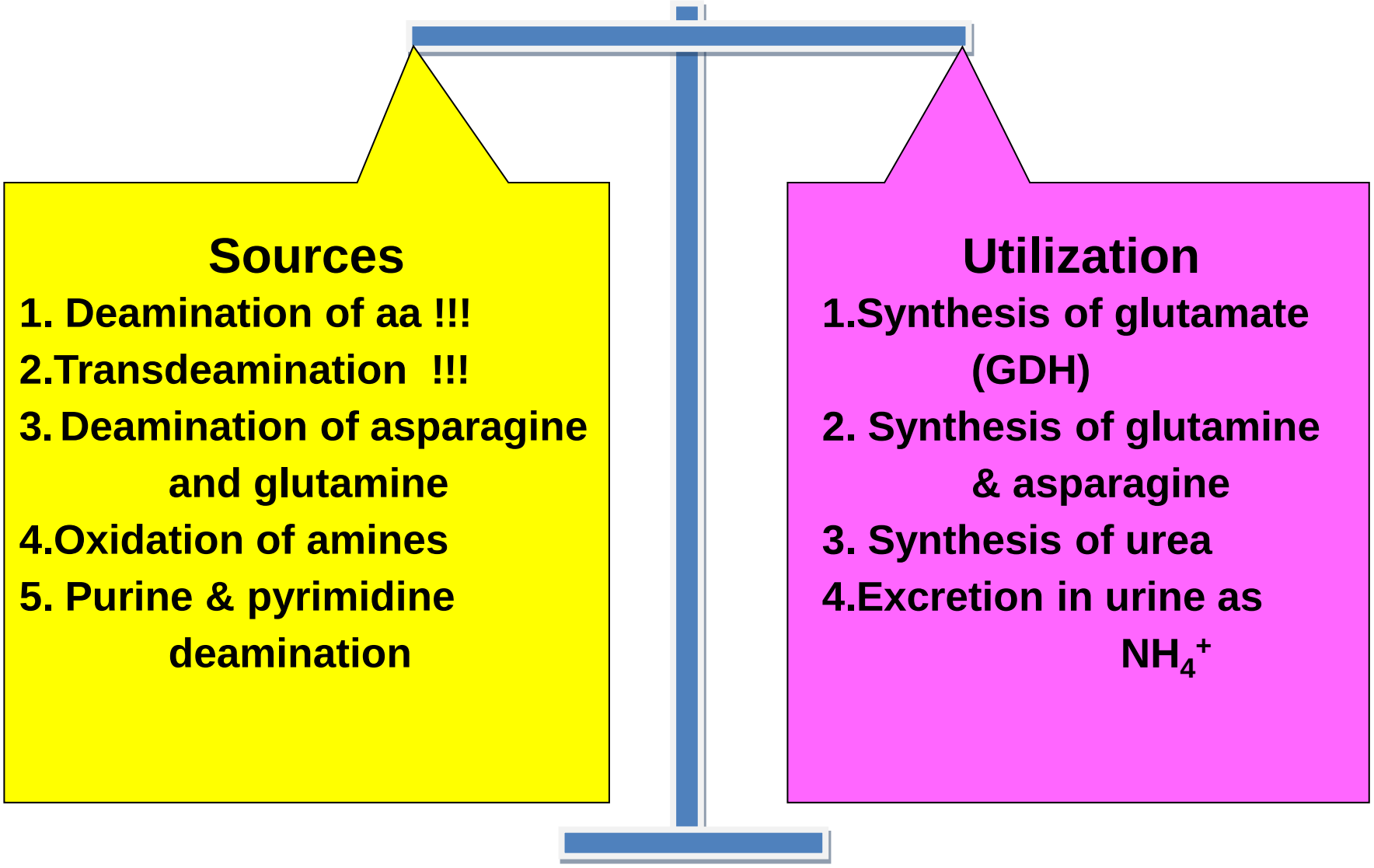
METABOLISM OF AMINO ACIDS

Lecture III

Ways for the formation and detoxification of ammonia

Balance in ammonia metabolism



Sources

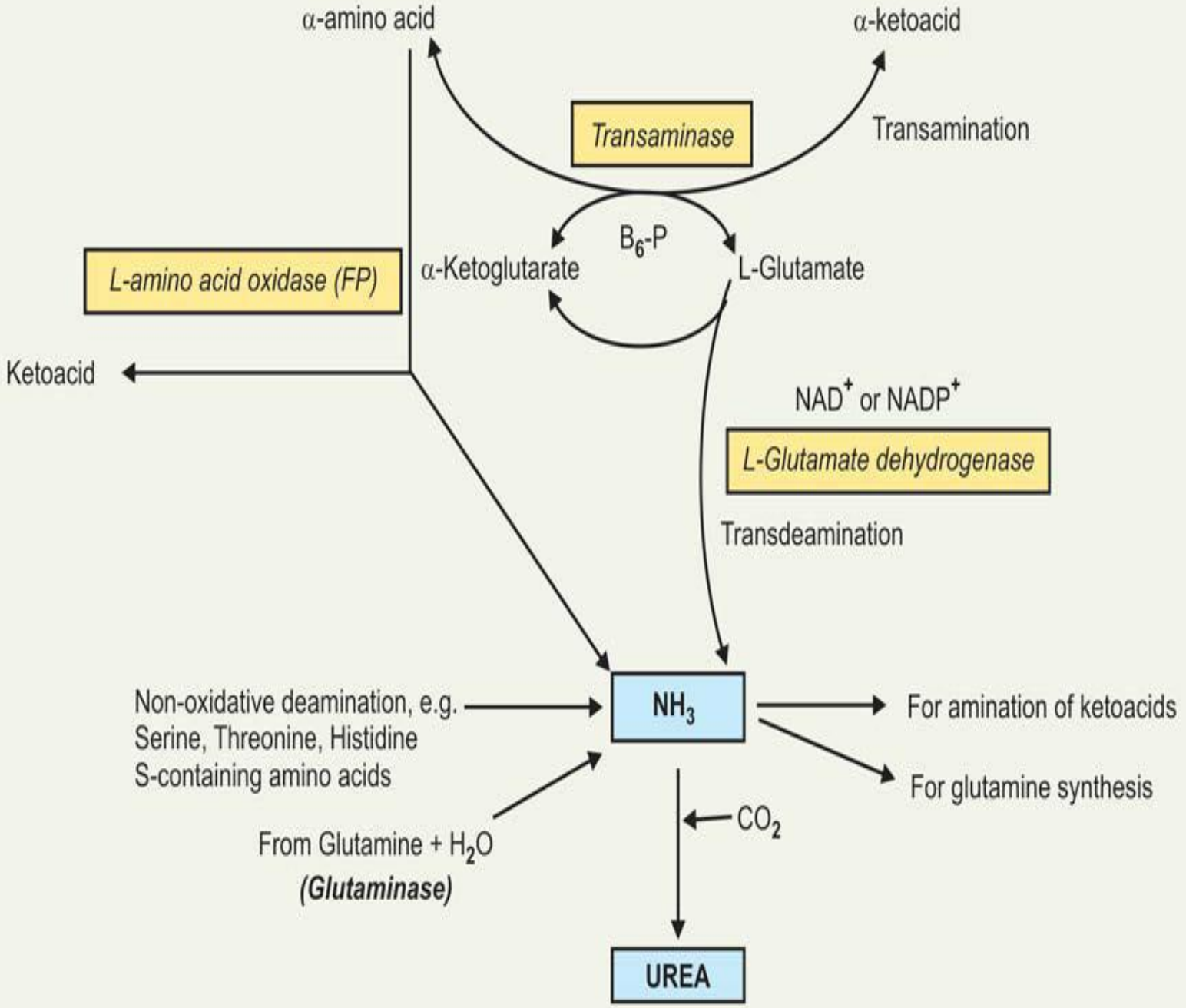
1. Deamination of aa !!!
2. Transdeamination !!!
3. Deamination of asparagine and glutamine
4. Oxidation of amines
5. Purine & pyrimidine deamination

Utilization

1. Synthesis of glutamate (GDH)
2. Synthesis of glutamine & asparagine
3. Synthesis of urea
4. Excretion in urine as NH_4^+

In addition to NH_3 formed in the tissues, a considerable quantity of NH_3 is produced in the gut by intestinal bacterial flora, both

- ***From dietary proteins,*** and
- ***From urea present in fluids secreted into the GI tract.***


α-amino acid
α-ketoacid
Transaminase
Transamination
B6-P
α-Ketoglutarate
L-Glutamate
L-amino acid oxidase (FP)
Ketoacid
NAD+ or NADP+
L-Glutamate dehydrogenase
Transdeamination
Non-oxidative deamination, e.g.
Serine, Threonine, Histidine
S-containing amino acids
NH3
For amination of ketoacids
For glutamine synthesis
CO2
From Glutamine + H2O
(Glutaminase)
UREA

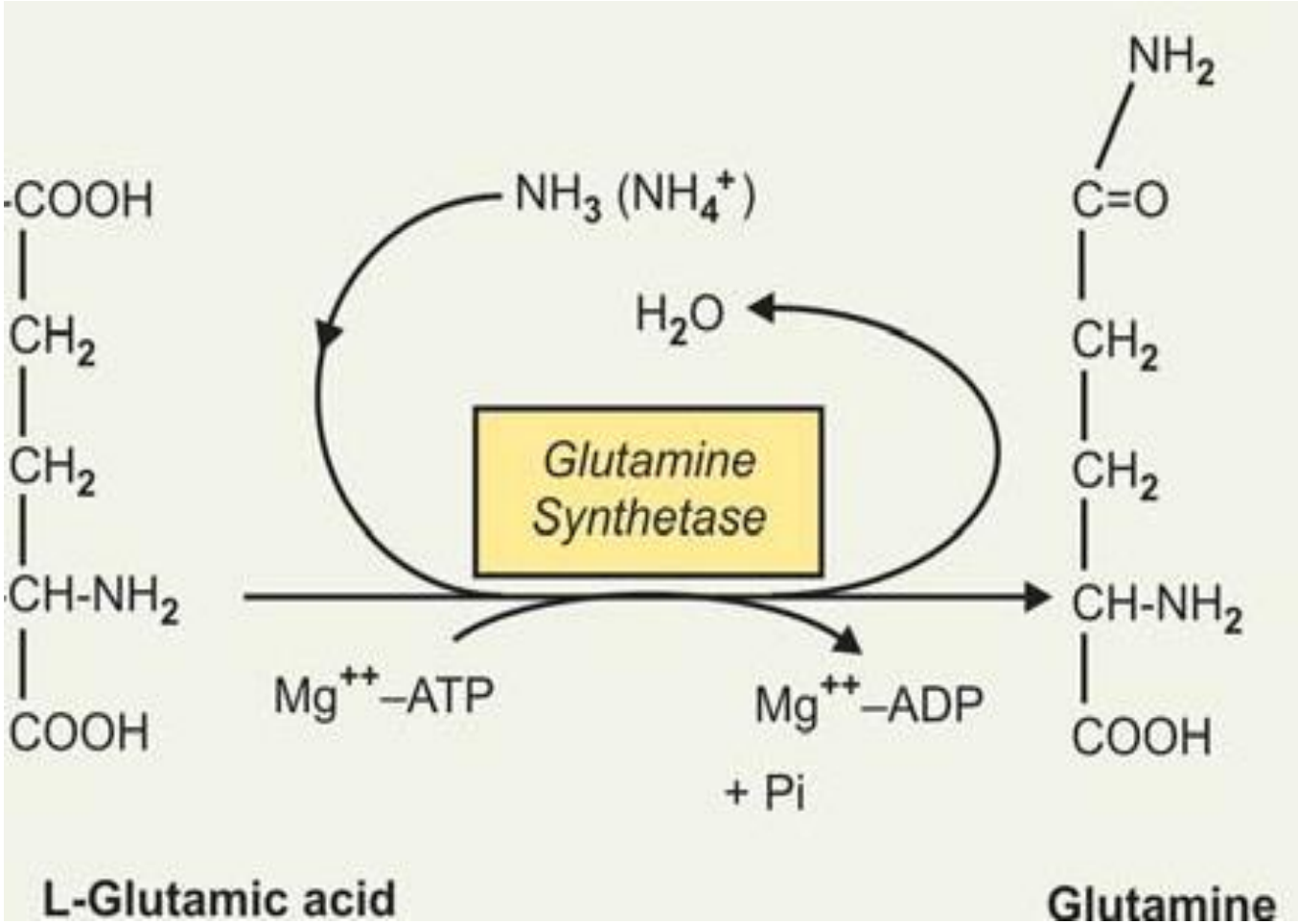
NH_3 and NH_4^+ are toxic, and at higher concentrations cause brain damage in particular.

Ammonia therefore has to be effectively inactivated and excreted.

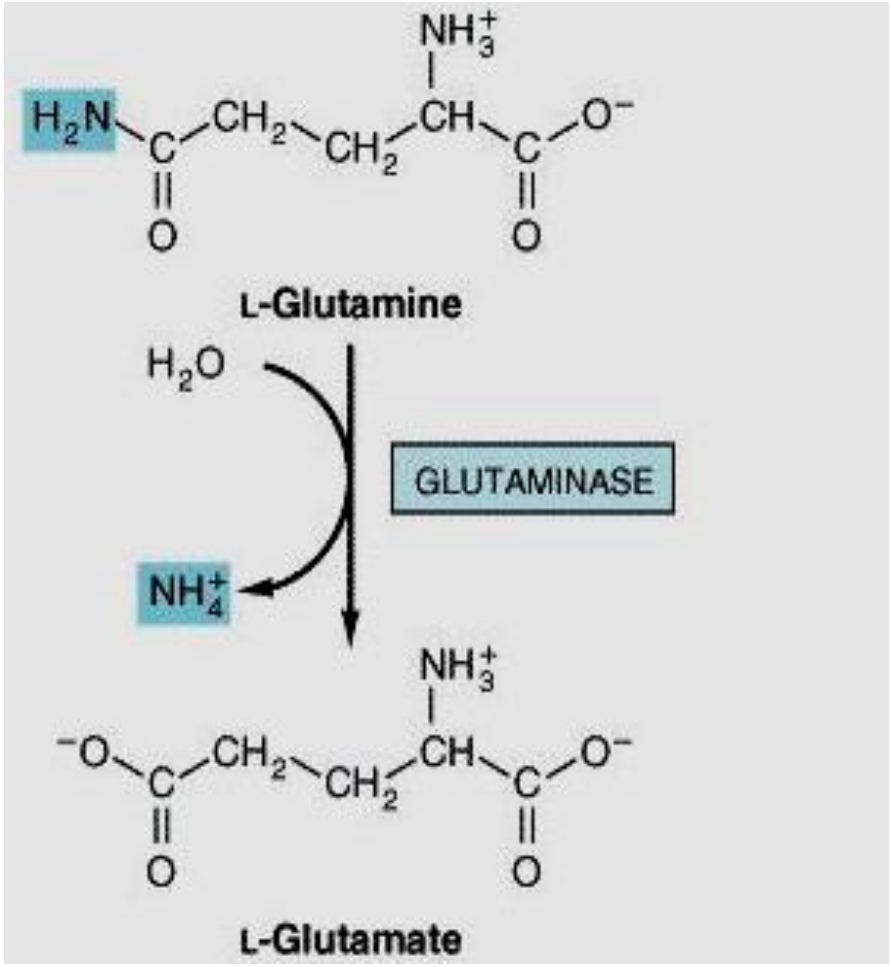
Terrestrial vertebrates, including humans, hardly excrete any NH_3, and instead, most ammonia is converted into urea before excretion (*ureotelic animals*).

