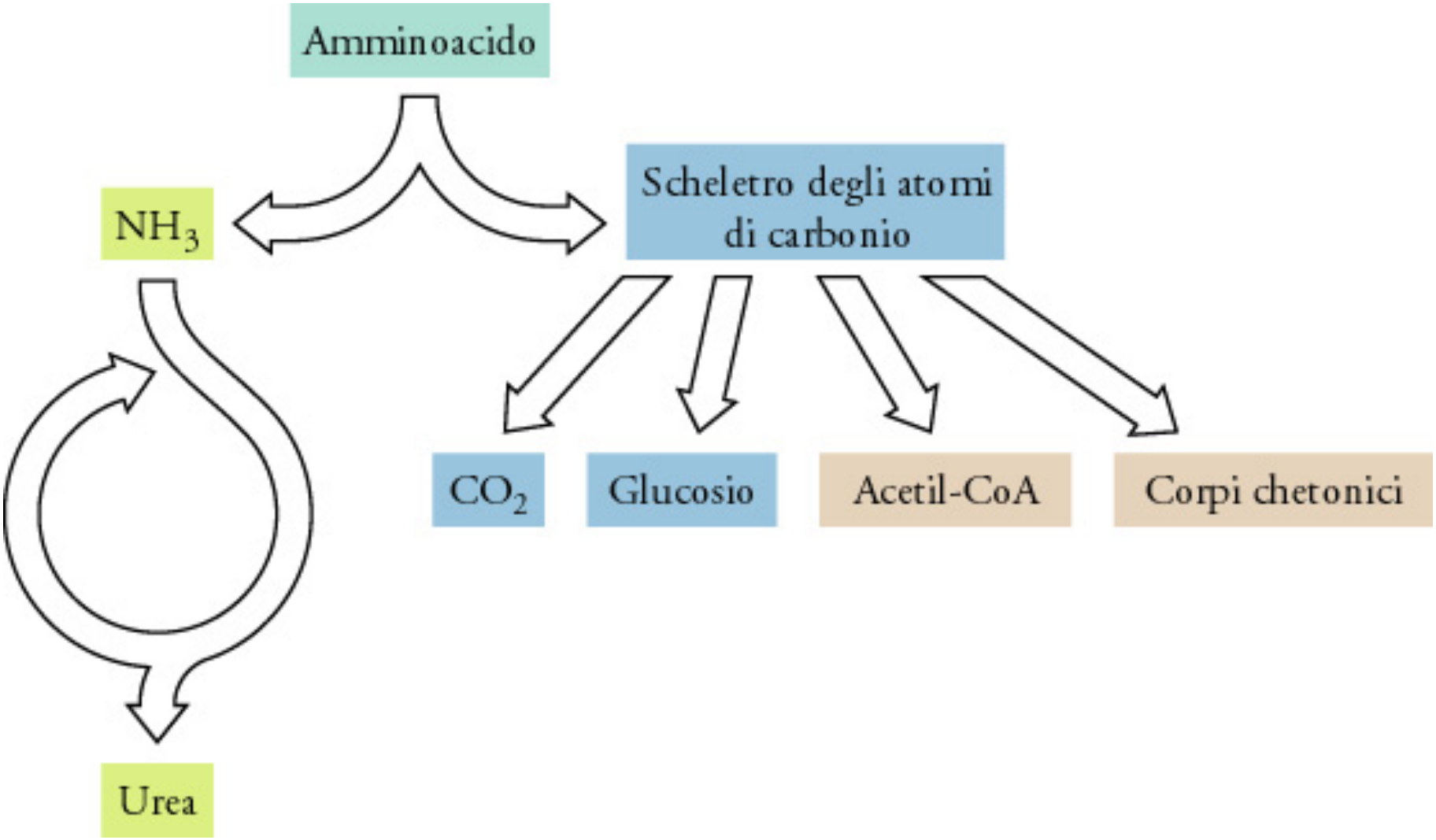
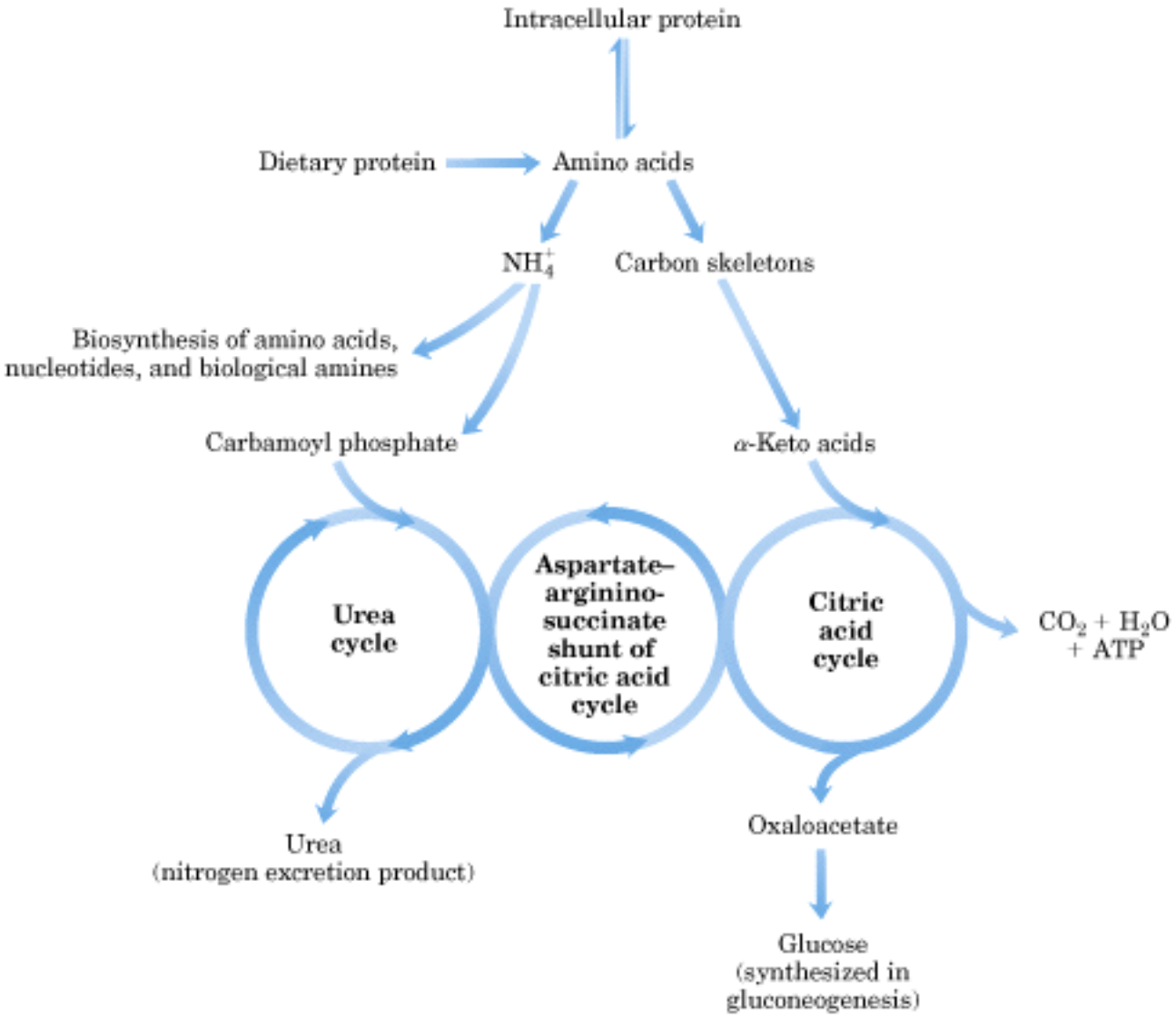
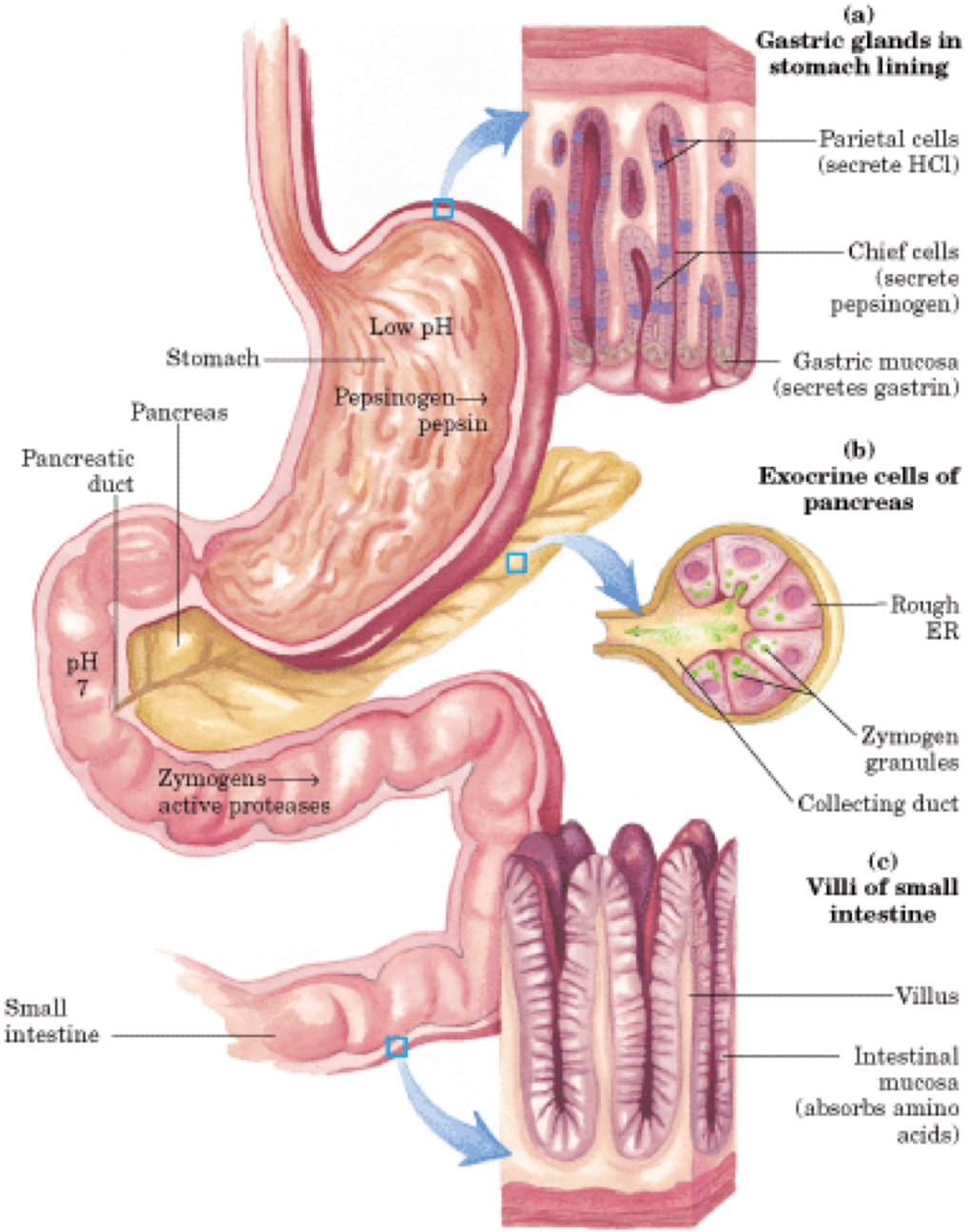
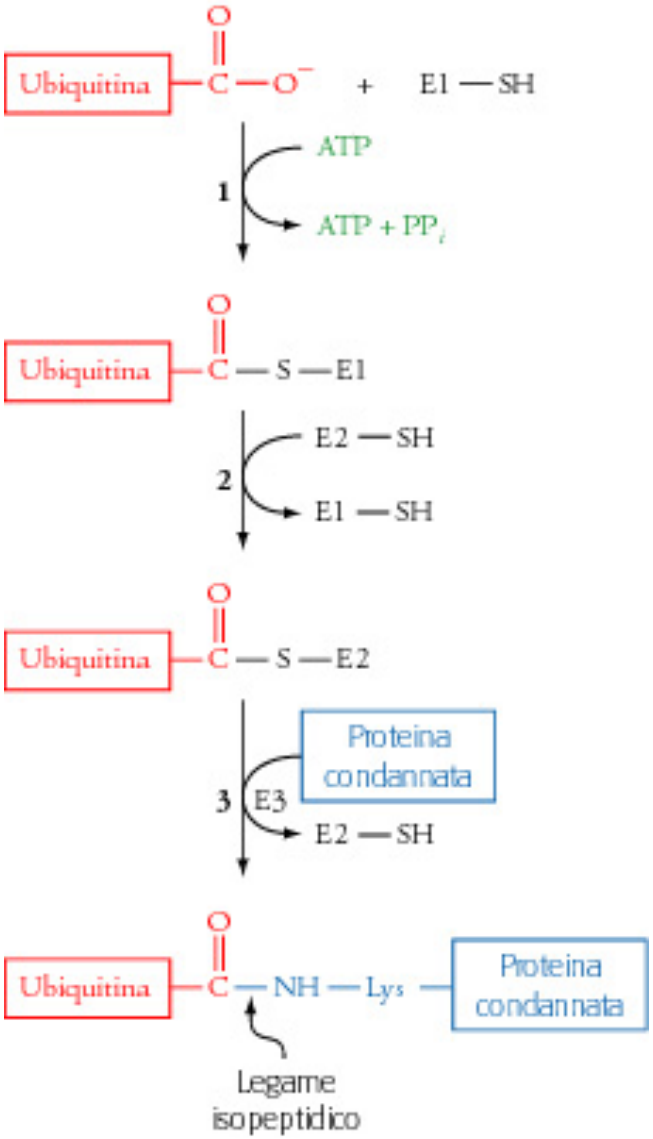
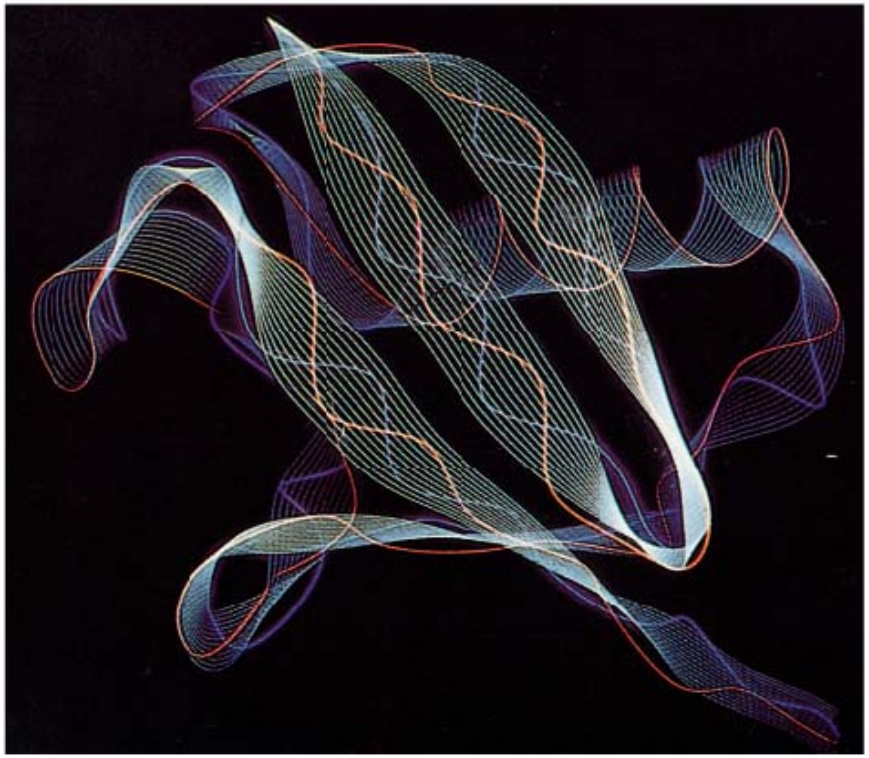
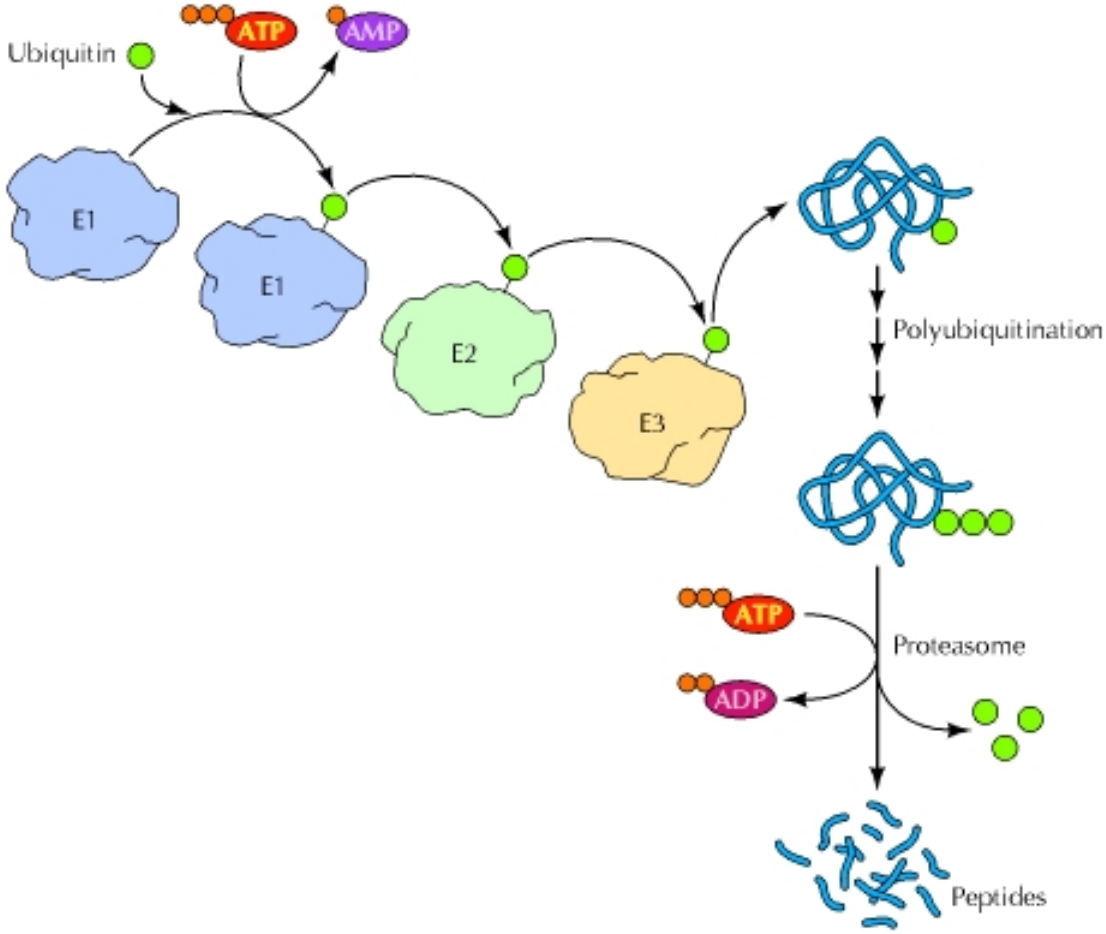