INTRACELLULAR DETOXIFICATION OF AMMONIA

In many tissues (brain, kidney, liver and muscle) the intracellular ammonia is immediately binds with glutamic acid (glutamate) to form glutamine:

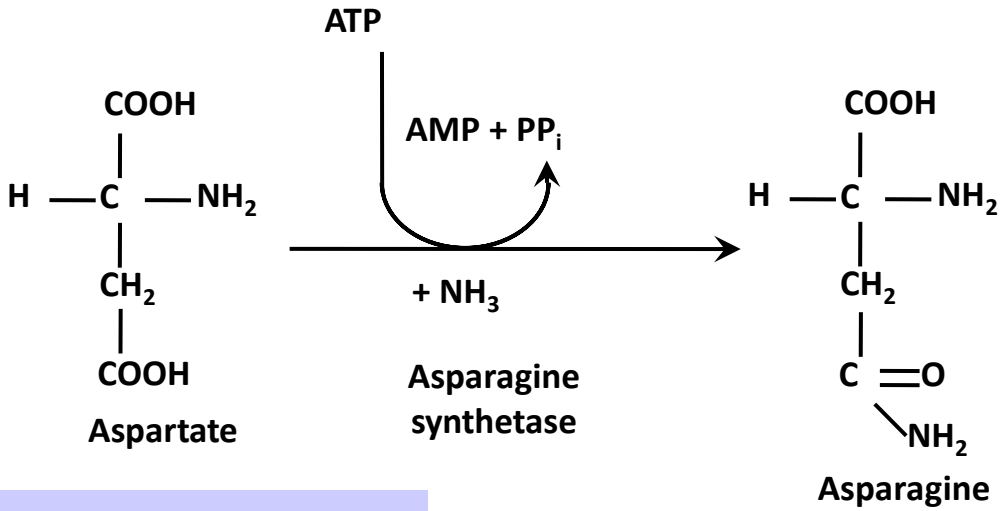


The glutamine is then transported to the liver, where the reaction is reversed by glutaminase:

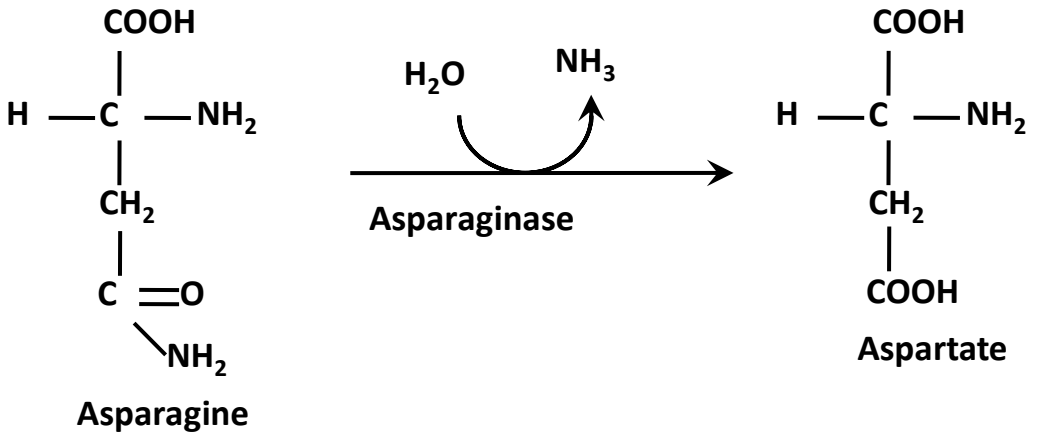


The ammonia, thus generated, is detoxified in the liver by synthesis of urea.

Aspartic acid may also undergo similar conversions:



The asparagine is then transported to the liver, where the reaction is reversed by asparaginase with the release of ammonia:



Glutamine and asparagine are the major transport forms of ammonia from brain to the liver.

ROLE OF AMMONIA IN THE MAINTENANCE OF ACID-BASE BALANCE IN THE BODY

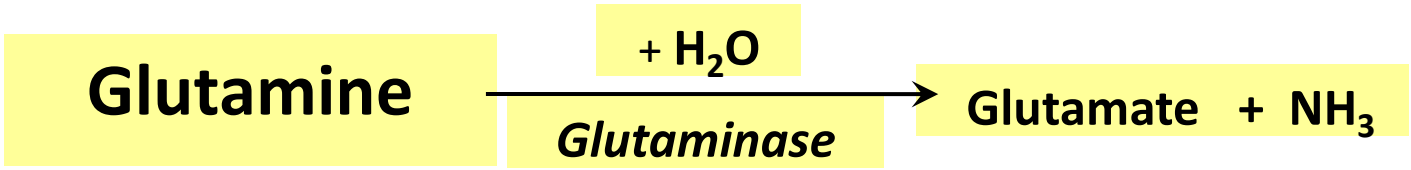
Normally, excretion of ammonia into urine is low but its excretion is increased in acidosis.

In acidosis, the uptake of glutamine by the kidney from the blood is increased.

Also, acidosis stimulates activity of the kidney

glutaminase

to produce ammonia by renal tubular cells:



Ammonia can easily diffuse through cell membrane into the tubular lumen. Organic acids (RH) are secreted to the lumen by tubular cells.

Salts are filtrated into the urine by renal glomeruli. In the urine, salts and organic acids dissociate to produce ions:

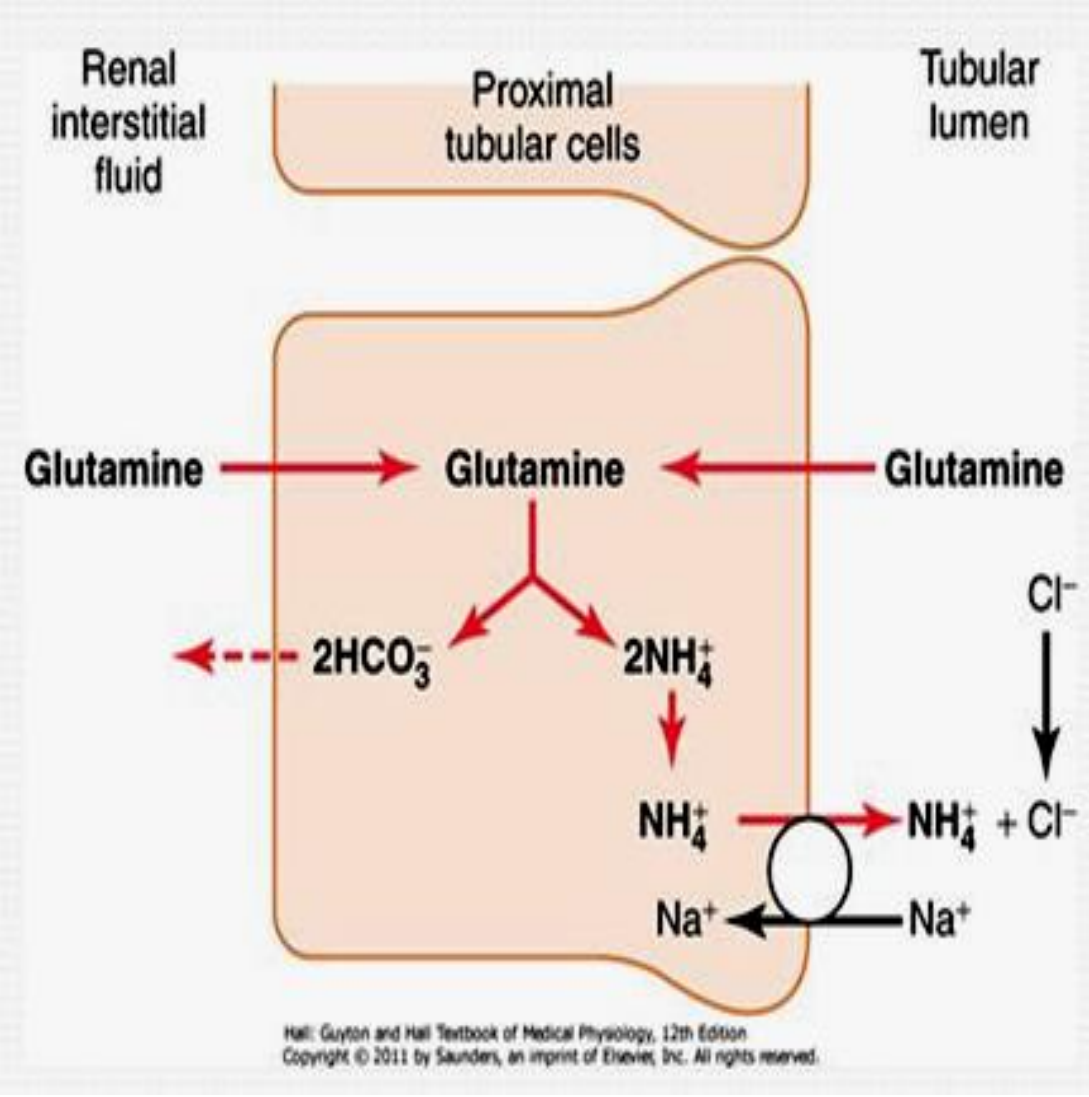
$$RH \rightleftharpoons R^- + H^+$$

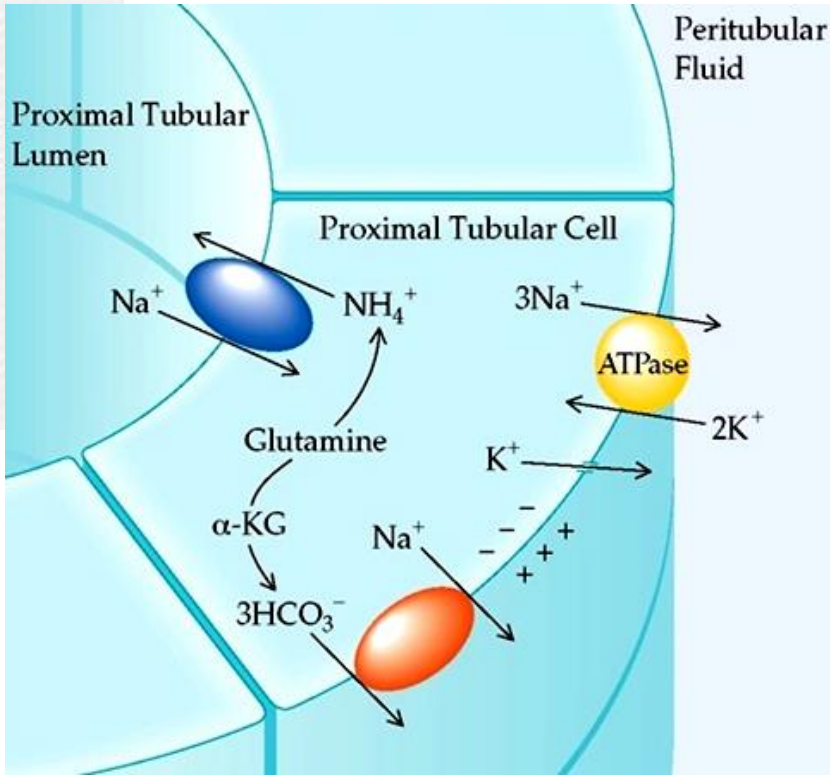
$$NaCl \rightleftharpoons Na^+ + Cl^-$$

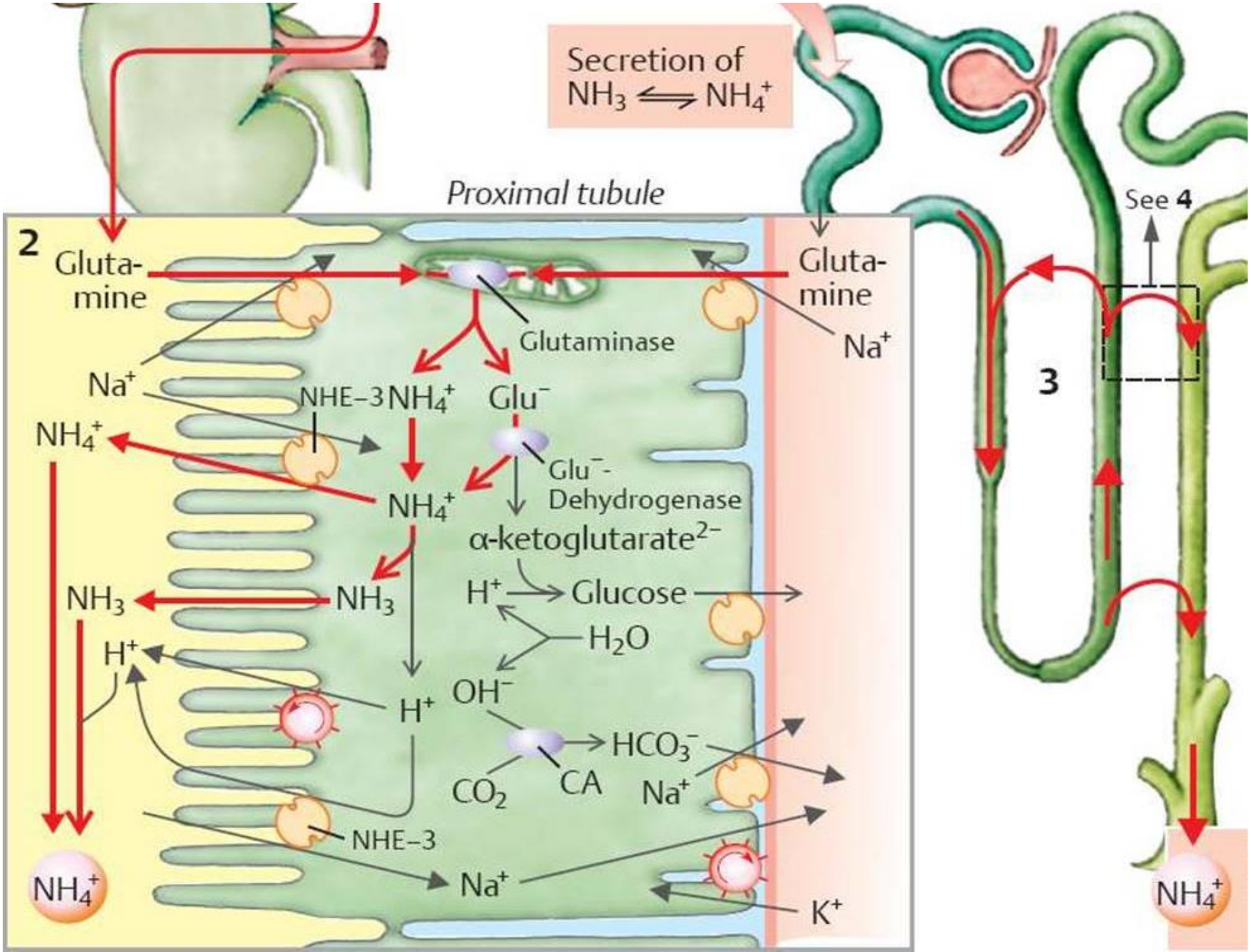
Ammonia binds with hydrogen ion (H^+) to form NH_4^+; the latter is neutralized by chloride-ion, and ammonium salt (NH_4Cl) is excreted through urine from the body:

$$NH_3 + H^+ \longrightarrow NH_4^+$$

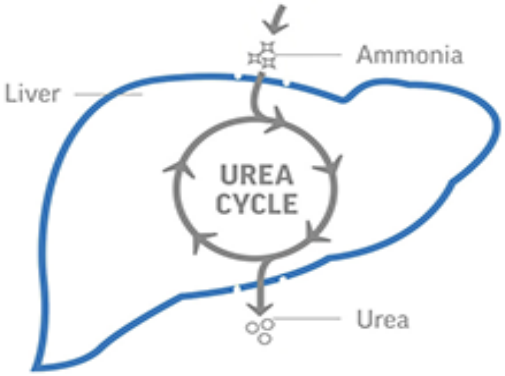
$$NH_4^+ + Cl^- \longrightarrow NH_4Cl$$


Renal interstitial fluid
Proximal tubular cells
Tubular lumen
Glutamine
Glutamine
Glutamine
$2HCO_3^-$
$2NH_4^+$
Cl^-
NH_4^+
$NH_4^+ + Cl^-$
Na^+
Na^+
Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition
Copyright © 2011 by Saunders, an imprint of Elsevier, Inc. All rights reserved.


Peritubular Fluid
Proximal Tubular Lumen
Proximal Tubular Cell
Na^+
NH_4^+
$3Na^+$
ATPase
$2K^+$
Glutamine
K^+
α-KG
Na^+
$3HCO_3^-$


Secretion of
$NH_3 \rightleftharpoons NH_4^+$
Proximal tubule
2
Gluta-
mine
Glutaminase
Na^+
NHE–3
NH_4^+
Glu^-
NH_4^+
Glu^--
Dehydrogenase
NH_4^+
α-ketoglutarate^{2-}
NH_3
NH_3
H^+
Glucose
H_2O
H^+
H^+
OH^-
HCO_3^-
CO_2
CA
Na^+
NHE–3
NH_4^+
Na^+
K^+
Gluta-
mine
Na^+
3
See 4
NH_4^+

BIOSYNTHESIS OF UREA

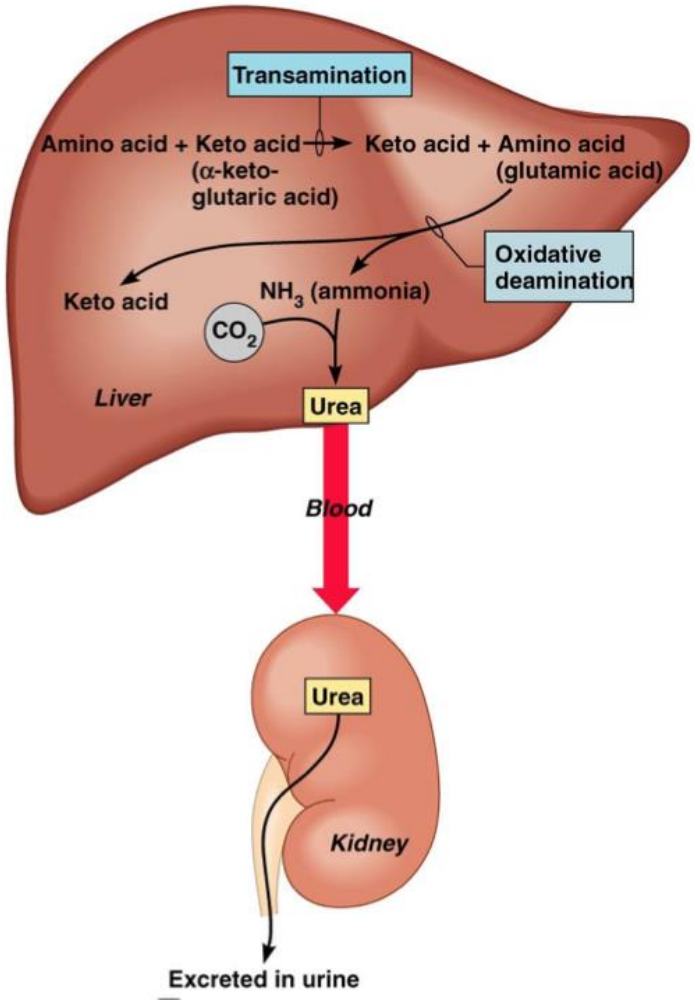


Urea is produced **only in the liver**, in a cyclic sequence of reactions (the **urea cycle**) that starts in the mitochondria and continues in the cytoplasm.

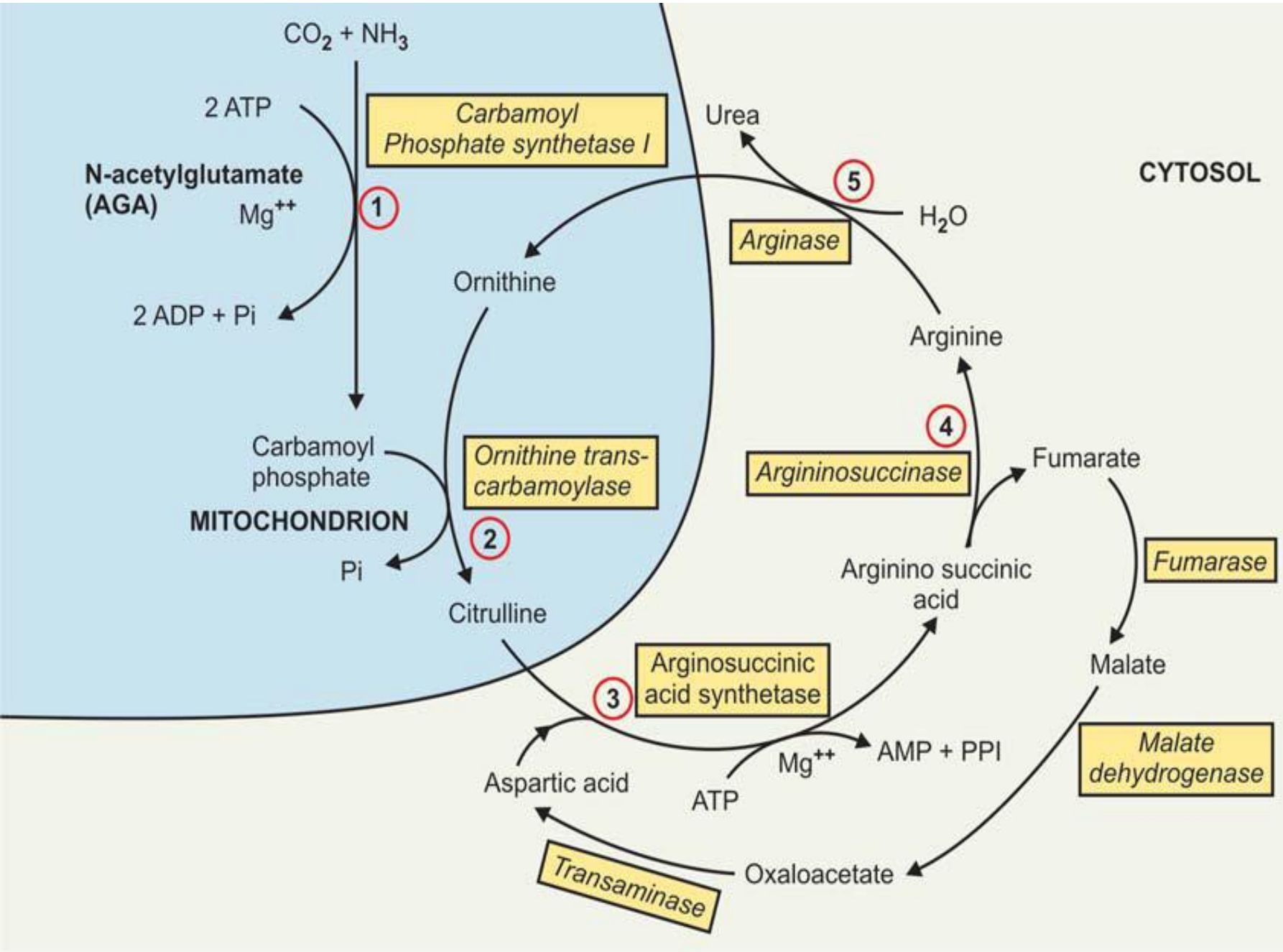
The two nitrogen atoms are derived from $\mathbf{NH_4^+}$ (the second has previously been incorporated into aspartate).

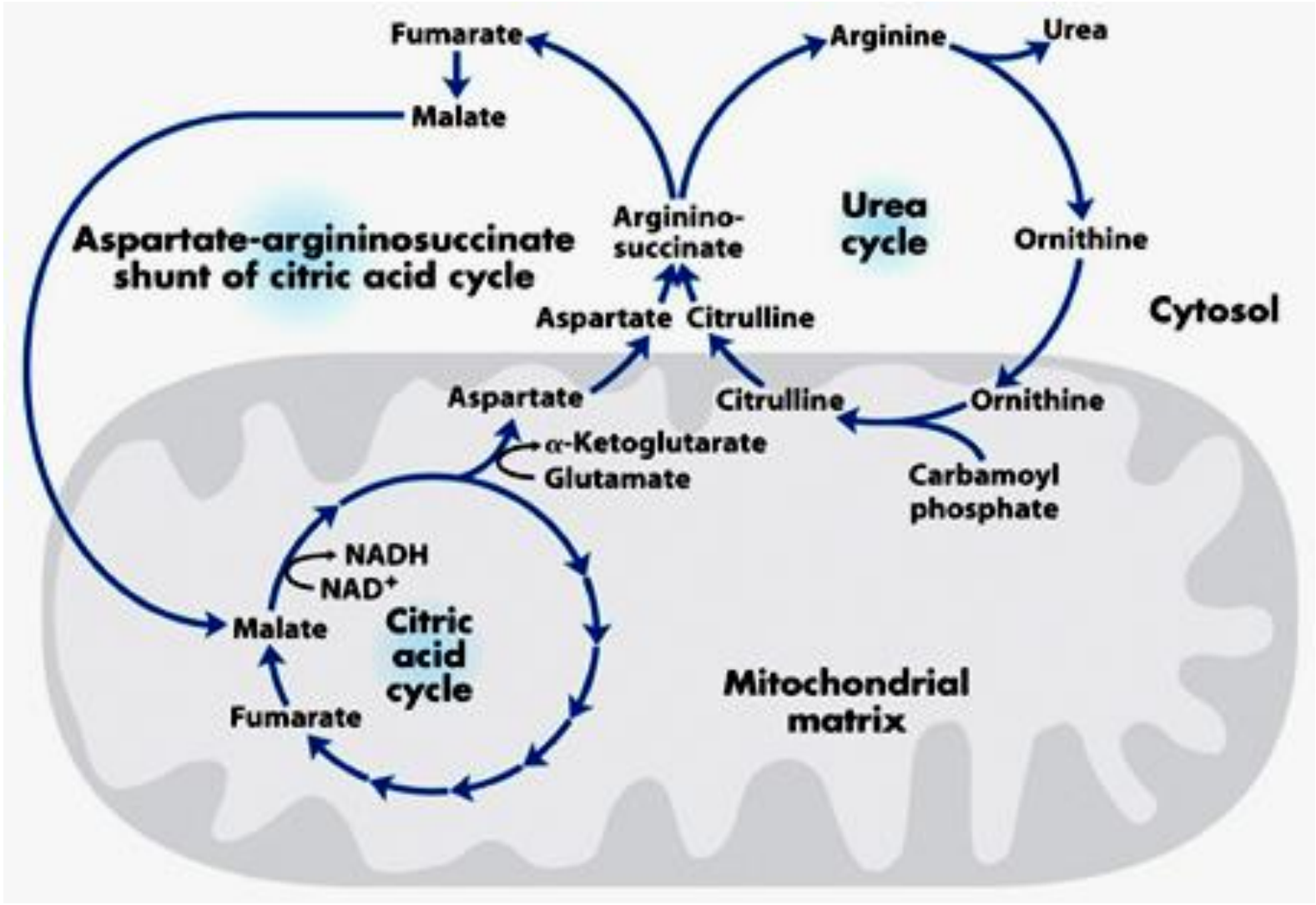
Bicarbonate, HCO_3^- ion, provides the carbon atom of urea.