Amminoacido
$NH_3$
Scheletro degli atomi di carbonio
$CO_2$
Glucosio
Acetil-CoA
Corpi chetonici
Urea


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 (synthesized in gluconeogenesis)


(a)
Gastric glands in stomach lining
Parietal cells (secrete HCl)
Chief cells (secrete pepsinogen)
Gastric mucosa (secretes gastrin)
Low pH
Stomach
Pepsinogen → pepsin
Pancreas
Pancreatic duct
pH 7
Zymogens → active proteases
(b)
Exocrine cells of pancreas
Rough ER
Zymogen granules
Collecting duct
(c)
Villi of small intestine
Villus
Intestinal mucosa (absorbs amino acids)
Small intestine

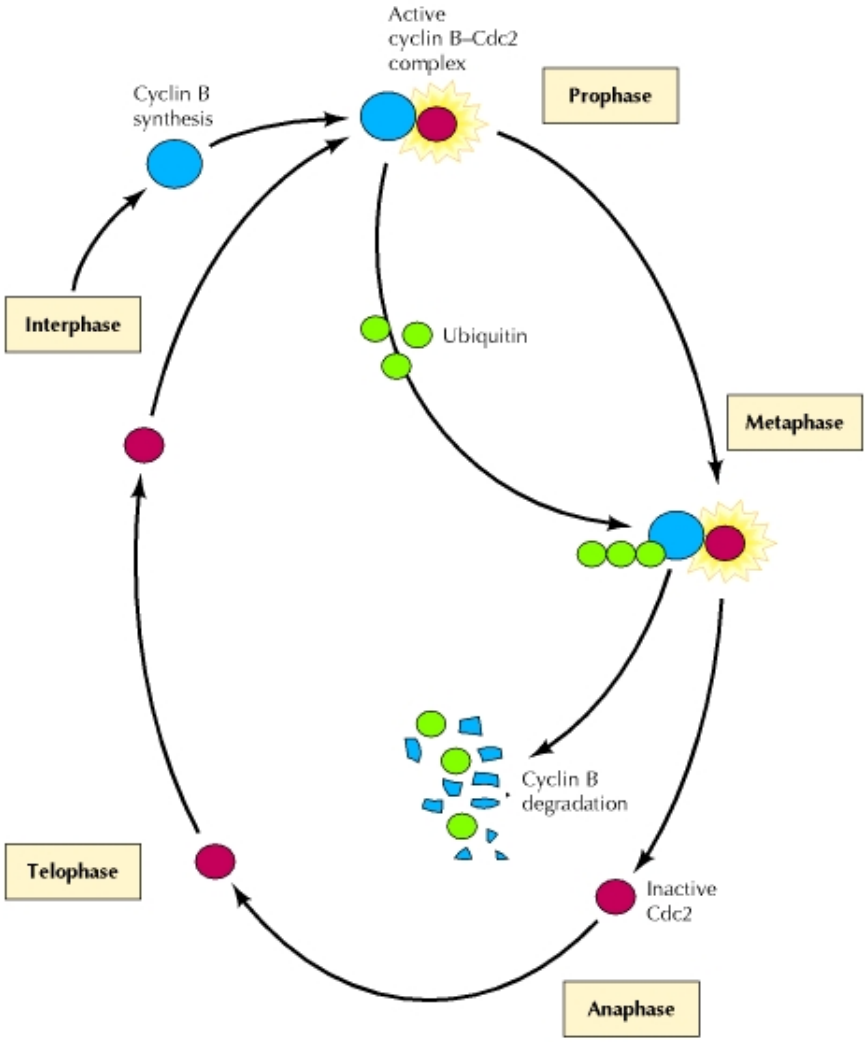

Ubiquitina
C
O⁻
+
E1 — SH
1
ATP
ATP + PPi
Ubiquitina
C — S — E1
2
E2 — SH
E1 — SH
Ubiquitina
C — S — E2
3
E3
Proteina condannata
E2 — SH
Ubiquitina
C — NH — Lys
Proteina condannata
Legame isopeptidico





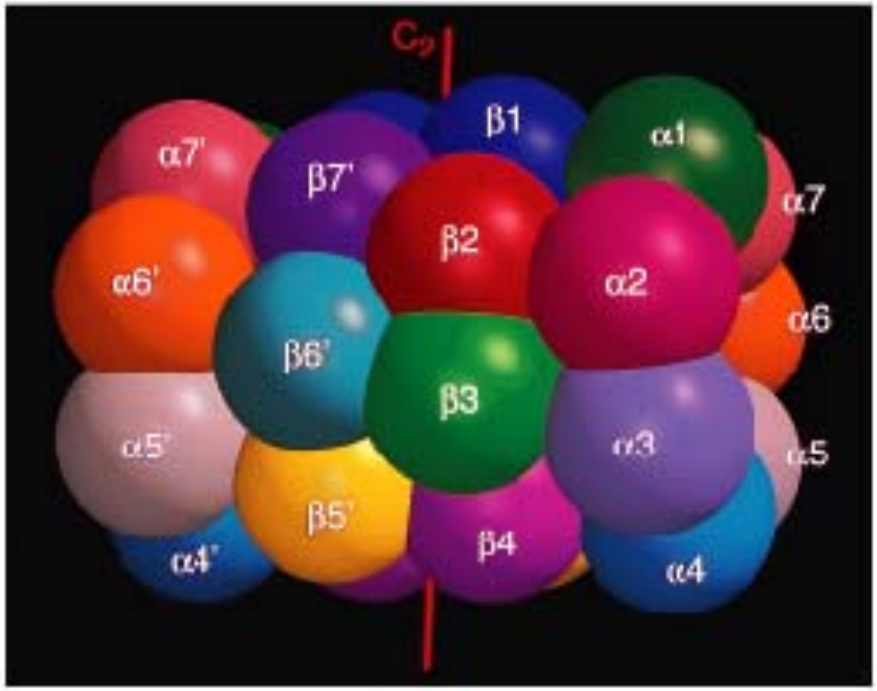

**The ubiquitin-proteasome pathway**

Proteins are marked for rapid degradation by the covalent attachment of several molecules of ubiquitin. Ubiquitin is first activated by the enzyme E1. Activated ubiquitin is then transferred to one of several different ubiquitin-conjugating enzymes (E2). In most cases, the ubiquitin is then transferred to a ubiquitin ligase (E3) and then to a specific target protein. Multiple ubiquitins are then added, and the polyubiquinated proteins are degraded by a protease complex (the proteasome).