In contrast to ammonia, urea is **neutral** and therefore relatively **non-toxic**. As a small, uncharged molecule, urea is able to cross biological membranes easily. In addition, it is easily transported in the blood and excreted in the urine.



BIOSYNTHESIS OF UREA




Fumarate
Malate
Arginine
Urea
Aspartate-argininosuccinate shunt of citric acid cycle
Arginino-succinate
Urea cycle
Ornithine
Aspartate
Citrulline
Cytosol
Aspartate
Citrulline
Ornithine
α-Ketoglutarate
Glutamate
Carbamoyl phosphate
NADH
NAD+
Malate
Citric acid cycle
Fumarate
Mitochondrial matrix

Under normal conditions of health, liver removes the NH_3 from the portal blood, so that blood leaving the liver is virtually NH_3-free.

This is essential since even small quantities of NH_3 are toxic to CNS.

Hyperammonaemia is associated with comatose states such as may occur in hepatic failure. May be of 2 types:

Acquired hyperammonaemia: it is usually the result of cirrhosis of the liver with the development of a collateral circulation, which shunts the portal blood around the organ, thereby severely reducing the synthesis of urea.

Inherited hyperammonaemia: results from genetic defects in the urea cycle enzymes.

The symptoms of NH_3 intoxication include:

- A peculiar flapping tremor
- Slurring of speech
- Blurring of vision
- In severe cases follows to coma and death.

Symptoms of

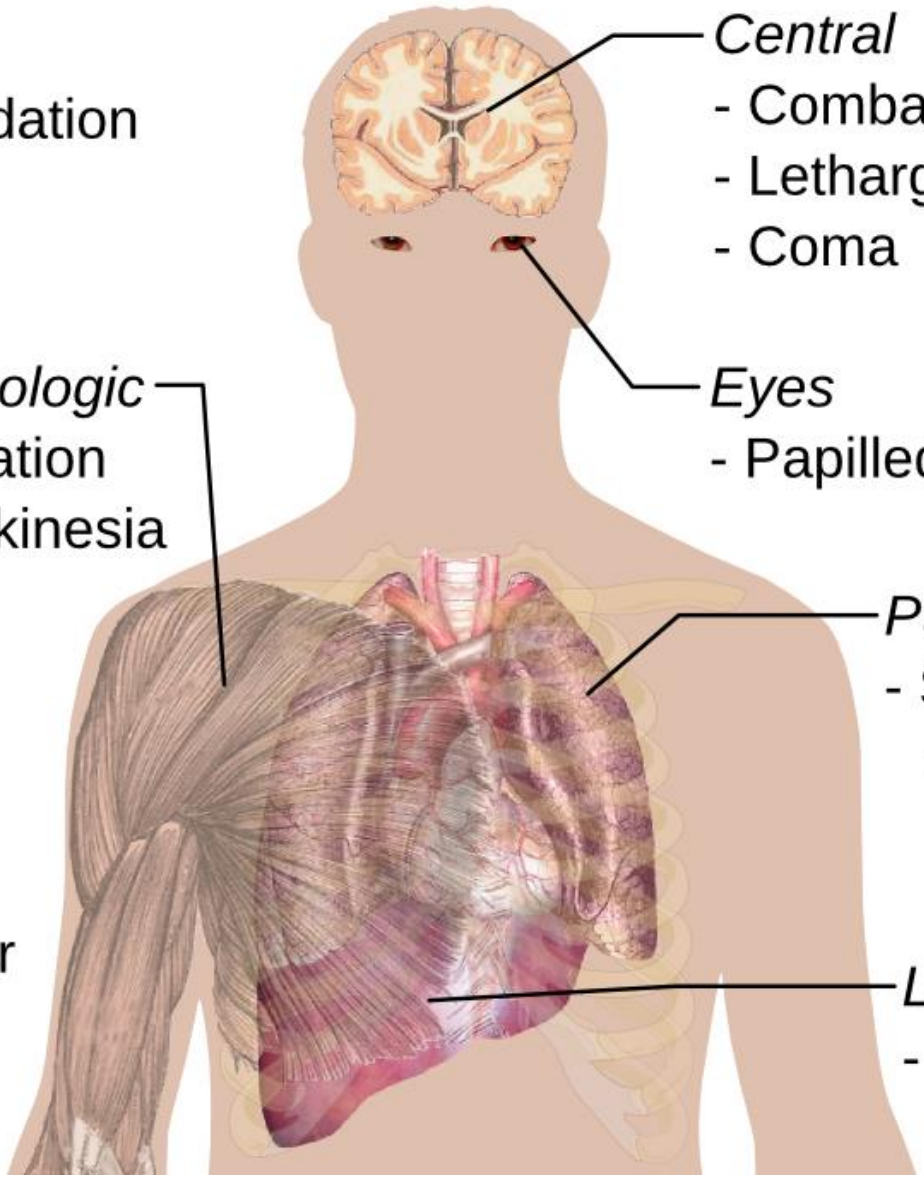
Hyperammonemia

General
- Growth retardation
- Hypothermia

Central
- Combativeness
- Lethargy
- Coma

Eyes
- Papilledema

Muscular/Neurologic
- Poor coordination
- Dysdiadochokinesia
- Hypotonia or hypertonia
- Ataxia
- Tremor
- Seizures
- Decorticate or decerebrate posturing



Pulmonary
- Shortness of breath

Liver
- Enlarge-ment

Normal concentrations of urea in the blood 2.5-8.33 mmol/L;

its excretion into the urine 333-583 mmol/day.

Increase in blood urea above normal is called *uraemia*.

Increases in blood urea may occur in a number of diseases in addition to those in which the kidneys are primarily involved. The causes can be classified as:

prerenal,

renal,

postrenal

Prerenal

- Salt and water depletion

Renal

- In acute glomerulonephritis.
- In early stages of type II nephritis (nephrosis)
- malignant nephrosclerosis, chronic pyelonephritis and mercurial poisoning.

Postrenal Diseases

These lead to increase in blood urea, when there is obstruction to urine flow. This causes retention of urine and so reduces the effective filtration pressure at the glomeruli; when prolonged, produces irreversible kidney damage.

Causes: *Enlargement of prostate,*

Stones in urinary tract,

Stricture of the urethra,

Tumours of the bladder affecting urinary flow.

Decreased levels

Decreases in blood urea levels are rare. It may be seen:

- **In some cases of severe liver damage,**
- **Physiological condition: Blood urea has been seen to be lower in pregnancy than in normal nonpregnant women.**

Genetic disorders of urea cycle

1. Hyperammonemia Type I:

enzyme deficiency: Carbamoyl-P Synthetase I, produces hyperammonemia and symptoms of ammonia toxicity.

2. Hyperammonemia Type II:

enzyme deficiency: Ornithine transcarbamoylase

3.Citrullinemia

A rare disorder. **Enzyme deficiency: Argininosuccinate synthetase.**

4. Argininosuccinate aciduria

A rare inherited disorder, usually fatal.

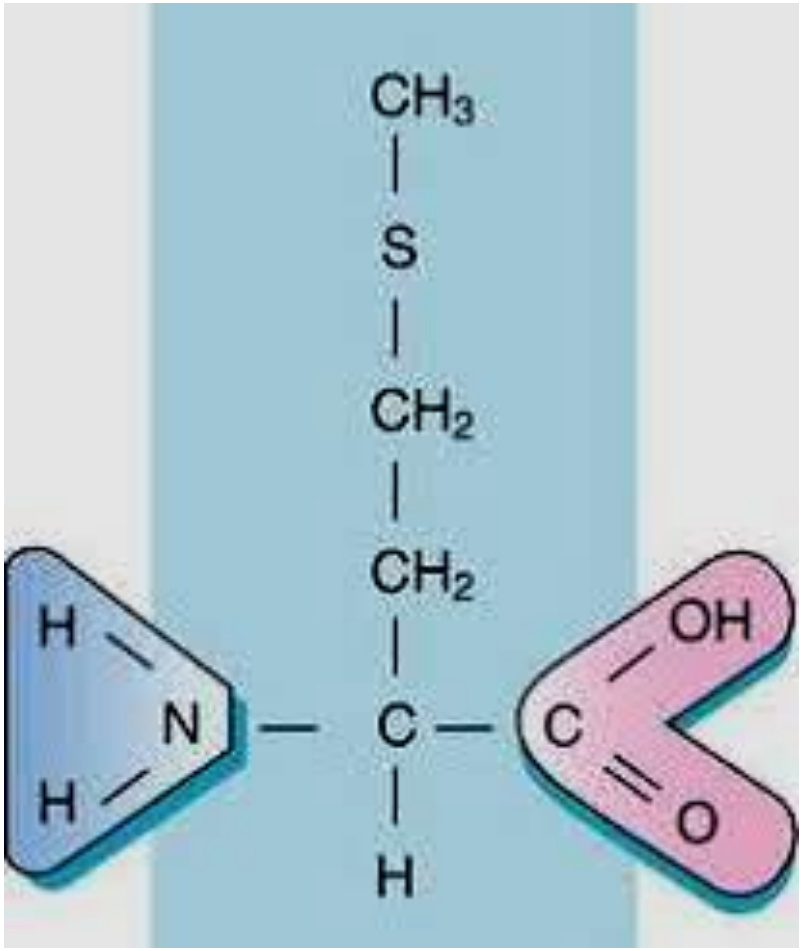
Enzyme deficiency: Argininosuccinate lyase.

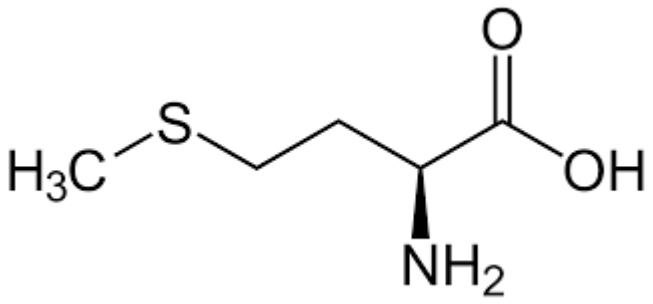
Usually manifest before 2 years of age and terminates fatally in early life.

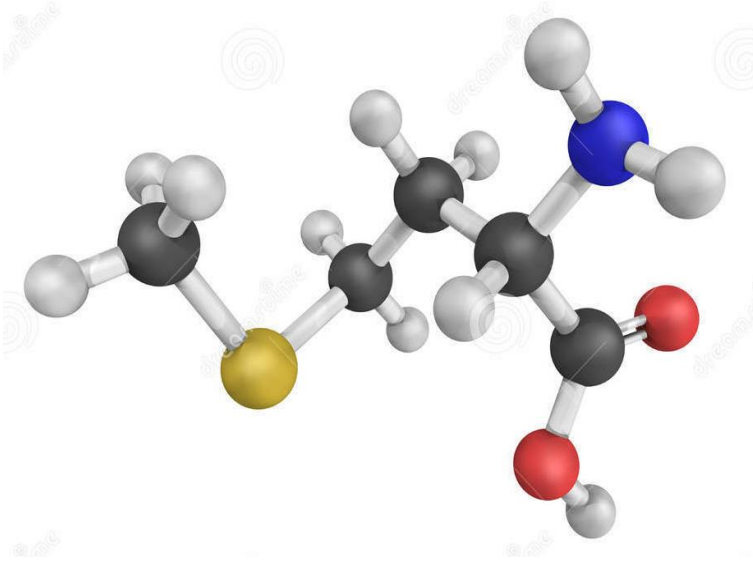
5. Hyperargininemia

Enzyme deficiency: Arginase.