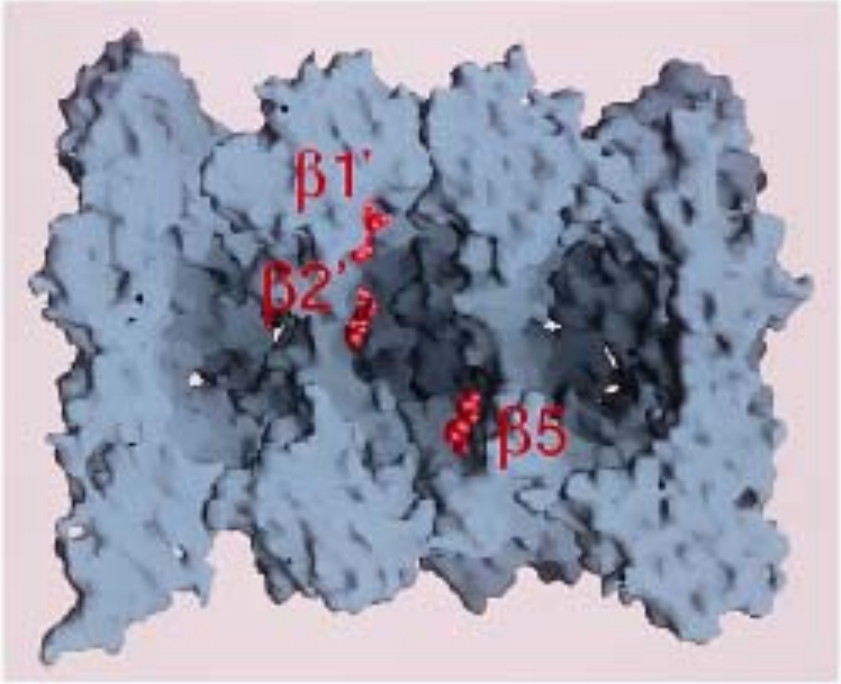



**Cyclin degradation during the cell cycle**

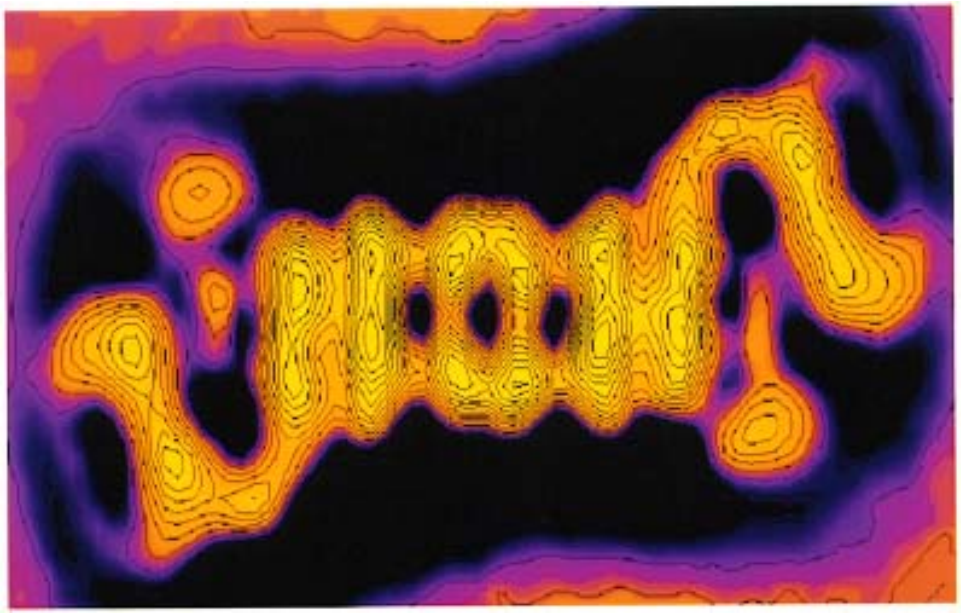
The progression of eukaryotic cells through the division cycle is controlled in part by the synthesis and degradation of cyclin B, which is a regulatory subunit of the Cdc2 protein kinase. Synthesis of cyclin B during interphase leads to the formation of an active cyclin B–Cdc2 complex, which induces entry into mitosis. Rapid degradation of cyclin B then leads to inactivation of the Cdc2 kinase, allowing the cell to exit mitosis and return to interphase of the next cell cycle.

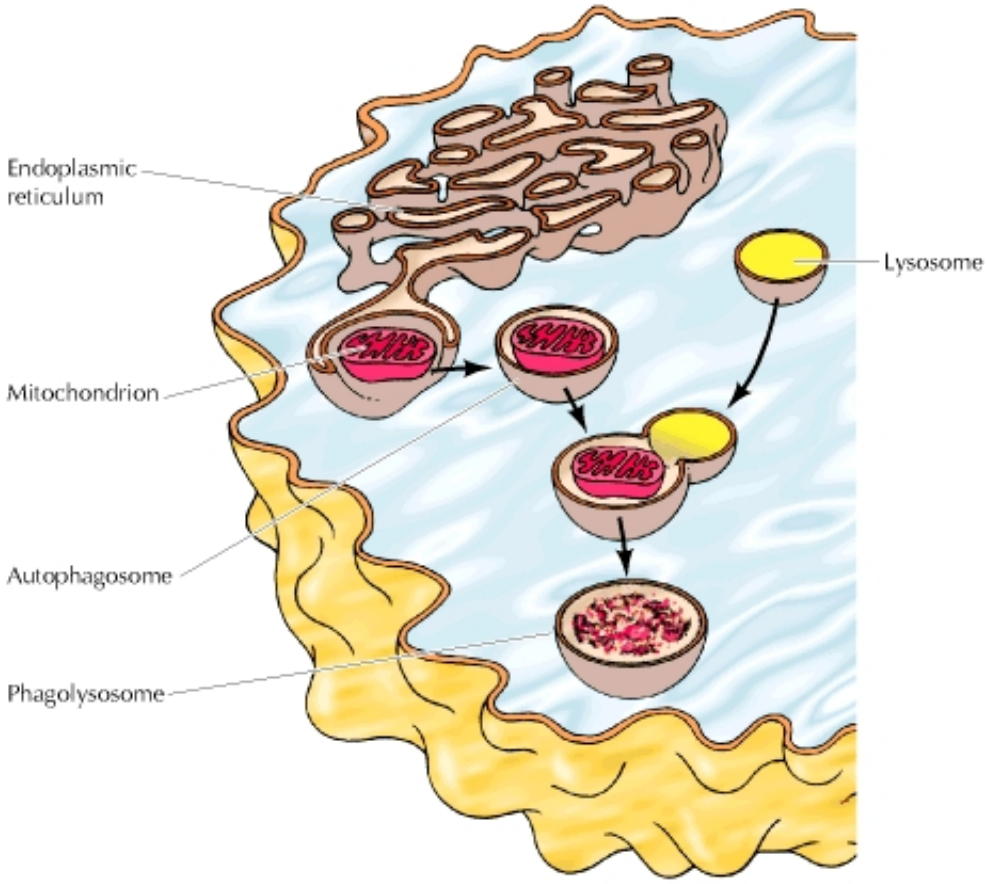



(a)



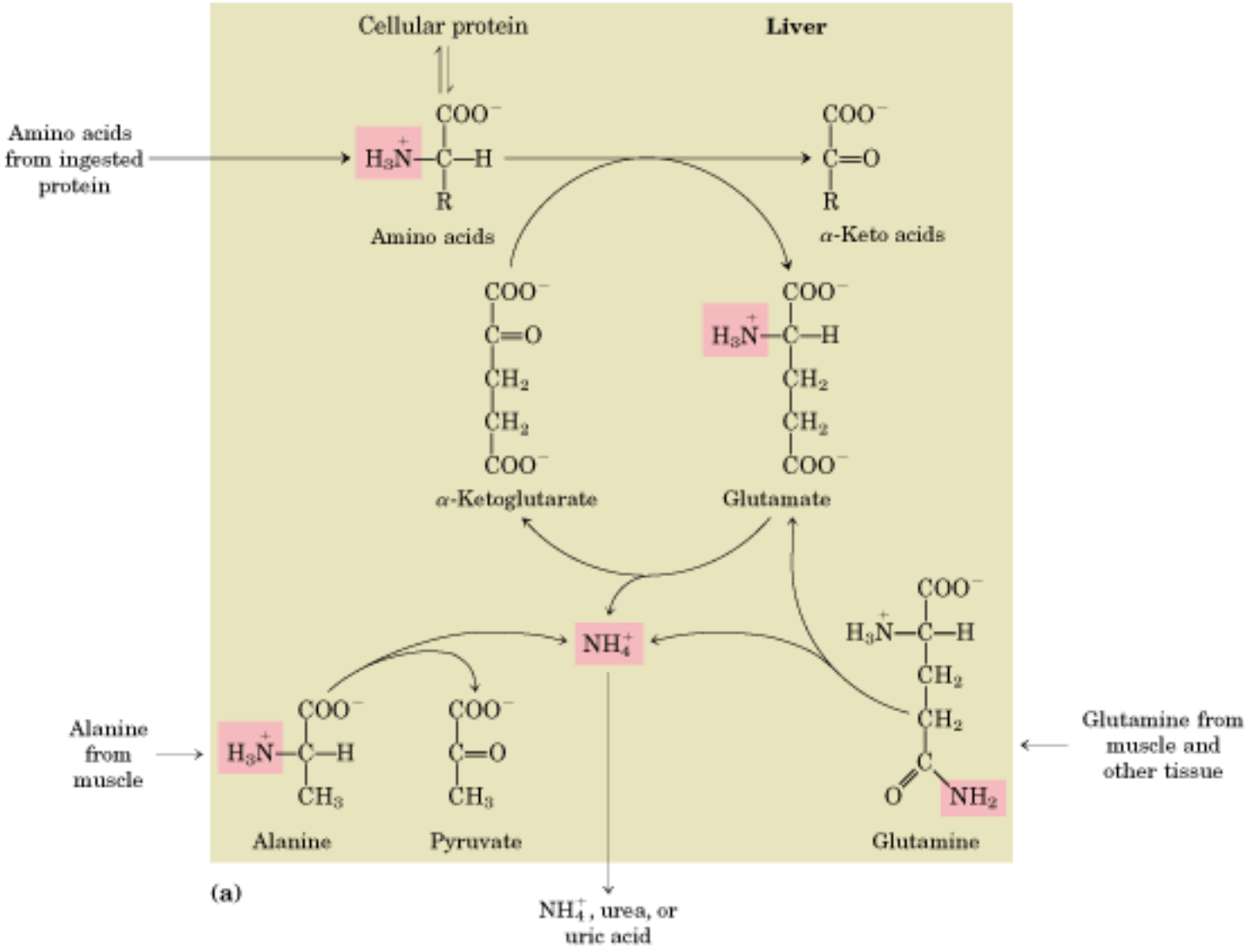

(b)





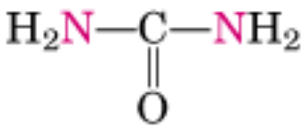

**The lysosome system**

Lysosomes contain various digestive enzymes, including proteases. Lysosomes take up cellular proteins by fusion with autophagosomes, which are formed by the enclosure of areas of cytoplasm or organelles (e.g., a mitochondrion) in fragments of the endoplasmic reticulum. This fusion yields a phagolysosome, which digests the contents of the autophagosome.


Cellular protein
Liver
Amino acids from ingested protein
Amino acids
α-Keto acids
α-Ketoglutarate
Glutamate
NH4+
Alanine from muscle
Alanine
Pyruvate
Glutamine
Glutamine from muscle and other tissue
(a)
NH4+, urea, or uric acid

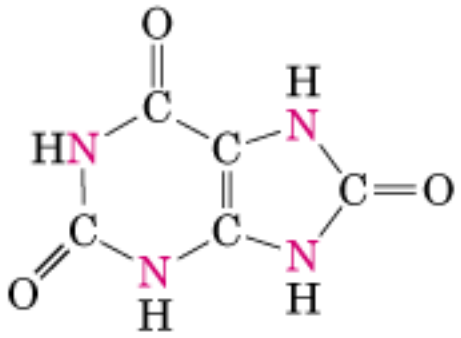
Ammonia (as ammonium ion)

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia



Urea

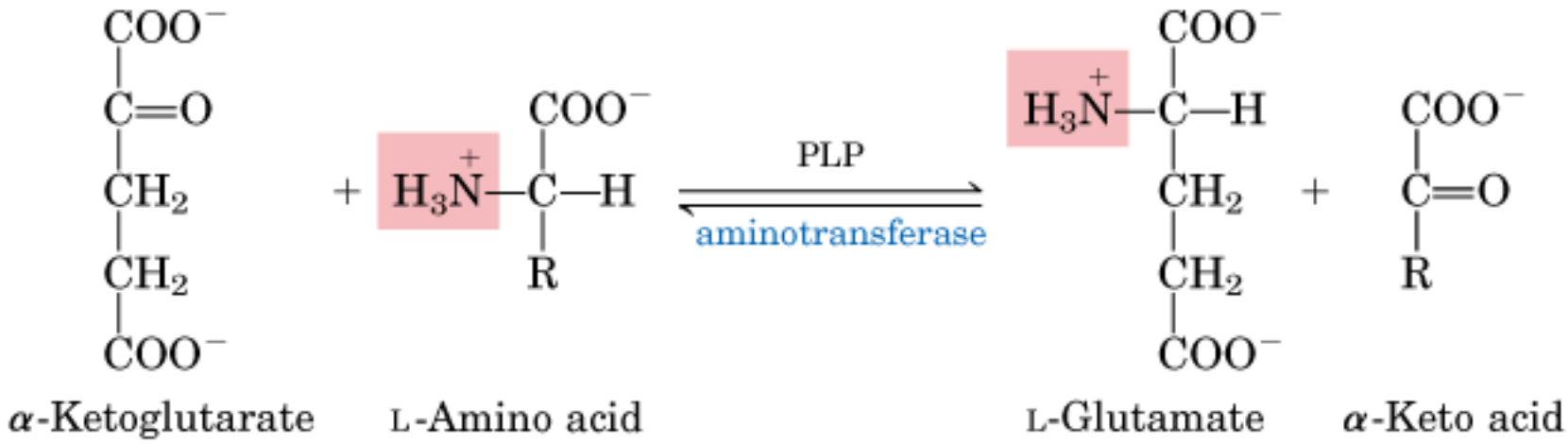
Ureotelic animals: many terrestrial vertebrates; also sharks