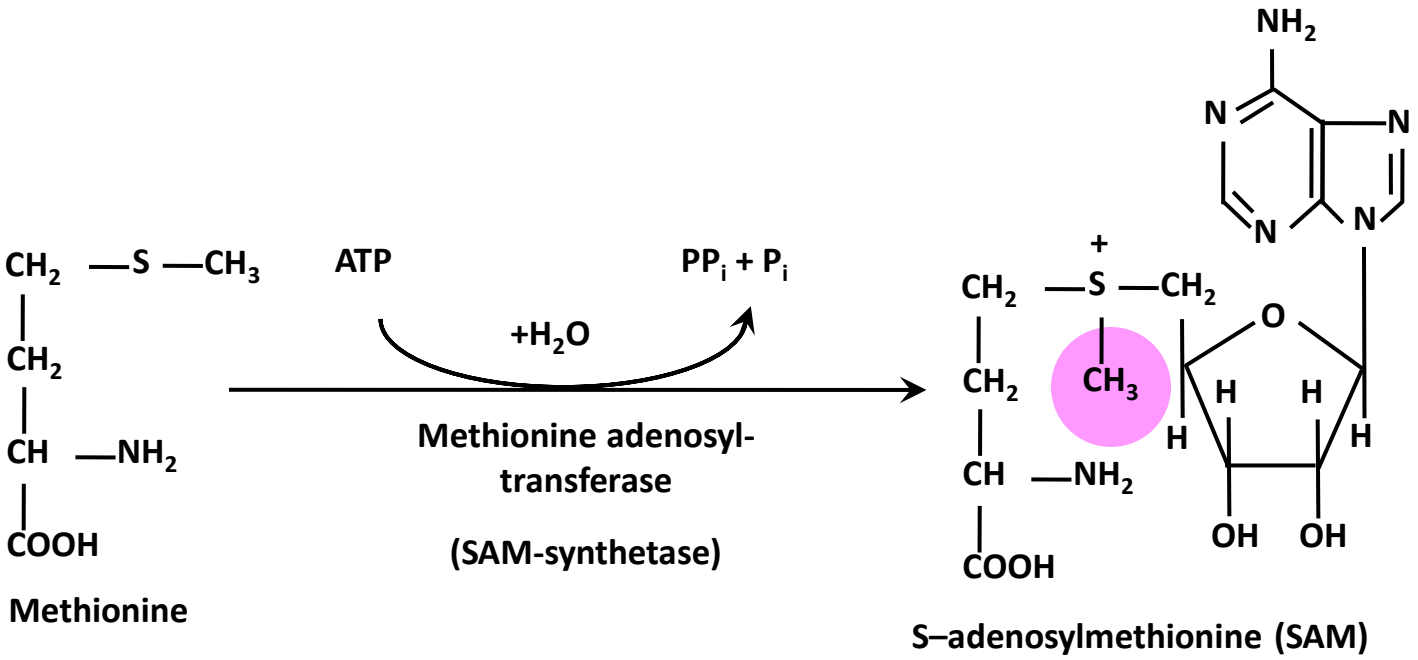
METABOLISM OF METHIONINE



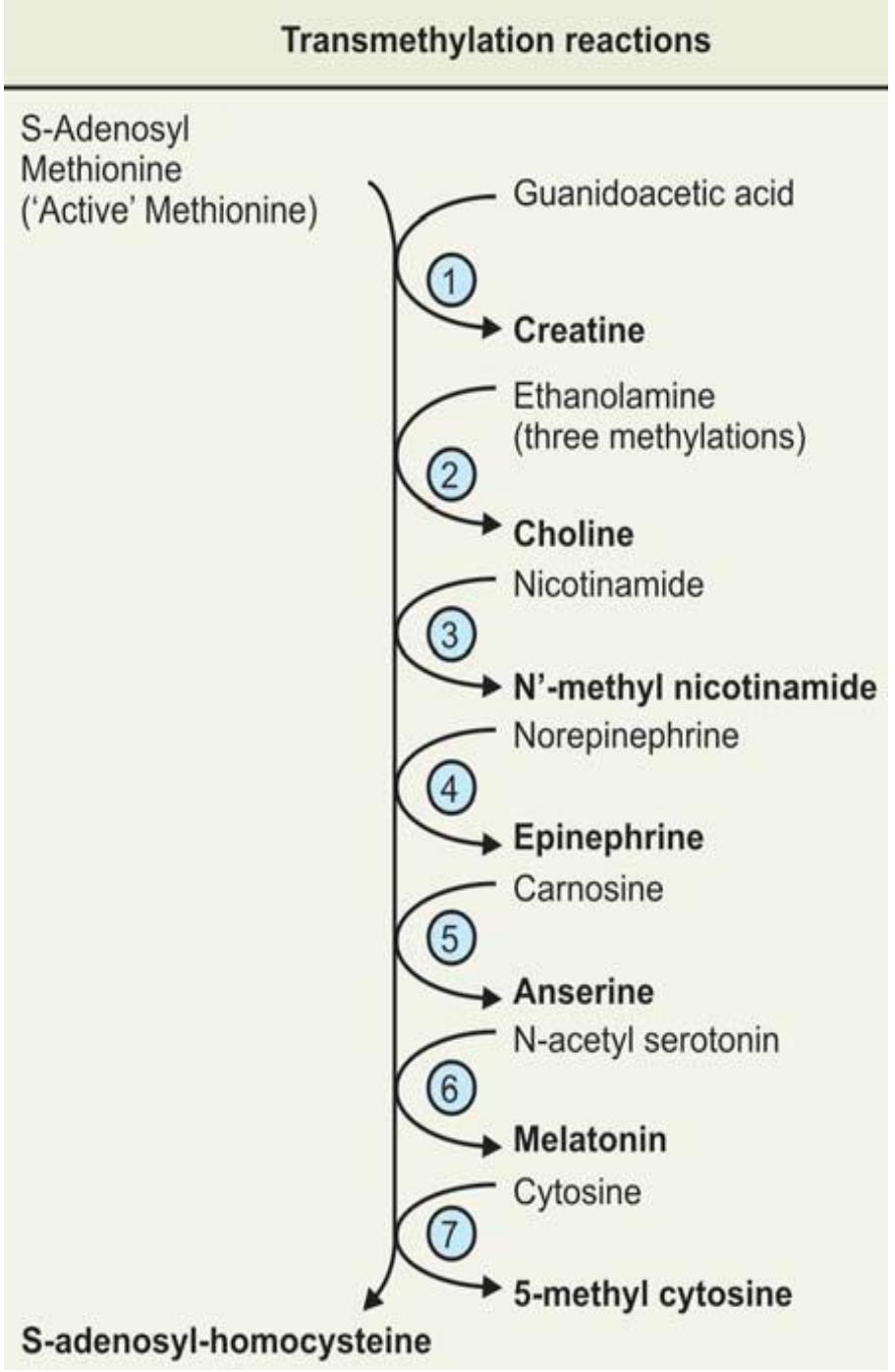


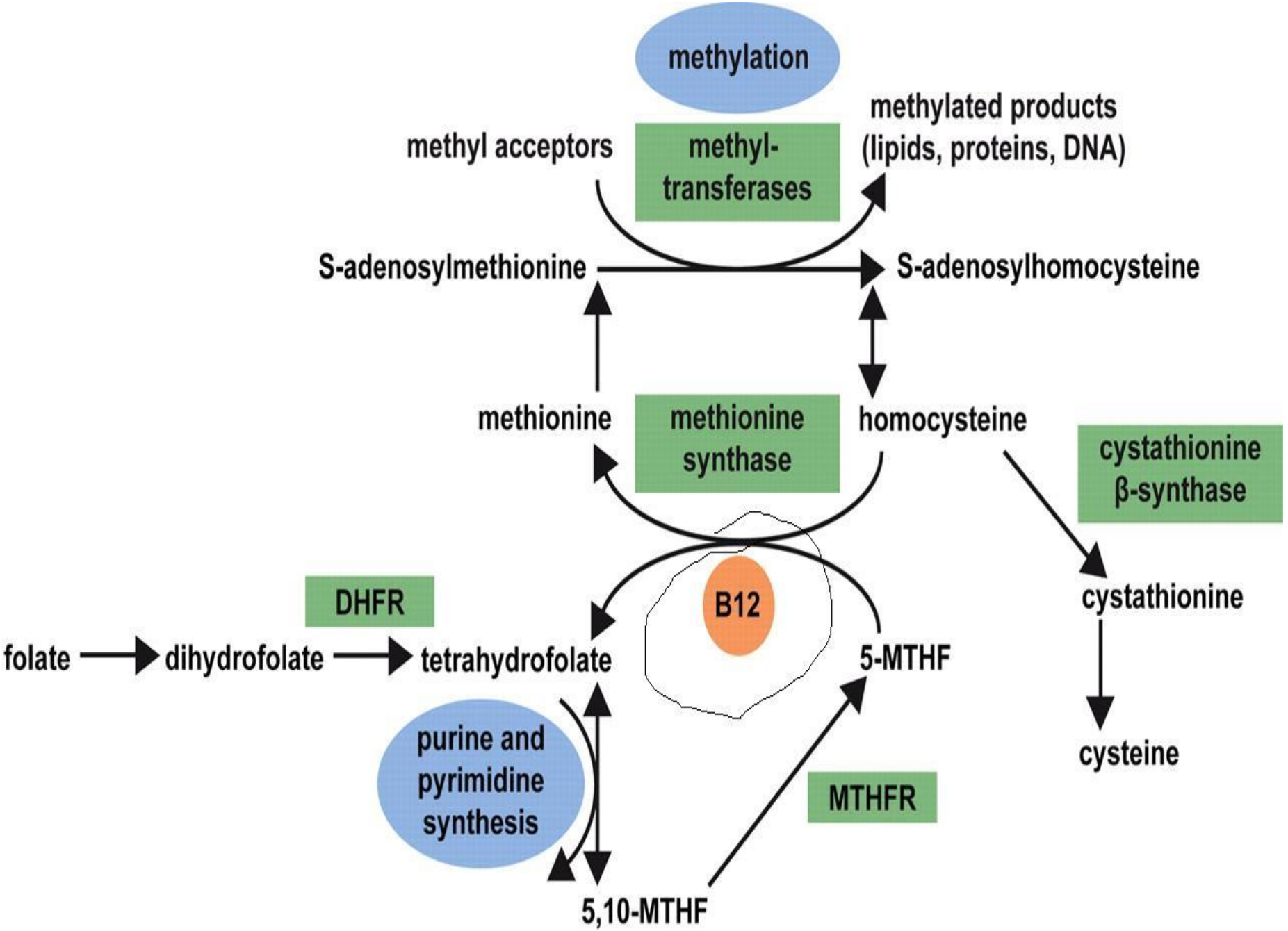


METABOLISM OF METHIONINE




Substrate
Methyl-substrate
SAM
SAH
Methyltransferase


Transmethylation reactions
S-Adenosyl
Methionine
('Active' Methionine)
Guanidoacetic acid
1
Creatine
Ethanolamine
(three methylations)
2
Choline
Nicotinamide
3
N'-methyl nicotinamide
Norepinephrine
4
Epinephrine
Carnosine
5
Anserine
N-acetyl serotonin
6
Melatonin
Cytosine
7
5-methyl cytosine
S-adenosyl-homocysteine


methylation
methylated products
(lipids, proteins, DNA)
methyl acceptors
methyl-
transferases
S-adenosylmethionine
S-adenosylhomocysteine
methionine
methionine
synthase
homocysteine
cystathionine
β-synthase
DHFR
B12
cystathionine
folate
dihydrofolate
tetrahydrofolate
5-MTHF
purine and
pyrimidine
synthesis
MTHFR
cysteine
5,10-MTHF

FOOD

Magnesium

METHIONINE

METHYLATION CYCLE

SAMe

B12
Folic Acid
As 5-MTHF

HOMOCYSTEINE

SULFURATION PATHWAY

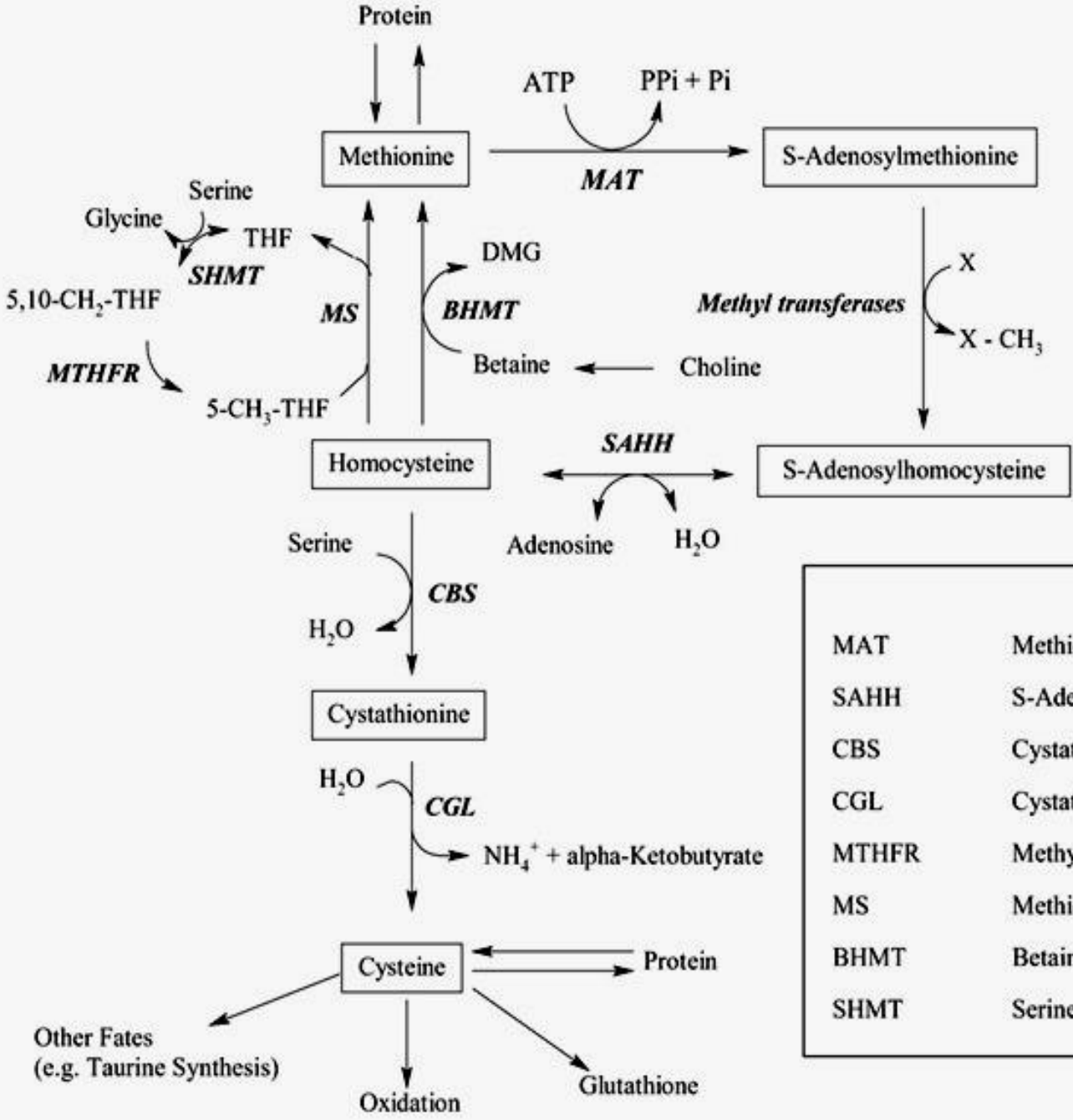
B6
Betaine

CYSTEINE

Magnesium
Glutamine
Glycine

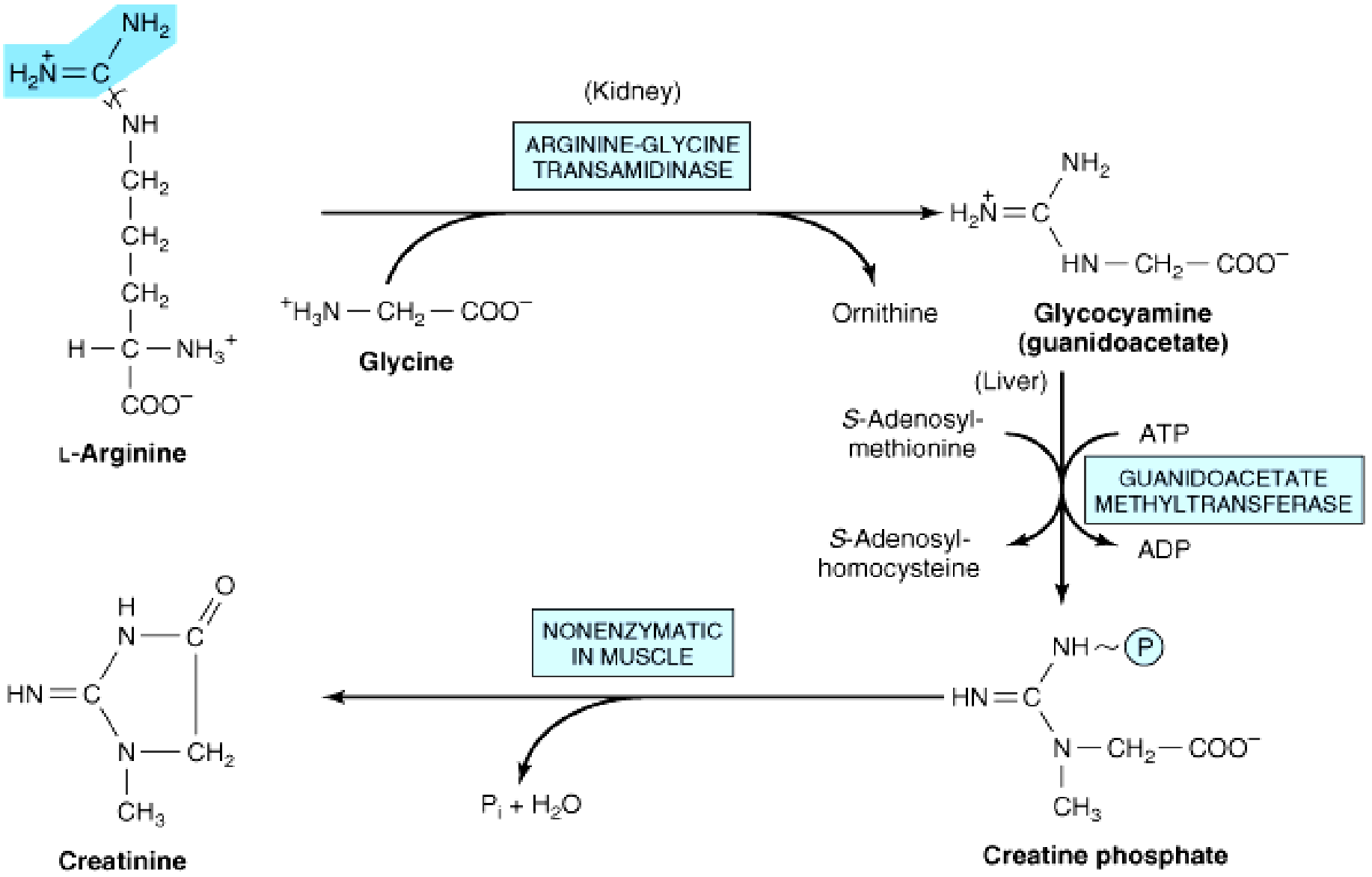
GLUTATHIONE

The total scheme of methionine metabolism

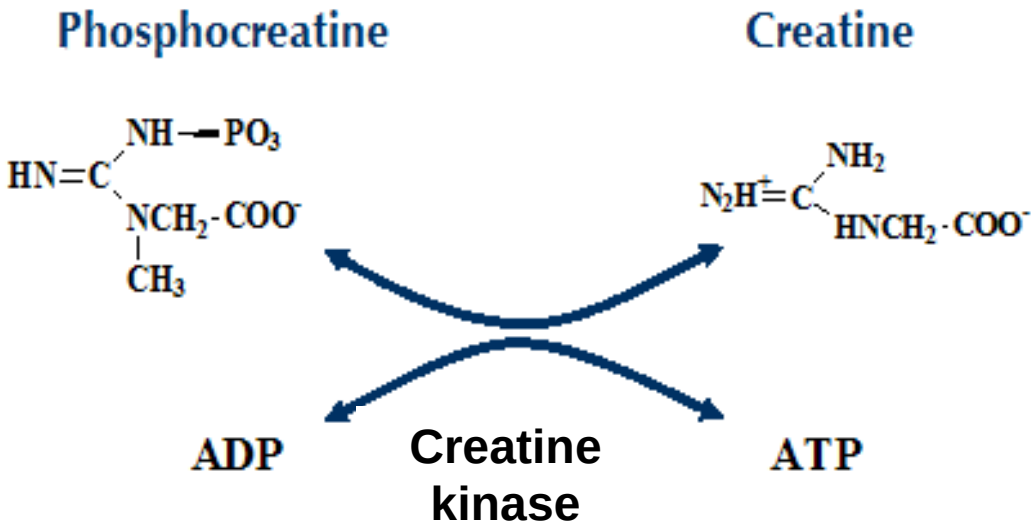


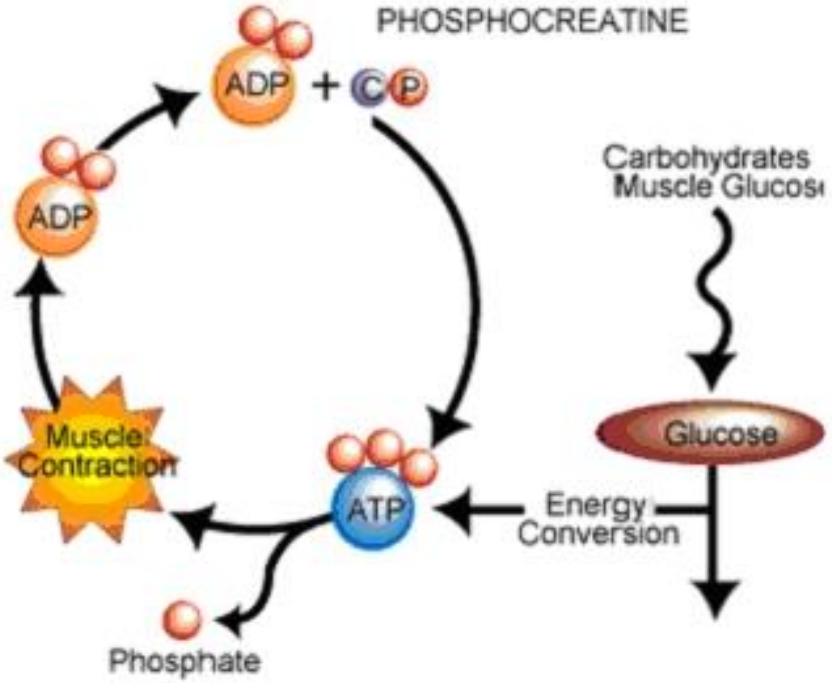
Abbreviations	
MAT	Methionine adenosyltransferase
SAHH	S-Adenosylhomocysteine hydrolase
CBS	Cystathionine β-synthase
CGL	Cystathionine γ-lyase
MTHFR	Methylenetetrahydrofolate reductase
MS	Methionine synthase
BHMT	Betaine:homocysteine methyltransferase
SHMT	Serine hydroxymethyltransferase

Synthesis of creatine



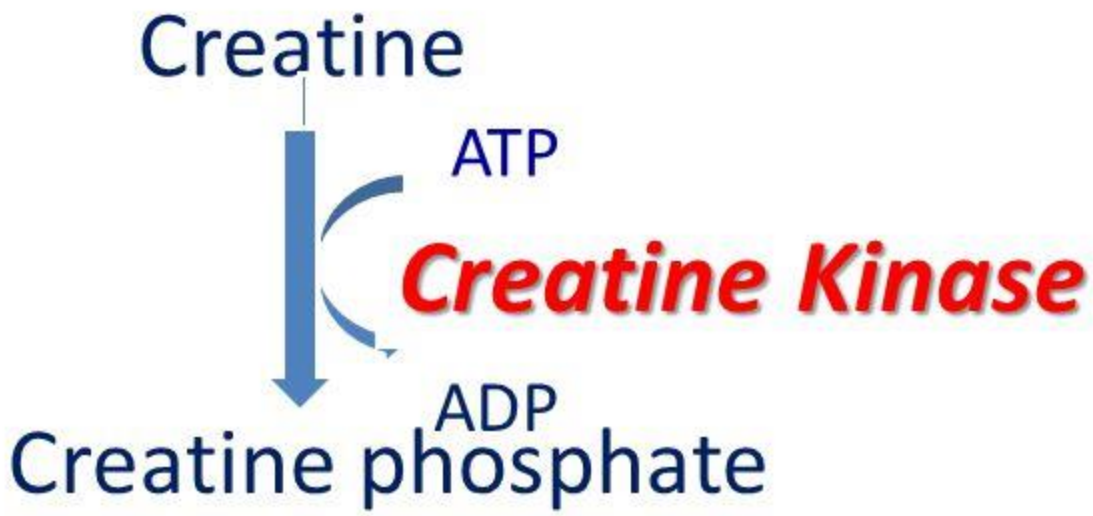
Phosphocreatine-ATP Interaction

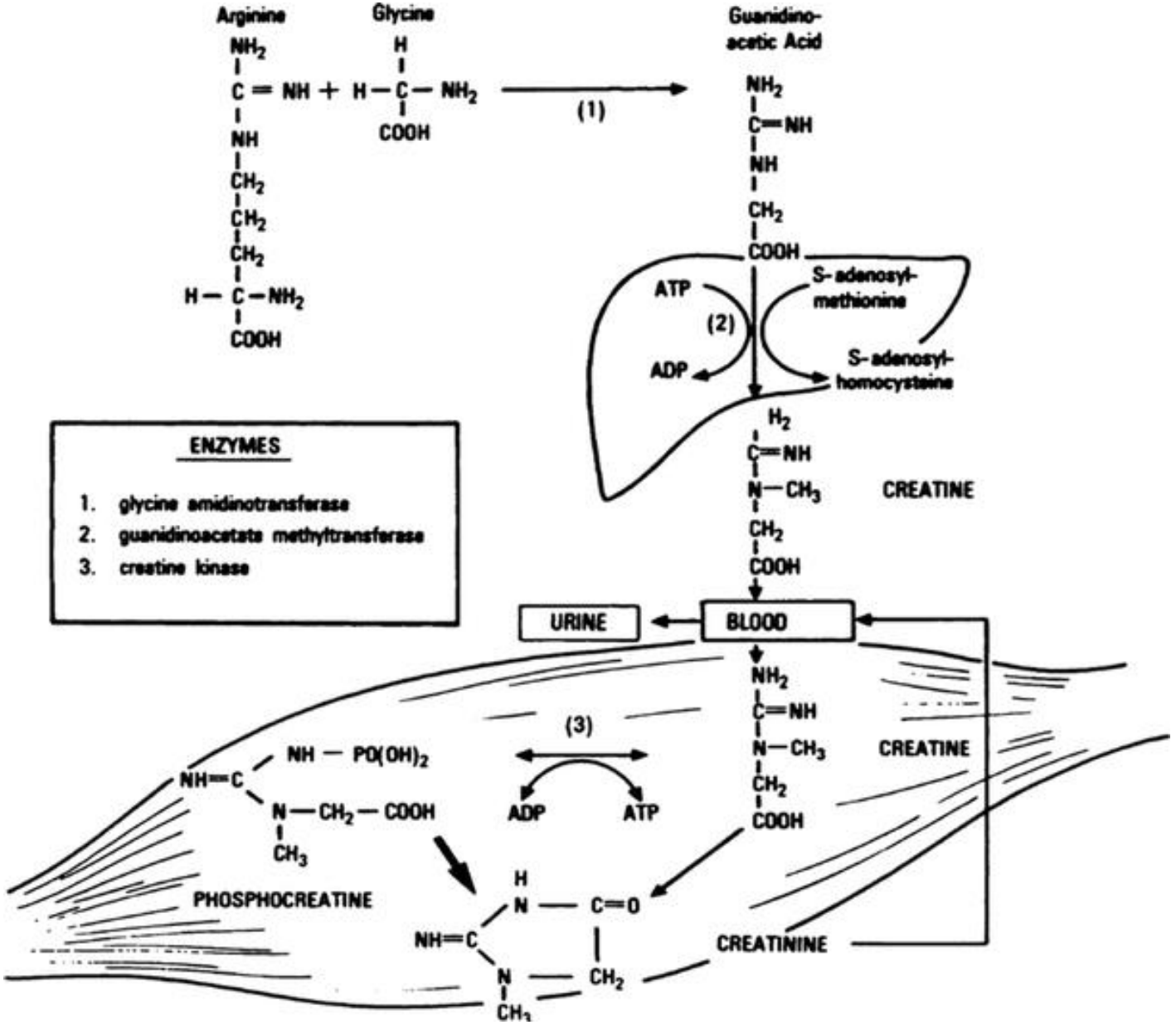




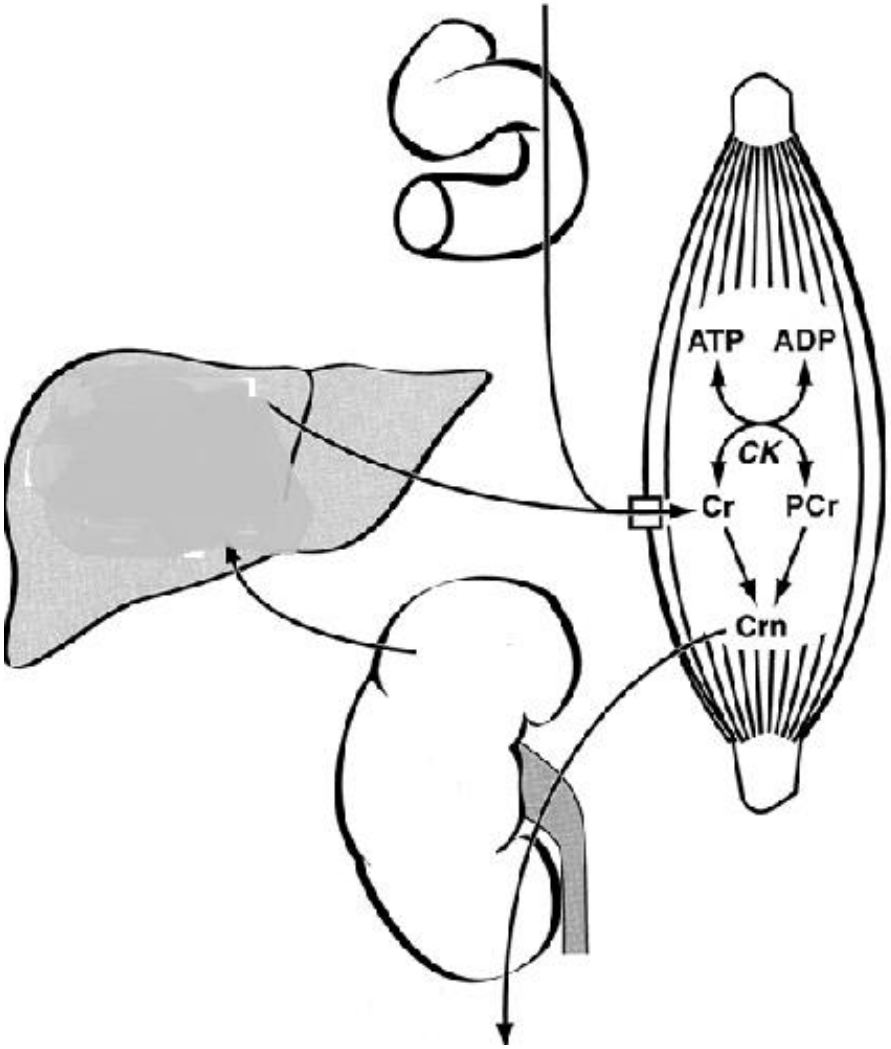
Plasma Creatine Kinase (CK)