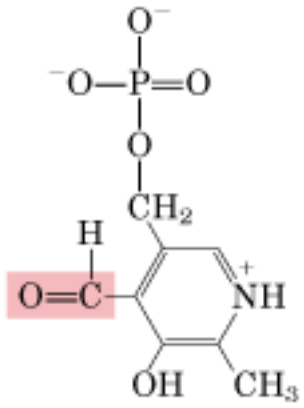


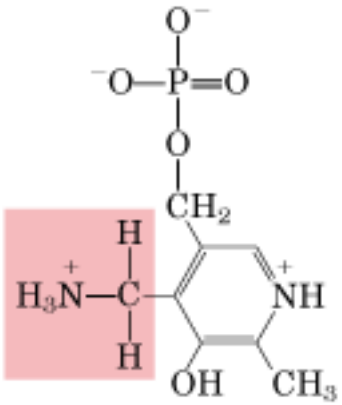
Uric acid

Uricotelic animals: birds, reptiles

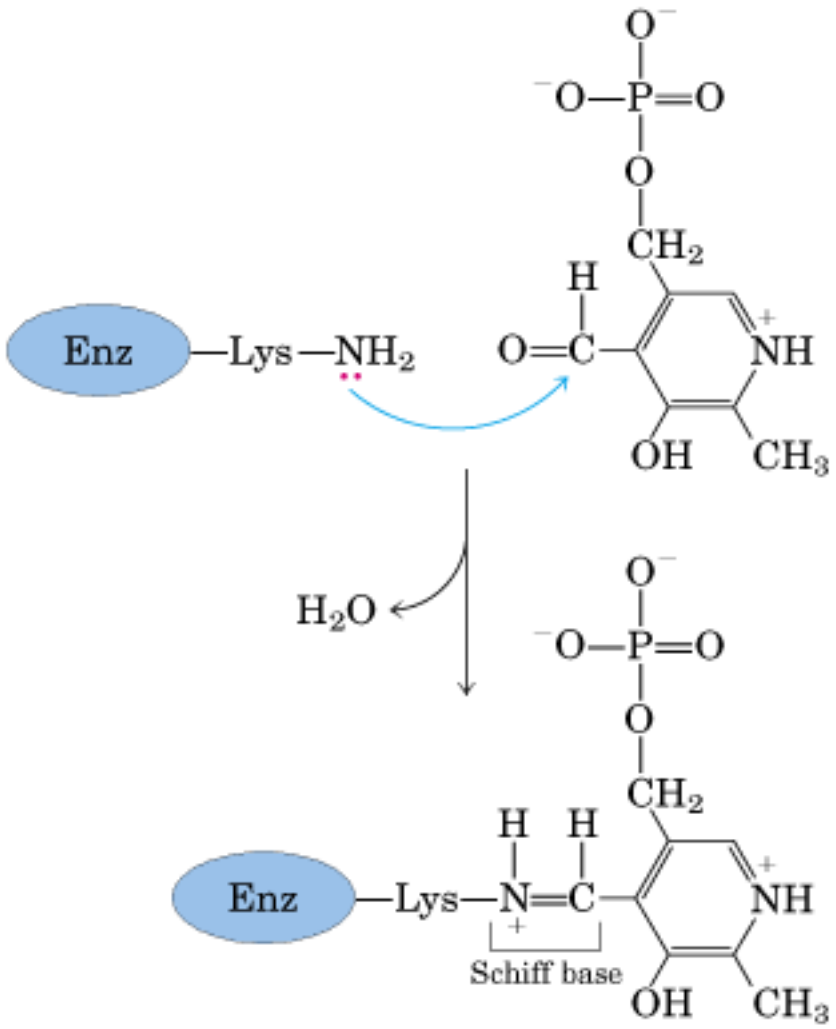
**(b)**


COO⁻
C=O
CH2
CH2
COO⁻
+
H3N⁺—C—H
COO⁻
R
PLP
aminotransferase
H3N⁺—C—H
COO⁻
CH2
CH2
COO⁻
+
C=O
COO⁻
R
α-Ketoglutarate
L-Amino acid
L-Glutamate
α-Keto acid


Pyridoxal phosphate
(PLP)

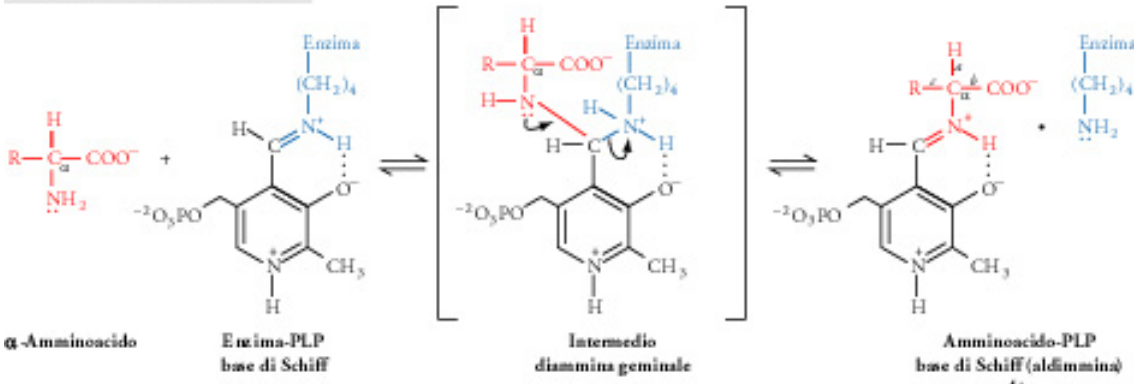

Pyridoxamine
phosphate

(a)

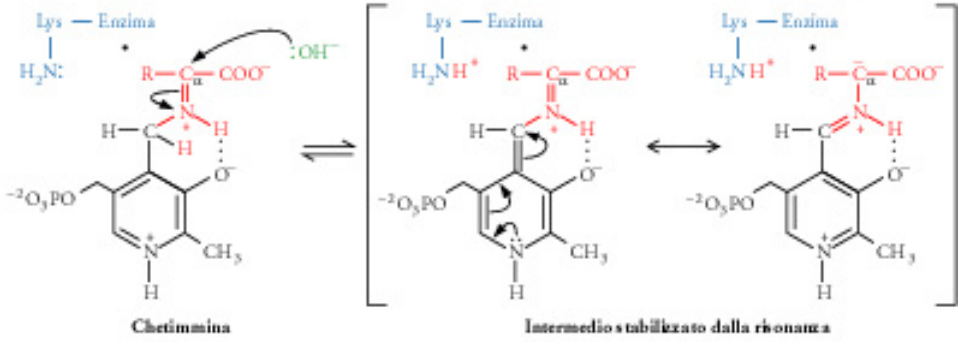

Enz
Lys
NH2
H2O
Enz
Lys
Schiff base

(b)