- ***Creatine Kinase*** **is responsible for the generation of creatine phosphate in contractile muscular tissues (intracellular).**
- ***Plasma CK levels*** **are changed in disorders of cardiac and skeletal muscle**



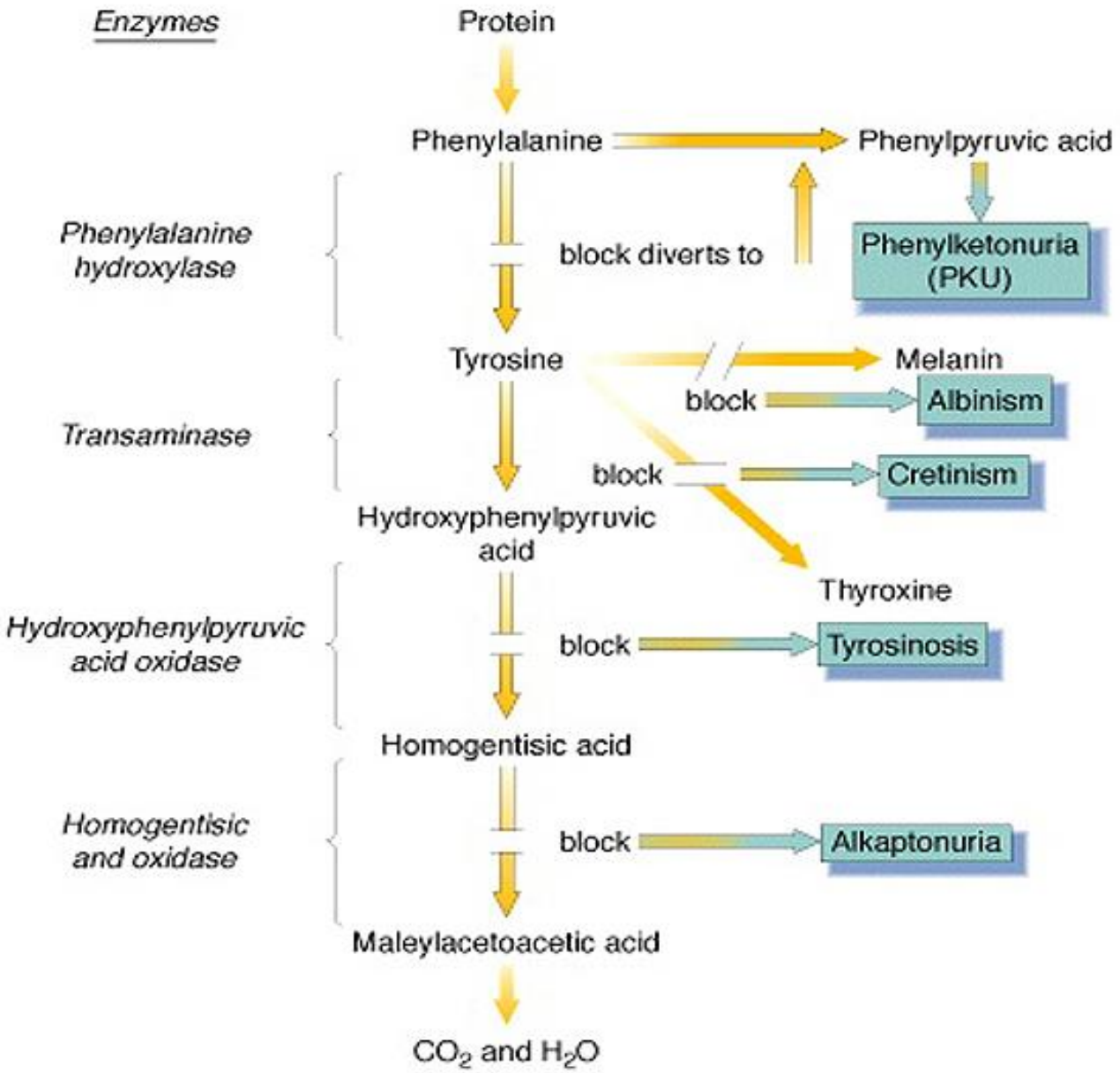

Arginine
Glycine
Guanidino-acetic Acid
(1)
ATP
ADP
(2)
S-adenosyl-methionine
S-adenosyl-homocysteine
ENZYMES
1. glycine amidinotransferase
2. guanidinoacetate methyltransferase
3. creatine kinase
CREATINE
URINE
BLOOD
(3)
ADP
ATP
PHOSPHOCREATINE
CREATINE
CREATININE

Dietary creatine

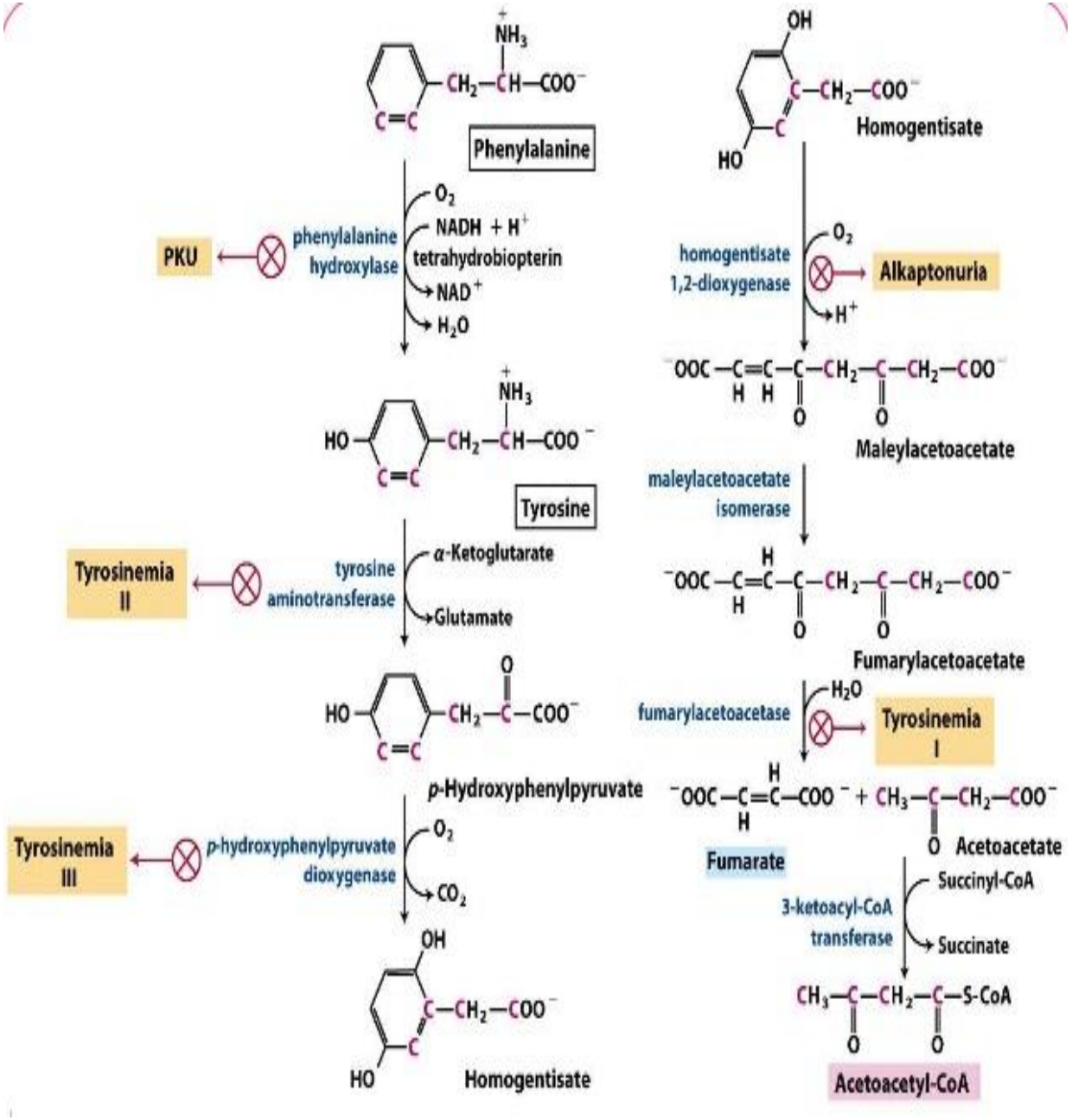


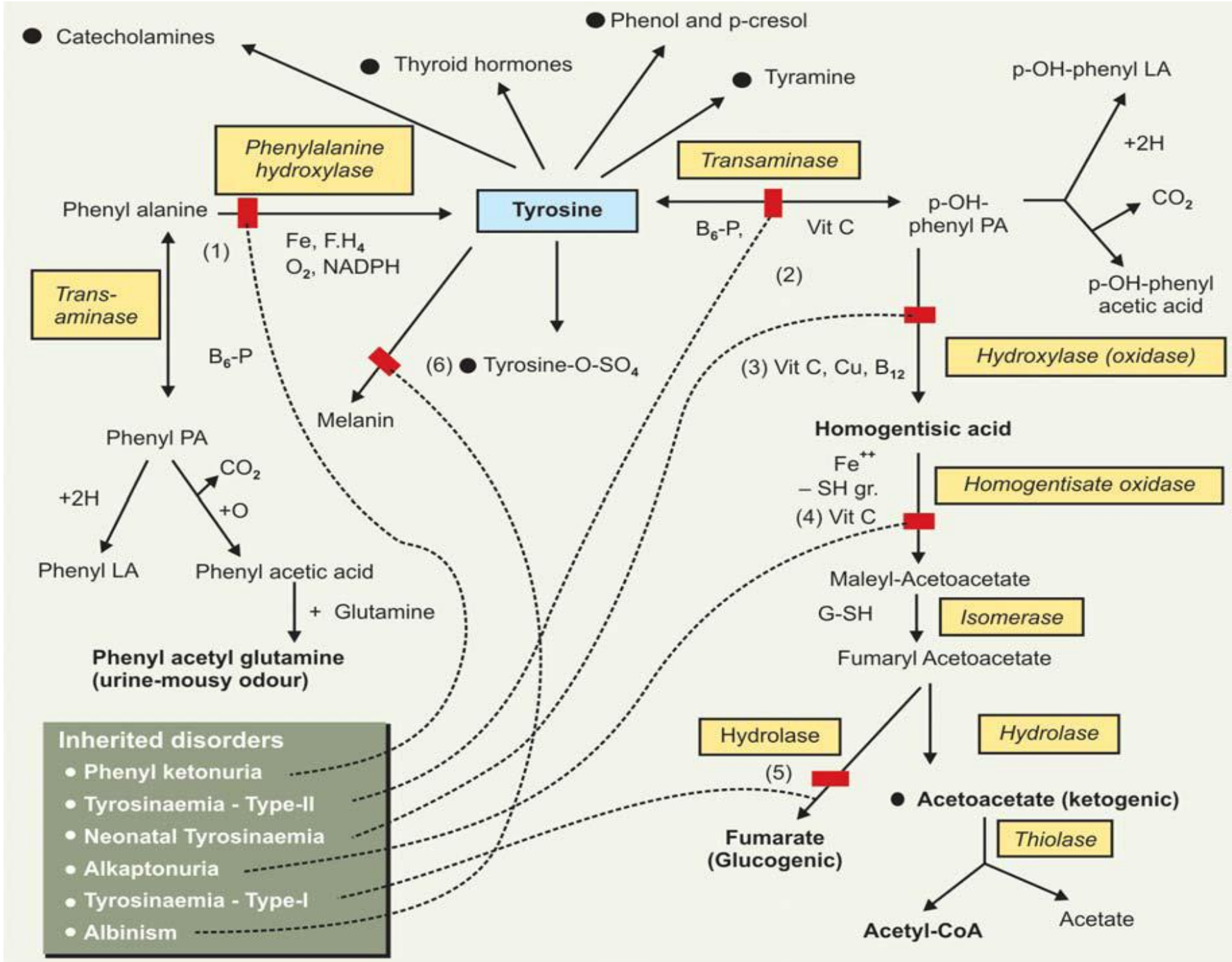
Urinary excretion of creatinine

Metabolism of phenylalanine and tyrosine.

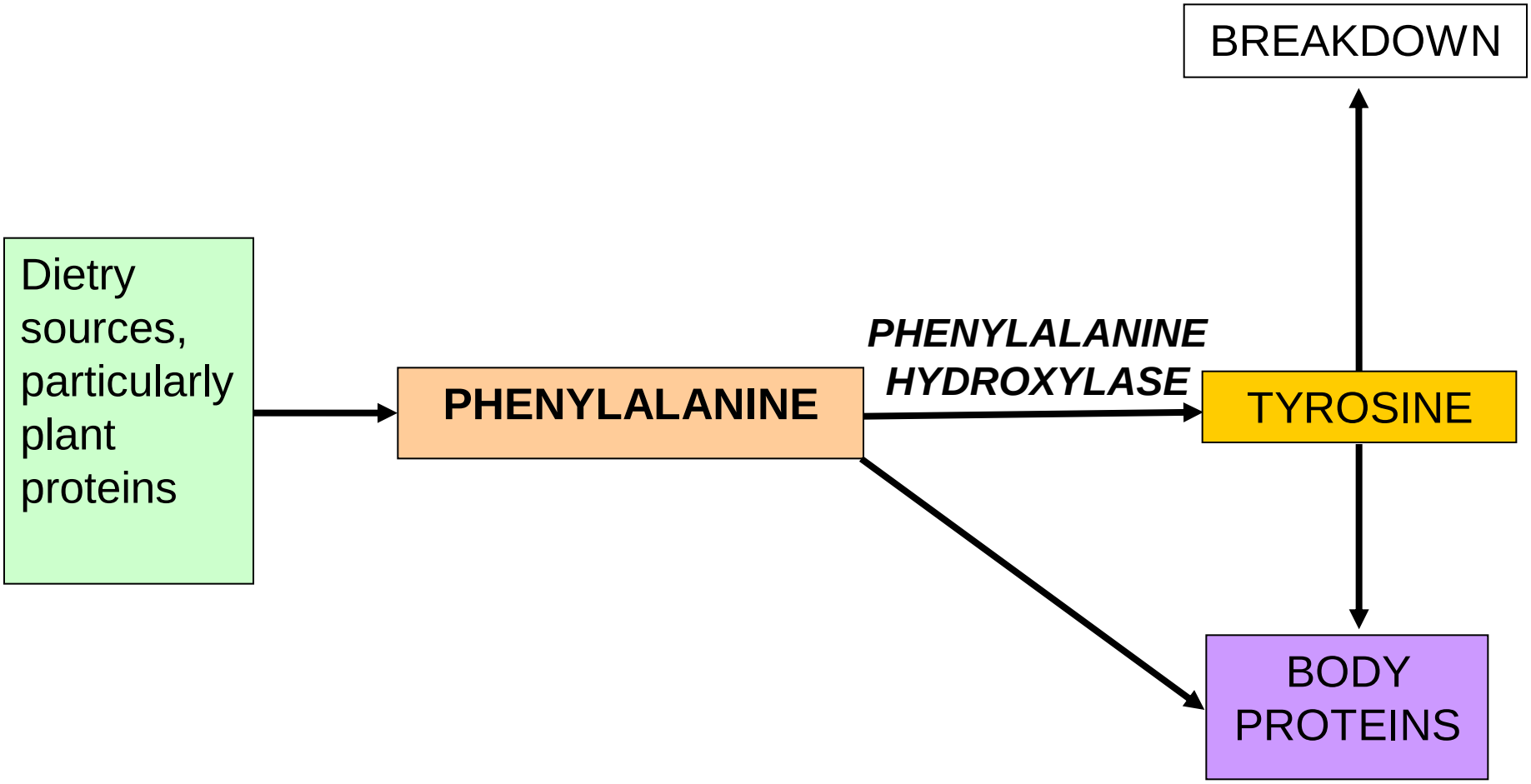


Metabolism of phenylalanine and tyrosine

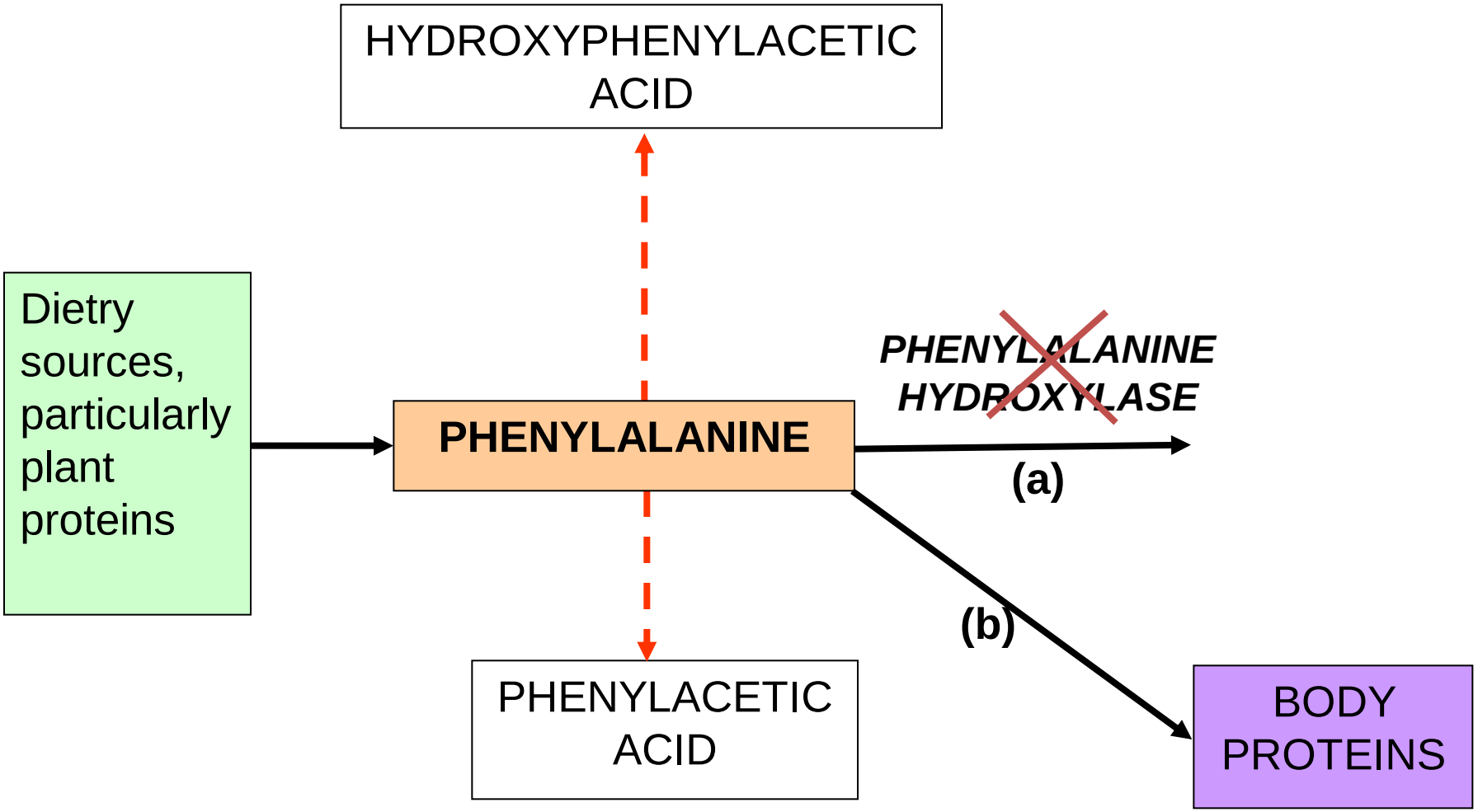



Catecholamines
Phenol and p-cresol
Thyroid hormones
Tyramine
p-OH-phenyl LA
+2H
CO2
p-OH-phenyl acetic acid
Phenylalanine hydroxylase
Transaminase
Phenyl alanine
Tyrosine
p-OH-phenyl PA
(1)
Fe, F.H4
O2, NADPH
B6-P,
Vit C
(2)
Trans-aminase
B6-P
(6) Tyrosine-O-SO4
Melanin
(3) Vit C, Cu, B12
Hydroxylase (oxidase)
Homogentisic acid
Phenyl PA
CO2
+2H
+O
Fe++
– SH gr.
(4) Vit C
Homogentisate oxidase
Phenyl LA
Phenyl acetic acid
+ Glutamine
Maleyl-Acetoacetate
G-SH
Isomerase
Phenyl acetyl glutamine
(urine-mousy odour)
Fumaryl Acetoacetate
Inherited disorders
• Phenyl ketonuria
• Tyrosinaemia - Type-II
• Neonatal Tyrosinaemia
• Alkaptonuria
• Tyrosinaemia - Type-I
• Albinism
Hydrolase
Hydrolase
(5)
Acetoacetate (ketogenic)
Fumarate
(Glucogenic)
Thiolase
Acetyl-CoA
Acetate

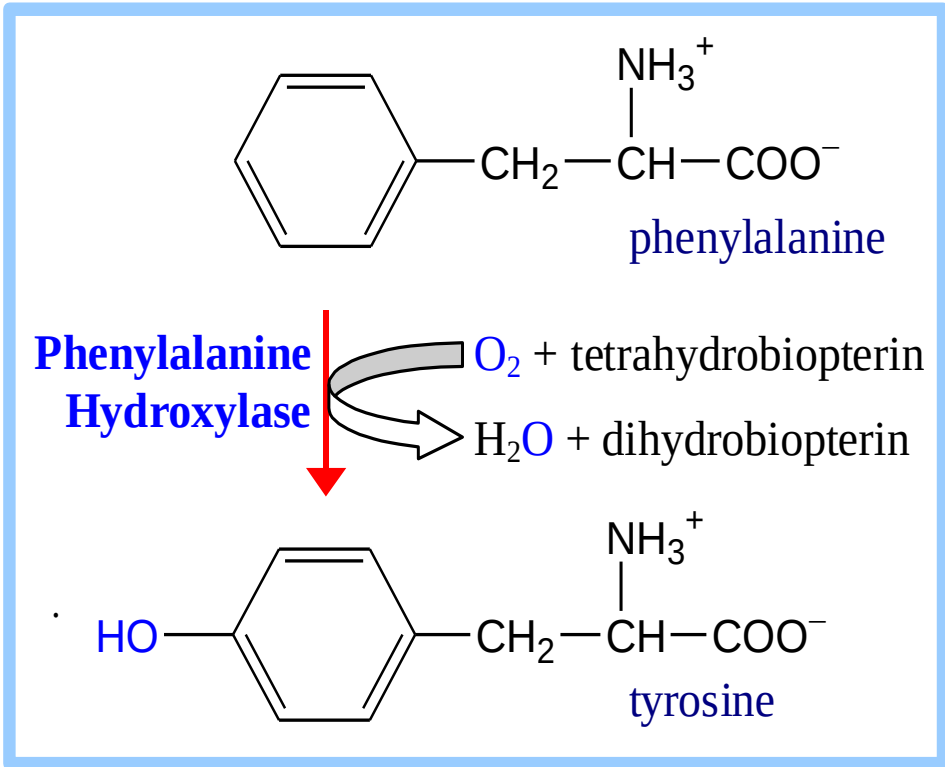
The normal metabolism of phenylalanine



The abnormal metabolism in phenylketonuric subjects



Genetic deficiency of ***Phenylalanine Hydroxylase*** leads to the disease **phenylketonuria**.



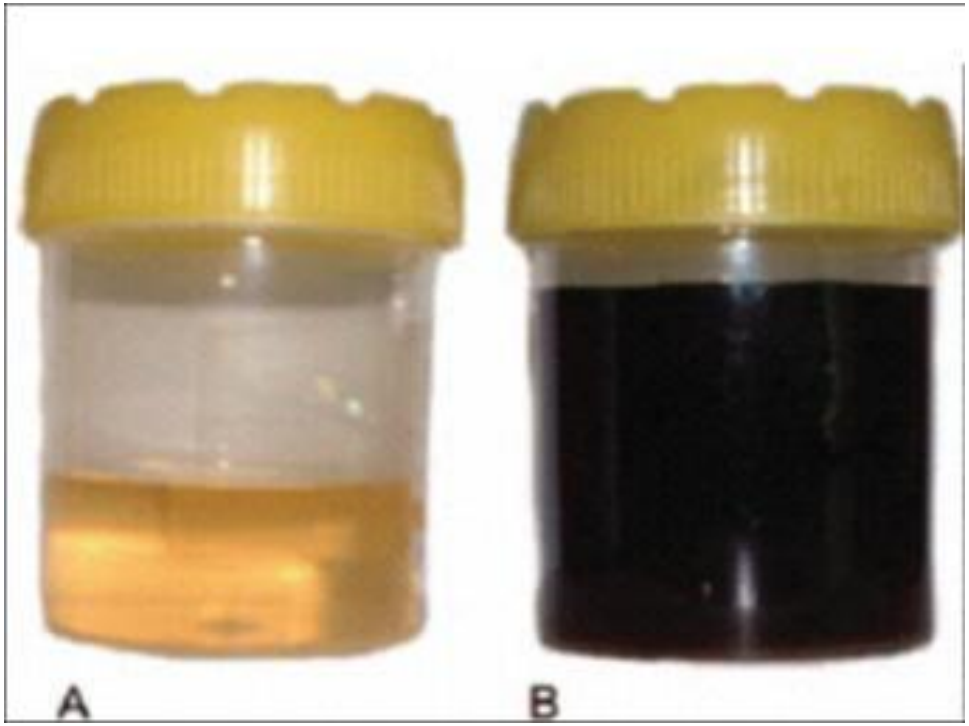
Phenylalanine & phenylpyruvate (the product of phenylalanine deamination via transaminase) **accumulate in blood & urine.**

Mental retardation results unless treatment begins immediately after birth. **Treatment** consists of **limiting phenylalanine intake** to levels barely adequate to support growth.
Tyrosine, an essential nutrient for individuals with phenylketonuria, must be supplied in the diet.

Albinism –

tyrosinase is deficient and melanine (black pigment of skin, hear and eyes) not produce, and affected individuals (called albinos) are extremely sensitive to sunlight.

Alcaptonuria - coused by a deficiency of ***homogentisate oxidase***. Large quantities of homogentisate (product of tyrosine metabolism) excreted in urine and autooxidizes, forming dark colored pigment (black urine).



In additional, pigment accumulates in various tissue and cause a degenerative arthritis.