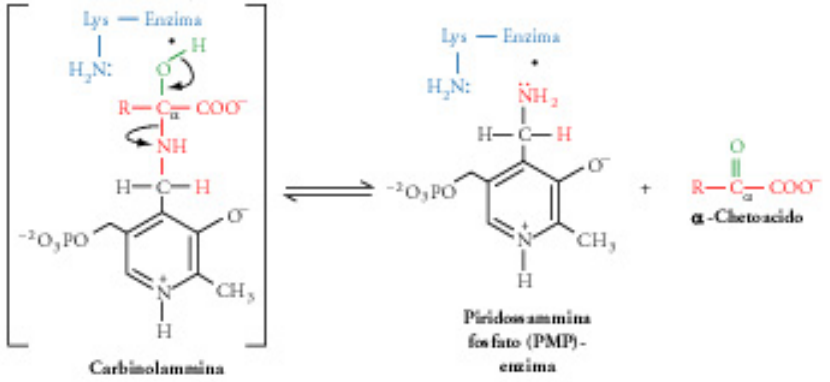
**Tappe 1 e 1': Transimminazione**

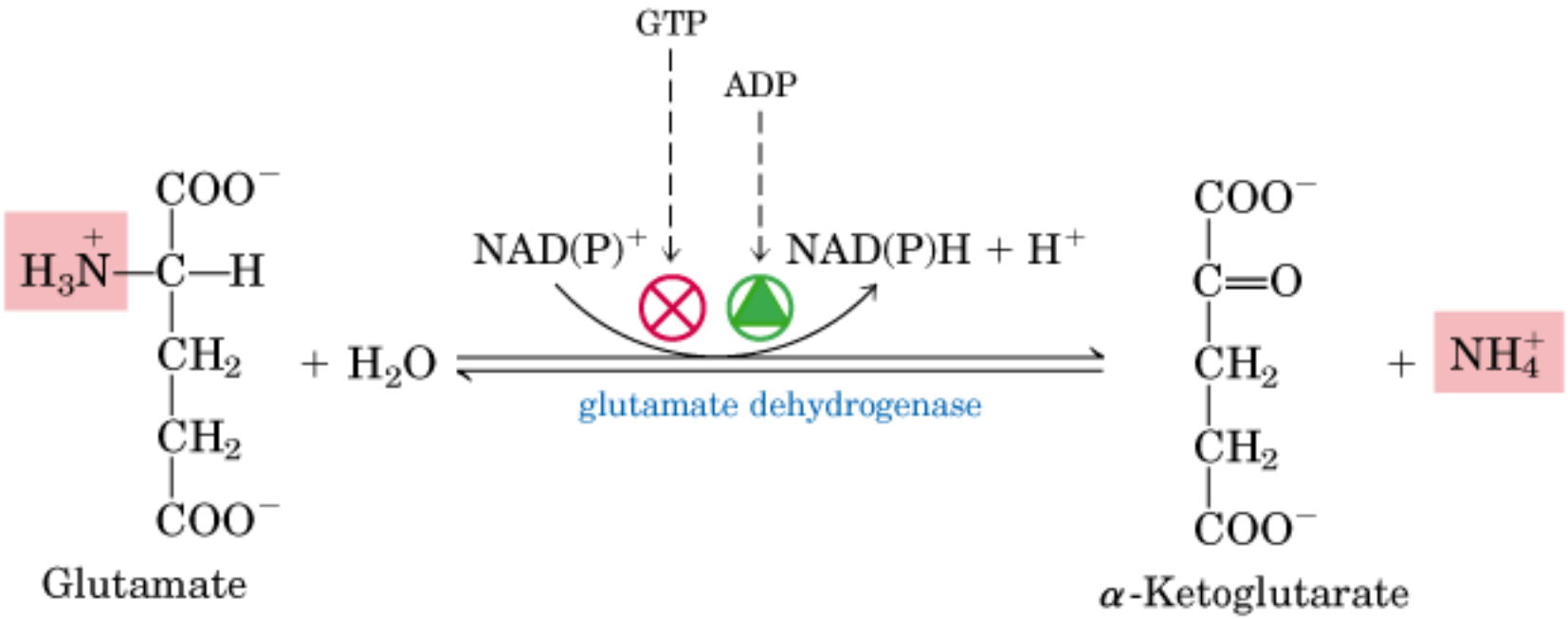


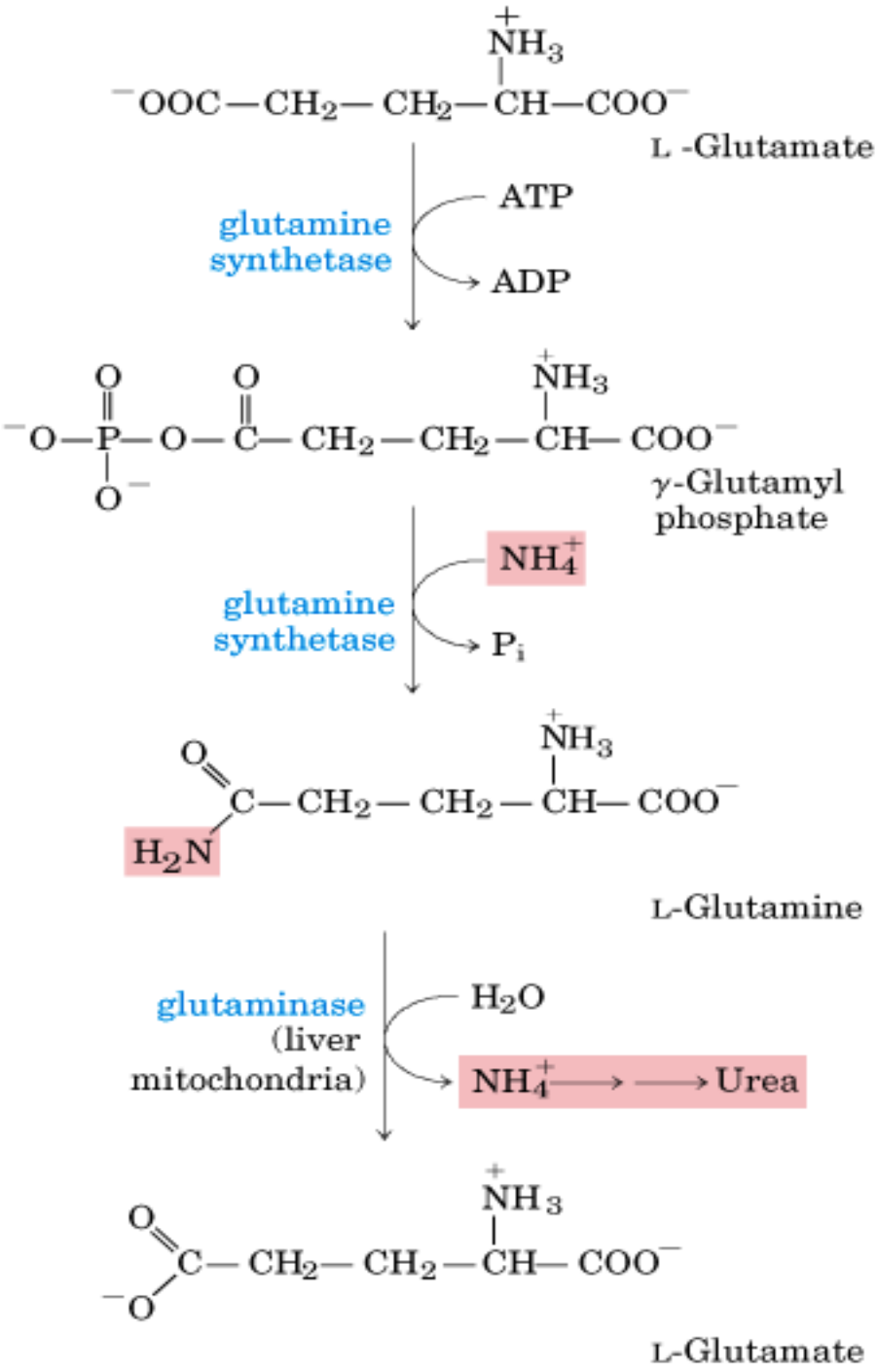

**Tappe 2 e 2': Tautomerizzazione**

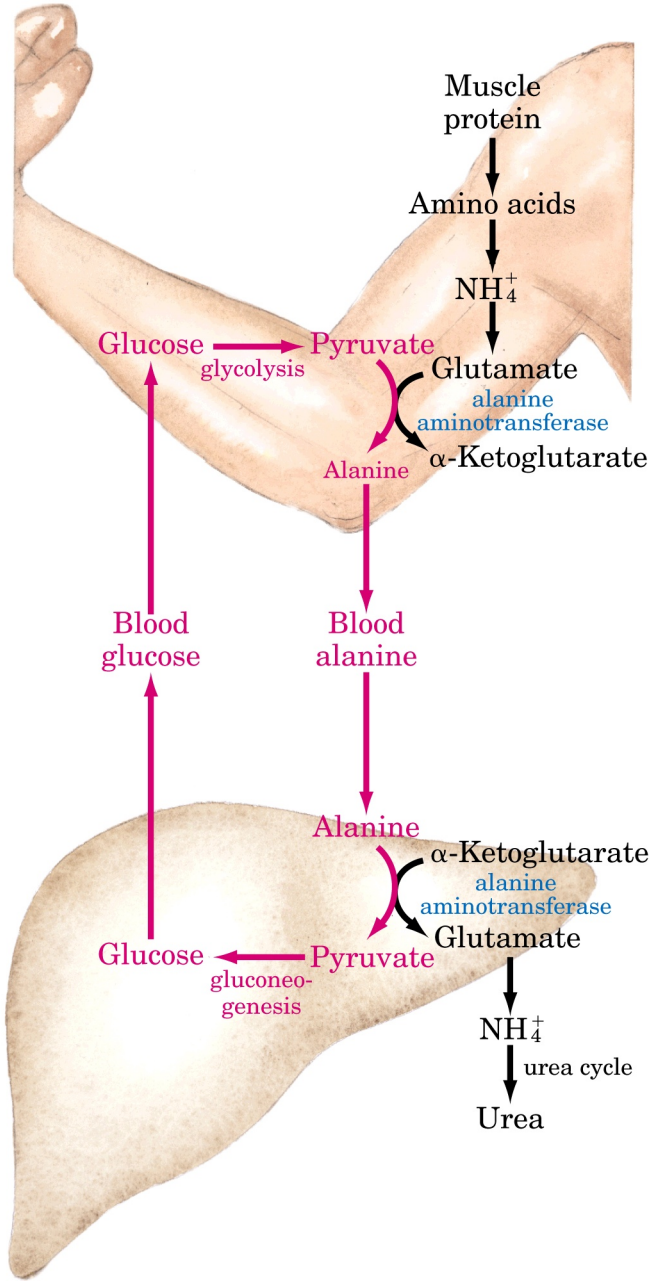


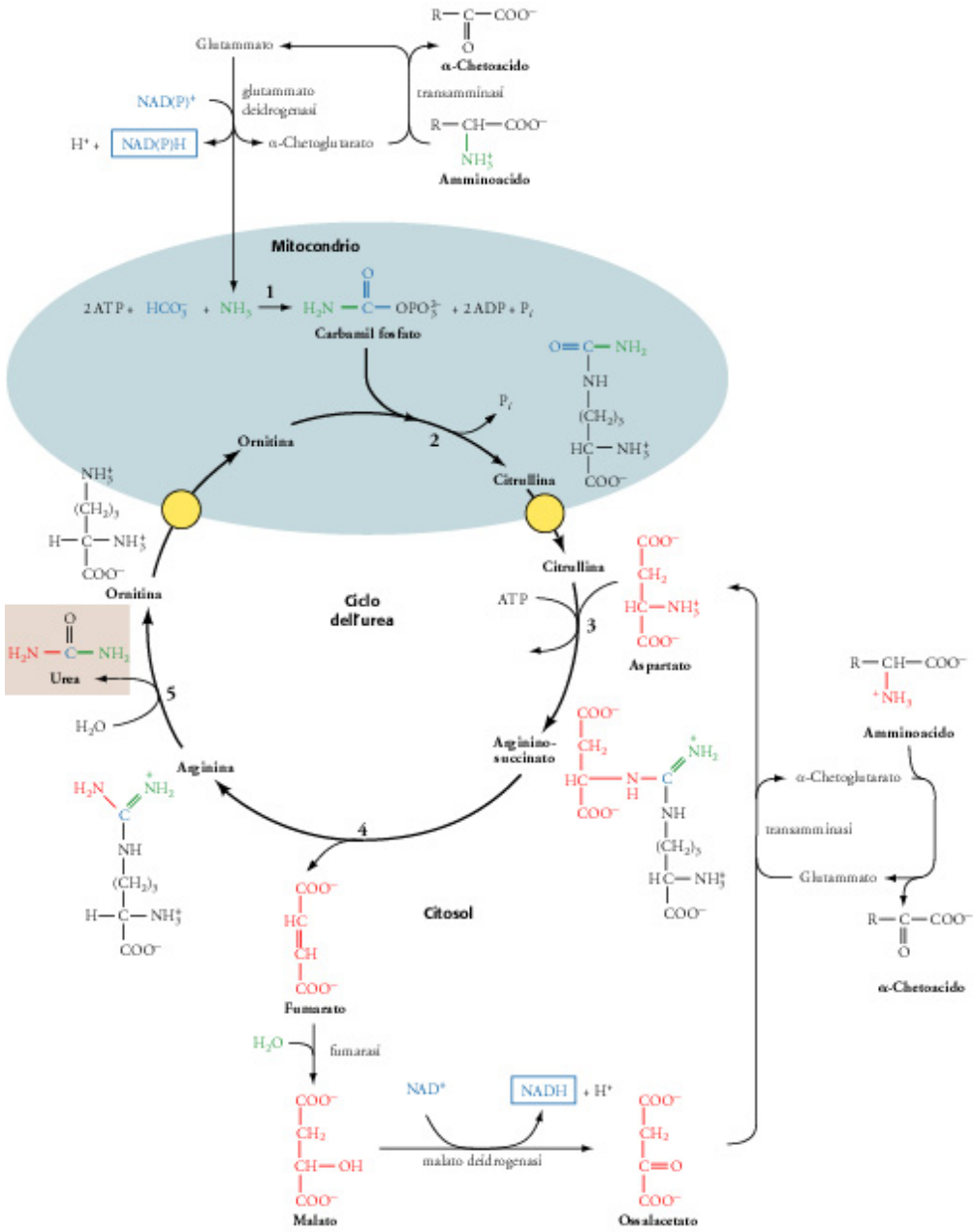

**Tappe 3 e 3': Idrolisi**

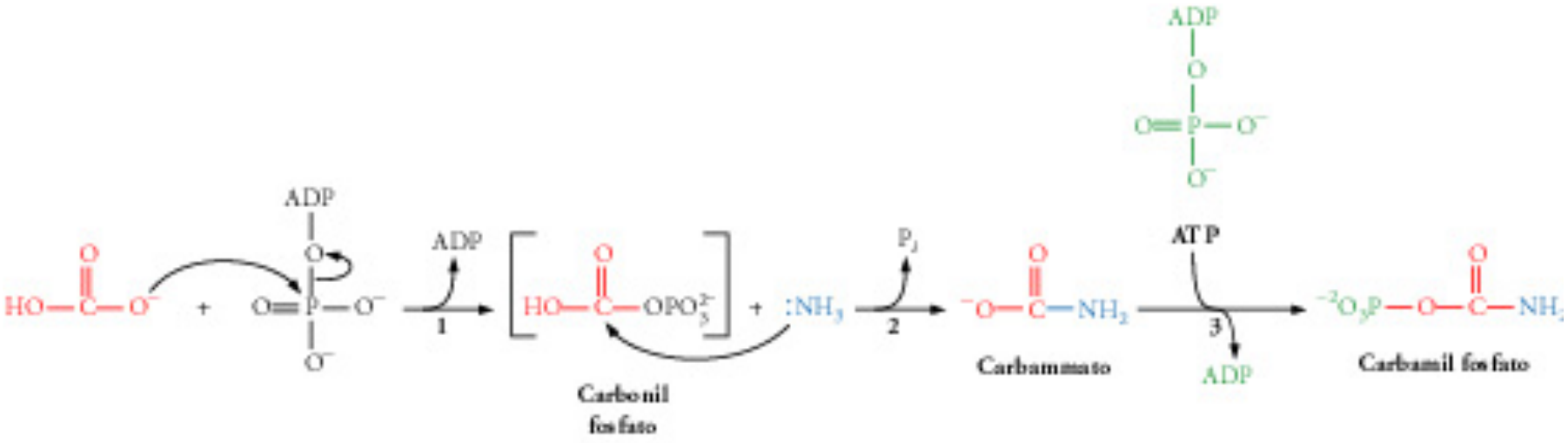


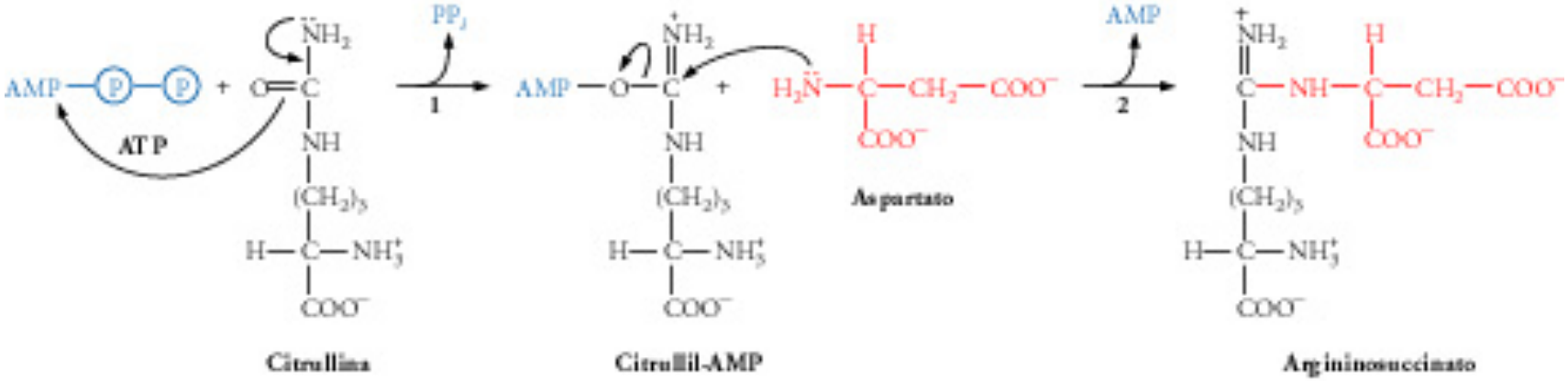

GTP
ADP
NAD(P)+
NAD(P)H + H+
glutamate dehydrogenase
+ H2O
+ NH4+
Glutamate
α-Ketoglutarate

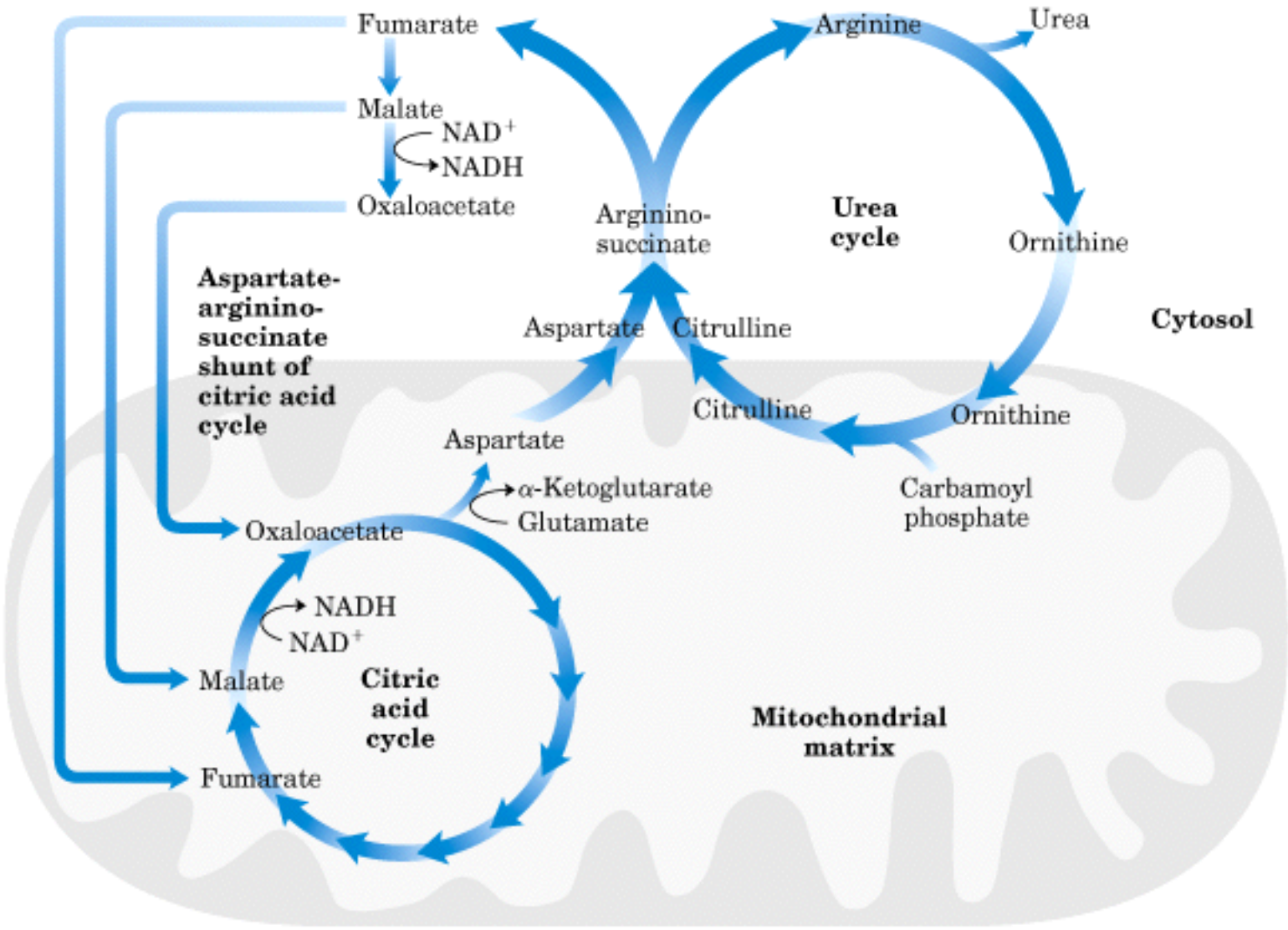

L -Glutamate
glutamine synthetase
ATP
ADP
γ-Glutamyl phosphate
glutamine synthetase
NH4+
Pi
L-Glutamine
glutaminase (liver mitochondria)
H2O
NH4+ → → Urea
L-Glutamate

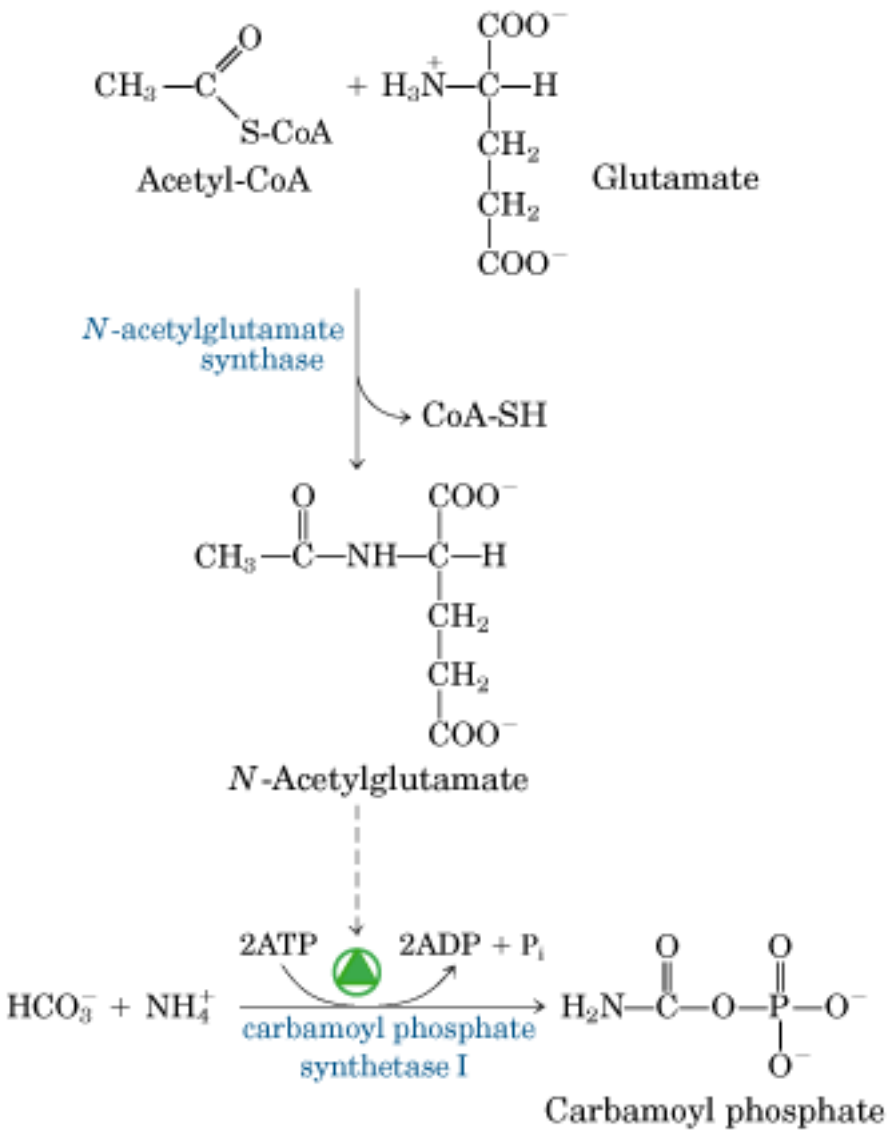

Muscle protein
Amino acids
$NH_4^+$
Glucose
glycolysis
Pyruvate
Glutamate
alanine aminotransferase
α-Ketoglutarate
Alanine
Blood glucose
Blood alanine
Alanine
α-Ketoglutarate
alanine aminotransferase
Glutamate
Glucose
gluconeo-genesis
Pyruvate
$NH_4^+$
urea cycle
Urea

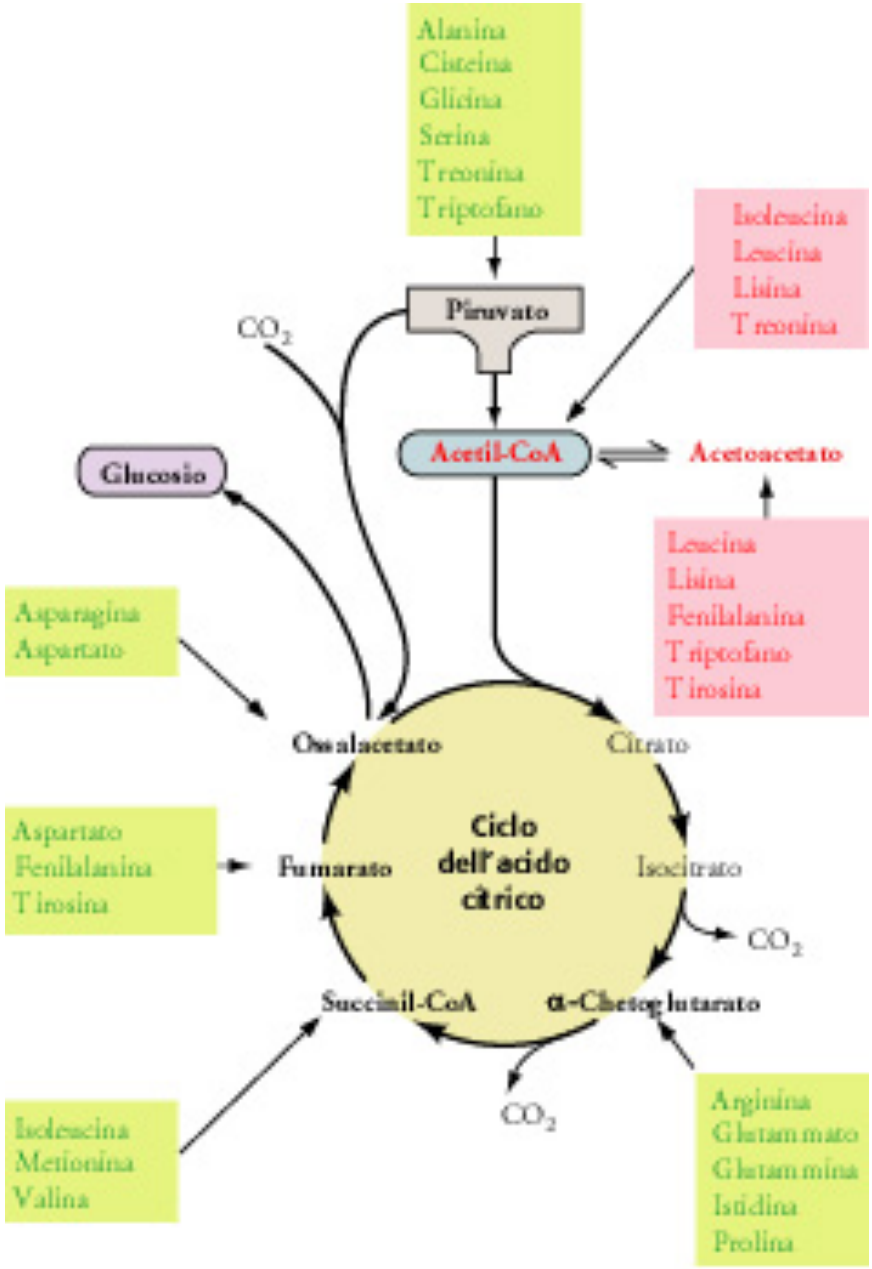

Glutammato
α-Chetoacido
glutammato deidrogenasi
transamminasi
NAD(P)+
H+ + NAD(P)H
α-Chetoglutarato
Amminoacido
Mitocondrio
2 ATP + HCO3− + NH3
1
Carbamil fosfato
Pi
Ornitina
2
Citrullina
Ornitina
Ciclo dell'urea
Citrullina
ATP
3
Aspartato
Urea
5
H2O
Agininosuccinato
Agmina
4
Citosol
Fumarato
H2O
fumarasi
NAD+
NADH + H+
malato deidrogenasi
Malato
Ossalacetato
Amminoacido
α-Chetoglutarato
transamminasi
Glutammato
α-Chetoacido

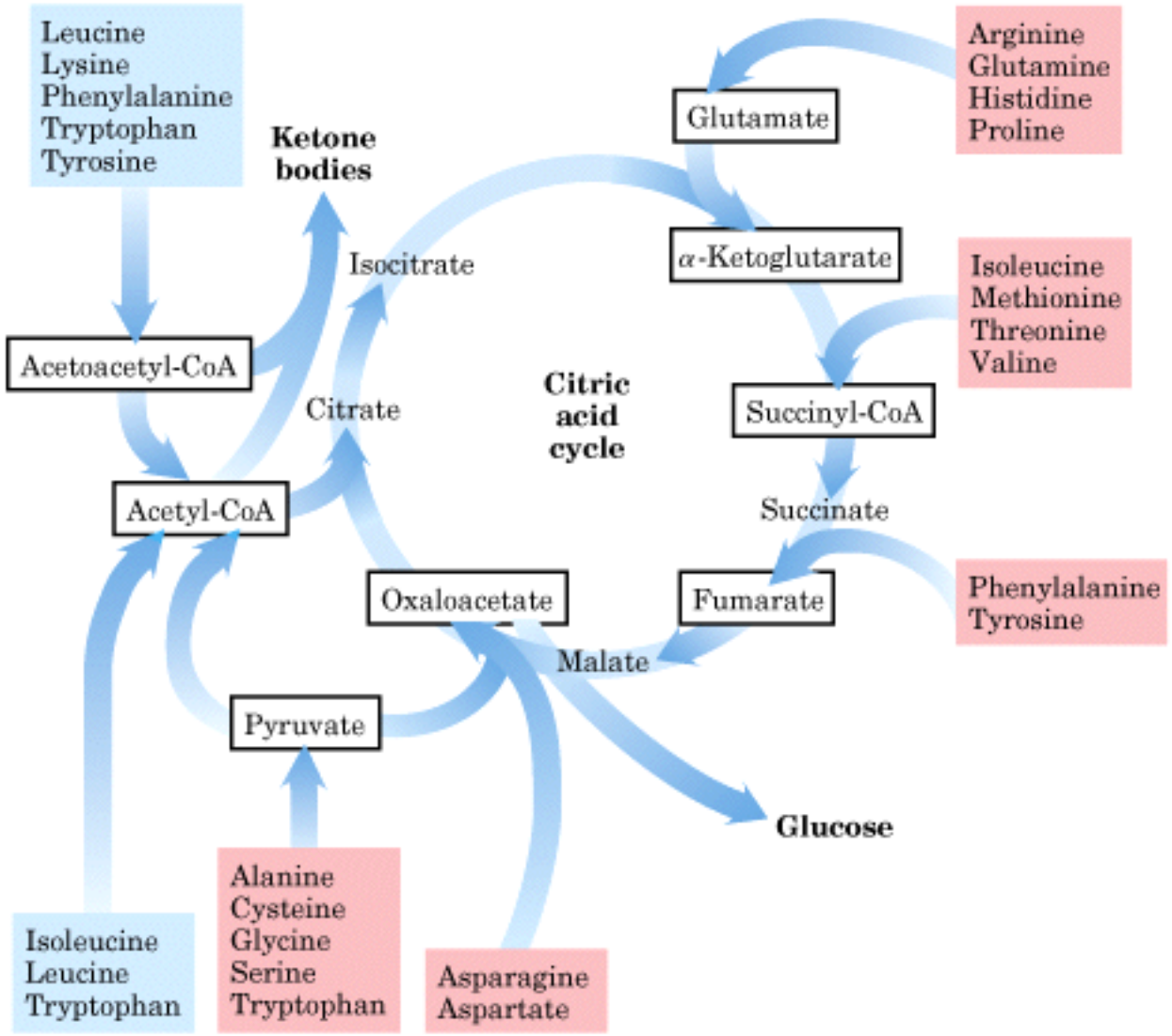

ADP
ADP
1
Carbonil fosfato
$P_i$
2
Carbammato
ATP
3
ADP
Carbamil fosfato

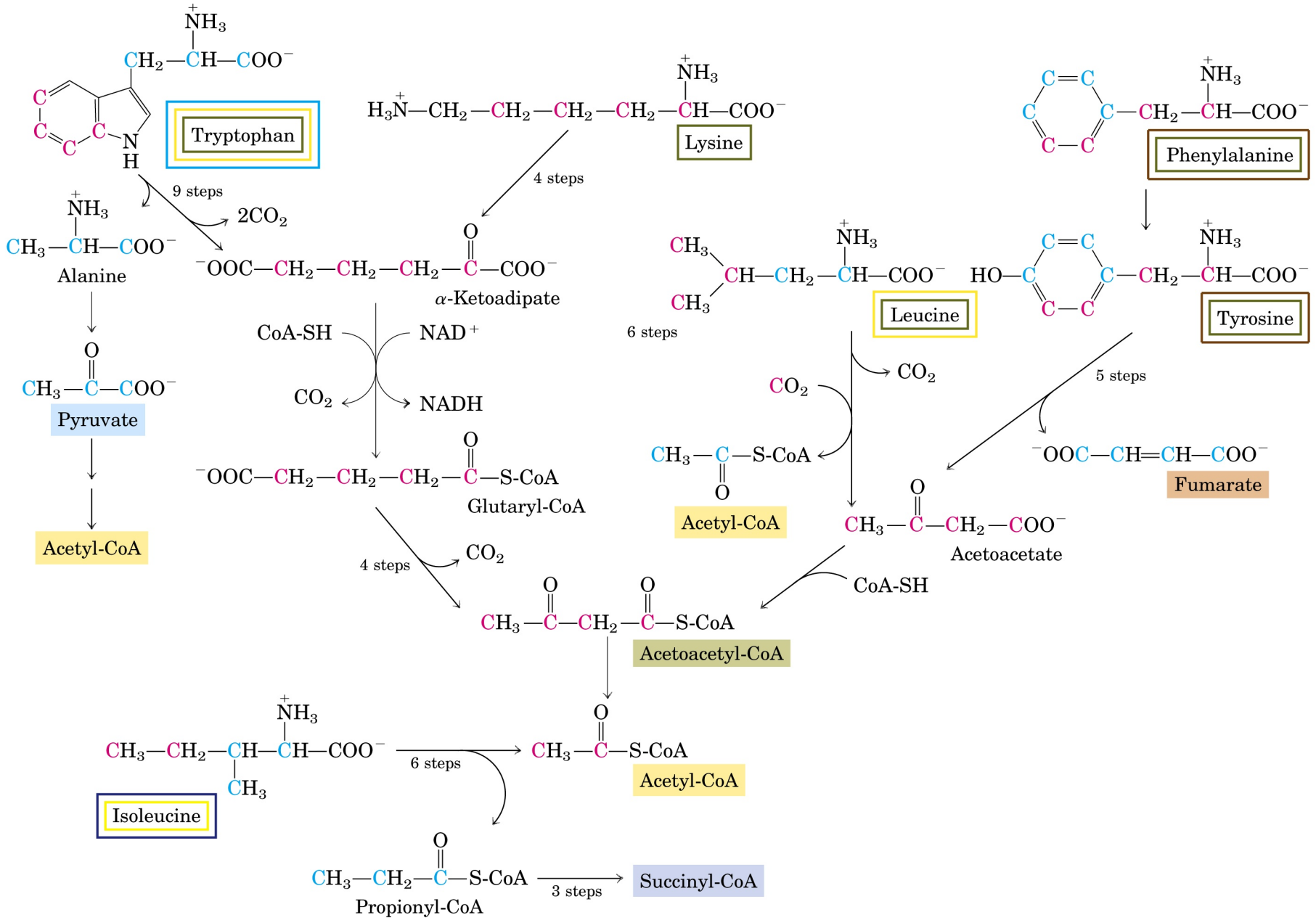

AMP
ATP
$PP_i$
1
Citrullina
AMP
Citrullil-AMP
Aspartato
AMP
2
Argininosuccinato

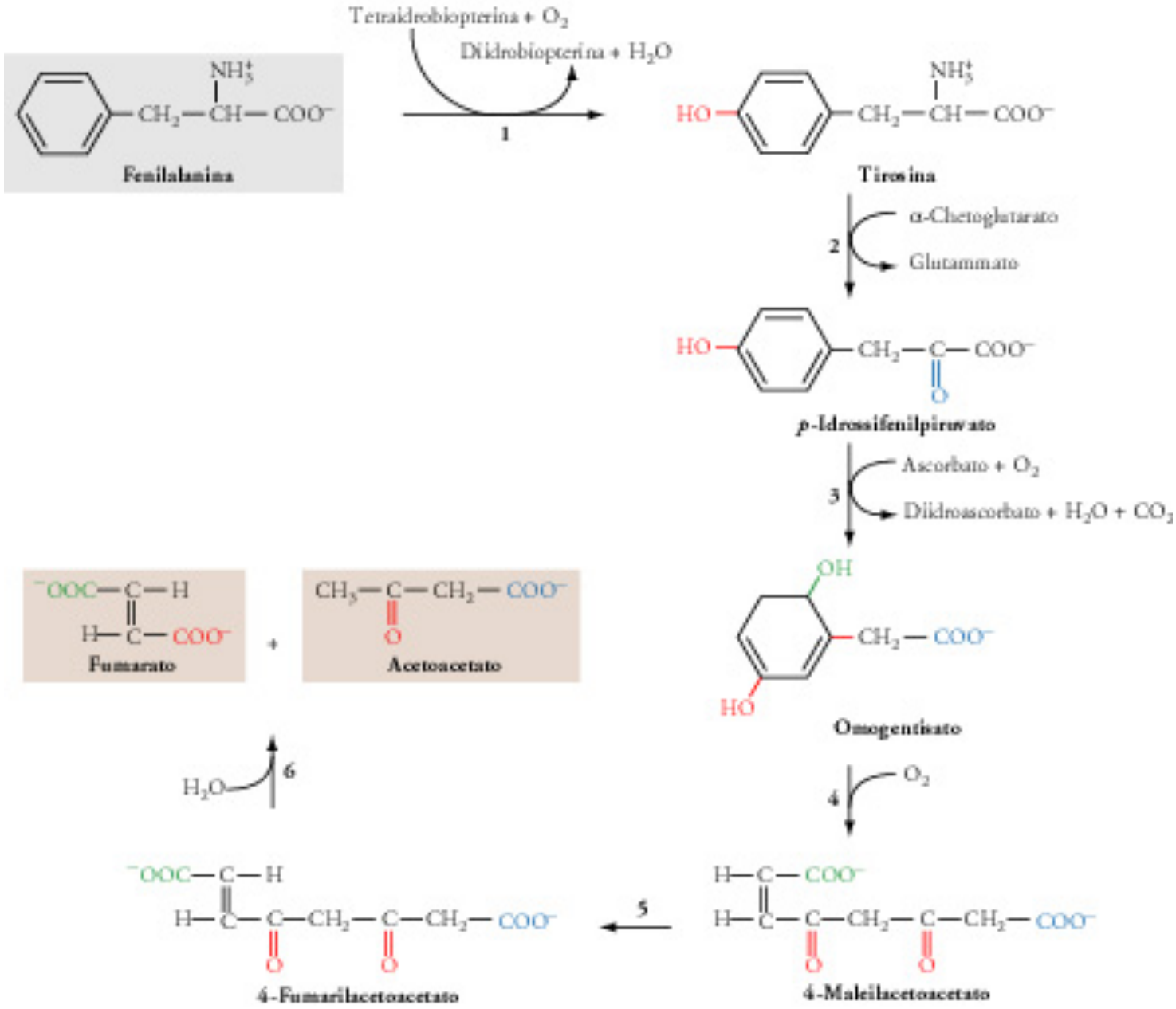

Fumarate
Malate
NAD+
NADH
Oxaloacetate
Arginino-
succinate
Arginine
Urea
Urea
cycle
Ornithine
Aspartate-
arginino-
succinate
shunt of
citric acid
cycle
Aspartate
Citrulline
Cytosol
Citrulline
Ornithine
Aspartate
α-Ketoglutarate
Glutamate
Carbamoyl
phosphate
Oxaloacetate
NADH
NAD+
Malate
Citric
acid
cycle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

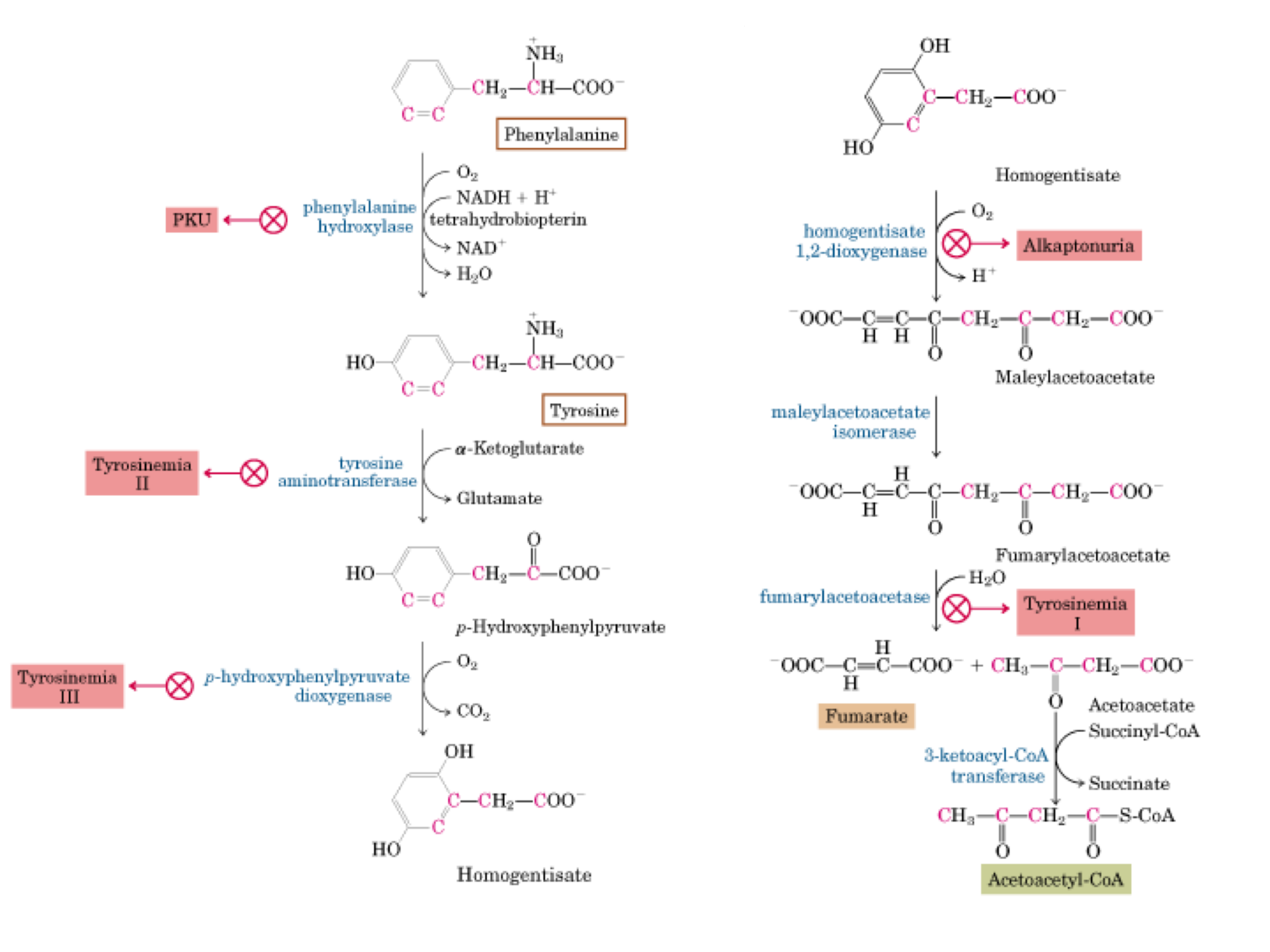

Acetyl-CoA
Glutamate
N-acetylglutamate synthase
CoA-SH
N-Acetylglutamate
2ATP
2ADP + Pi
carbamoyl phosphate synthetase I
Carbamoyl phosphate

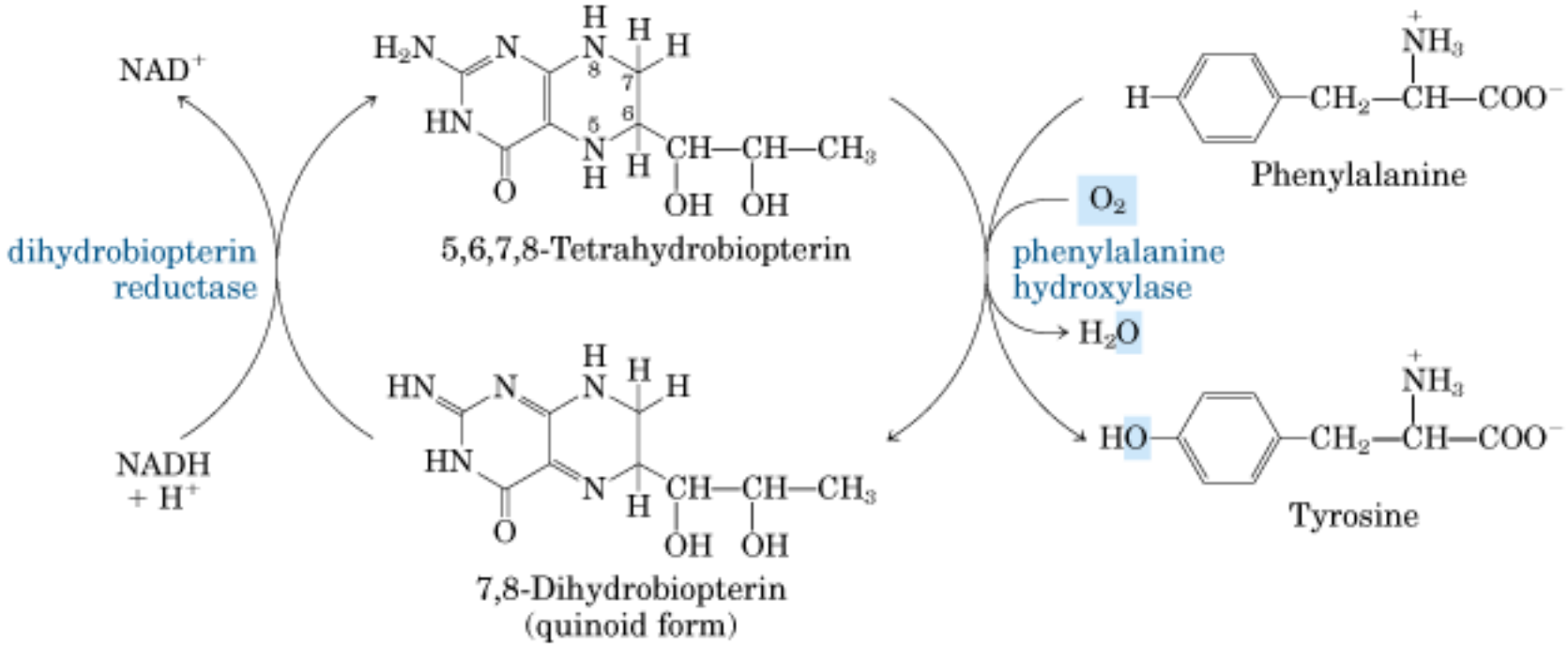

Alanina
Cisteina
Glicina
Serina
Treonina
Triptofano
Isoleucina
Leucina
Lisina
Treonina
Piruvato
$CO_2$
Acetil-CoA
Acetoacetato
Glucosio
Leucina
Lisina
Fenilalanina
Triptofano
Tirosina
Asparagina
Aspartato
Ossalacetato
Citrato
Aspartato
Fenilalanina
Tirosina
Fumarato
Ciclo dell'acido citrico
Isocitrato
$CO_2$
Succinil-CoA
α-Chetoglutarato
$CO_2$
Isoleucina
Metionina
Valina
Arginina
Glutammato
Glutammina
Istidina
Prolina

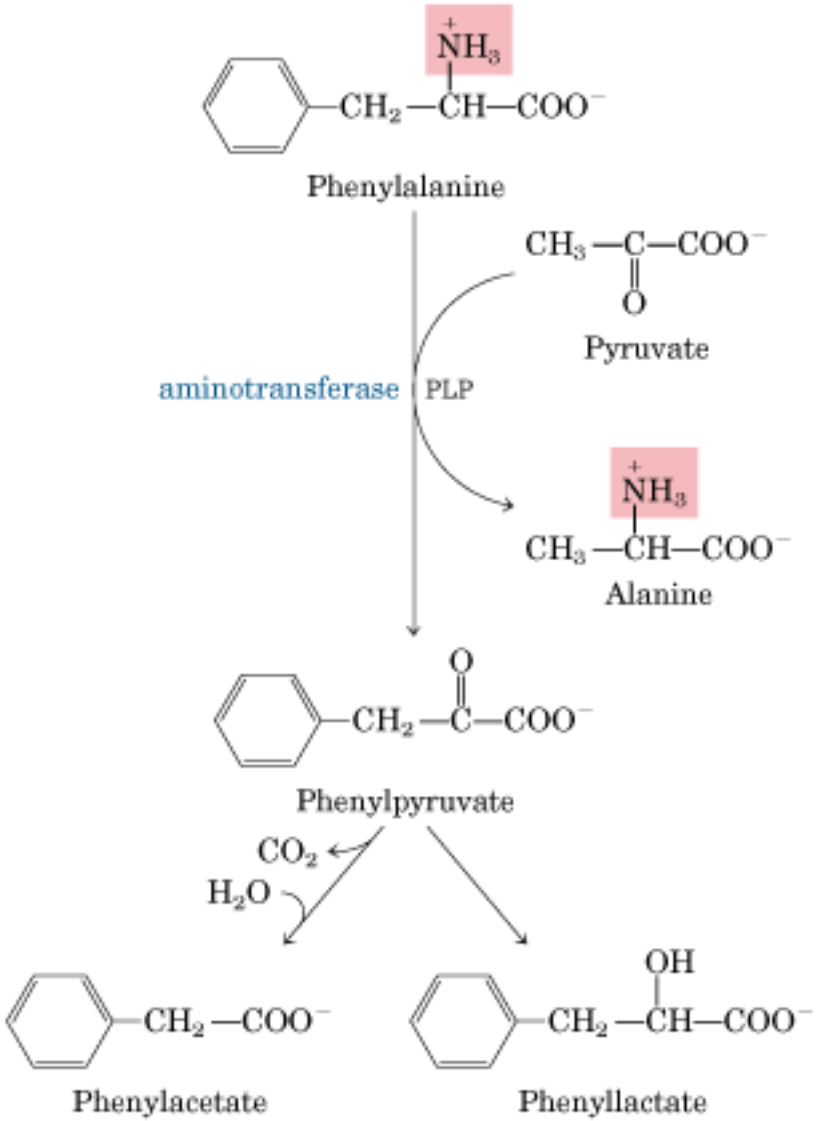

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Arginine
Glutamine
Histidine
Proline
Glutamate
Isocitrate
α-Ketoglutarate
Isoleucine
Methionine
Threonine
Valine
Acetoacetyl-CoA
Citrate
Citric acid cycle
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
Malate
Pyruvate
Glucose
Alanine
Cysteine
Glycine
Serine
Tryptophan
Isoleucine
Leucine
Tryptophan
Asparagine
Aspartate


Tryptophan
9 steps
2CO2
Alanine
Pyruvate
Acetyl-CoA
Lysine
4 steps
α-Ketoadipate
CoA-SH
NAD+
CO2
NADH
Glutaryl-CoA
4 steps
CO2
Leucine
6 steps
CO2
CO2
Acetyl-CoA
Phenylalanine
Tyrosine
5 steps
Fumarate
Acetoacetate
CoA-SH
Acetoacetyl-CoA
Isoleucine
6 steps
Acetyl-CoA
Propionyl-CoA
3 steps
Succinyl-CoA


Tetraidrobiopterina + $O_2$
Diidrobiopterina + $H_2O$
1
Fenilalanina
Tirosina
2
α-Chetoglutarato
Glutammato
p-Idrossifenilpiruvato
3
Ascorbato + $O_2$
Diidroascorbato + $H_2O$ + $CO_2$
Omogentisato
4
$O_2$
4-Maleilacetoacetato
5
4-Fumarilacetoacetato
6
$H_2O$
Fumarato
+
Acetoacetato


Phenylalanine
PKU
phenylalanine hydroxylase
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
Tyrosine
Tyrosinemia II
tyrosine aminotransferase
α-Ketoglutarate
Glutamate
p-Hydroxyphenylpyruvate
Tyrosinemia III
p-hydroxyphenylpyruvate dioxygenase
O2
CO2
Homogentisate
Homogentisate
homogentisate 1,2-dioxygenase
O2
H+
Alkaptonuria
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
H2O
Tyrosinemia I
Fumarate
Acetoacetate
3-ketoacyl-CoA transferase
Succinyl-CoA
Succinate
Acetoacetyl-CoA


NAD+
NADH
+ H+
dihydrobiopterin
reductase
5,6,7,8-Tetrahydrobiopterin
7,8-Dihydrobiopterin
(quinoid form)
O2
phenylalanine
hydroxylase
H2O
Phenylalanine
Tyrosine


Phenylalanine
Pyruvate
aminotransferase
PLP
Alanine
Phenylpyruvate
$CO_2$
$H_2O$
Phenylacetate
Phenyllactate

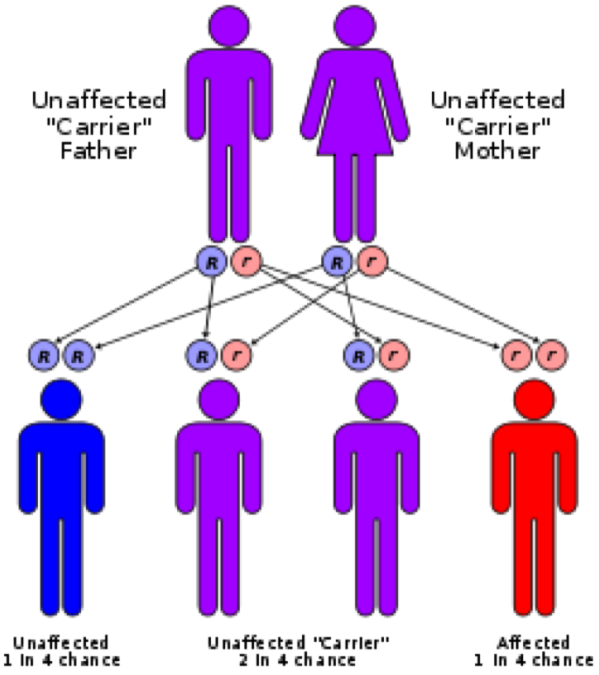

Unaffected
"Carrier"
Father
Unaffected
"Carrier"
Mother
R
r
R
r
R R
R r
R r
r r
Unaffected
1 in 4 chance
Unaffected "Carrier"
2 in 4 chance
Affected
1 in 4 chance

table 18–2

**Some Human Genetic Disorders Affecting Amino Acid Catabolism**

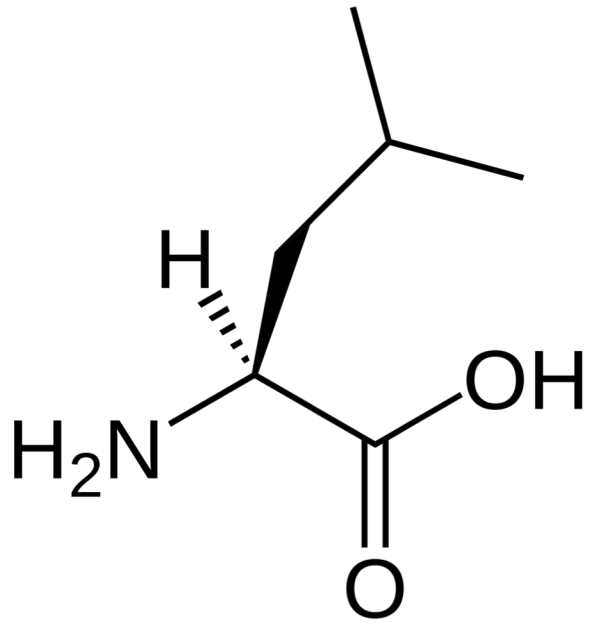
| Medical condition | Approximate incidence (per 100,000 births) | Defective process | Defective enzyme | Symptoms and effects |
|---|---|---|---|---|
| Albinism | 3 | Melanin synthesis from tyrosine | Tyrosine 3-mono-oxygenase (tyrosinase) | Lack of pigmentation; white hair, pink skin |
| Alkaptonuria | 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 | Argininosuccinate lyase | 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 $\beta$-synthase | Faulty bone development, mental retardation |
| Maple syrup urine disease (branched-chain ketoaciduria) | 0.4 | Isoleucine, leucine, and valine degradation | Branched-chain $\alpha$-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 phenyl-alanine to tyrosine | Phenylalanine hydroxylase | Neonatal vomiting; mental retardation |

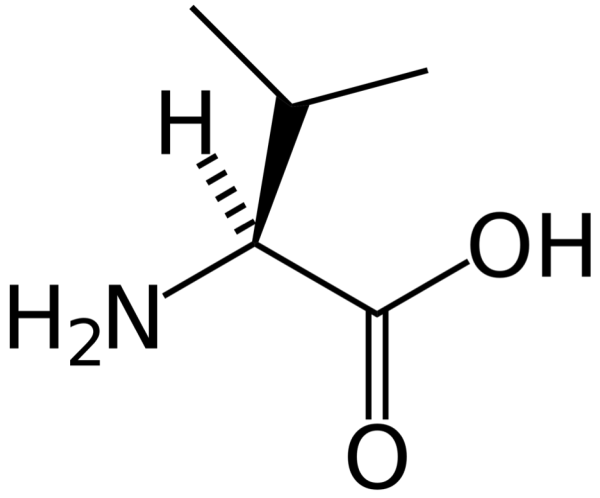
table 18–1

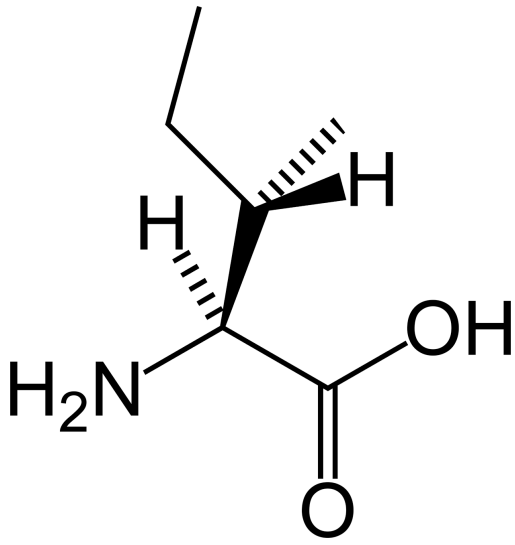
## Nonessential and Essential Amino Acids for Humans and the Albino Rat

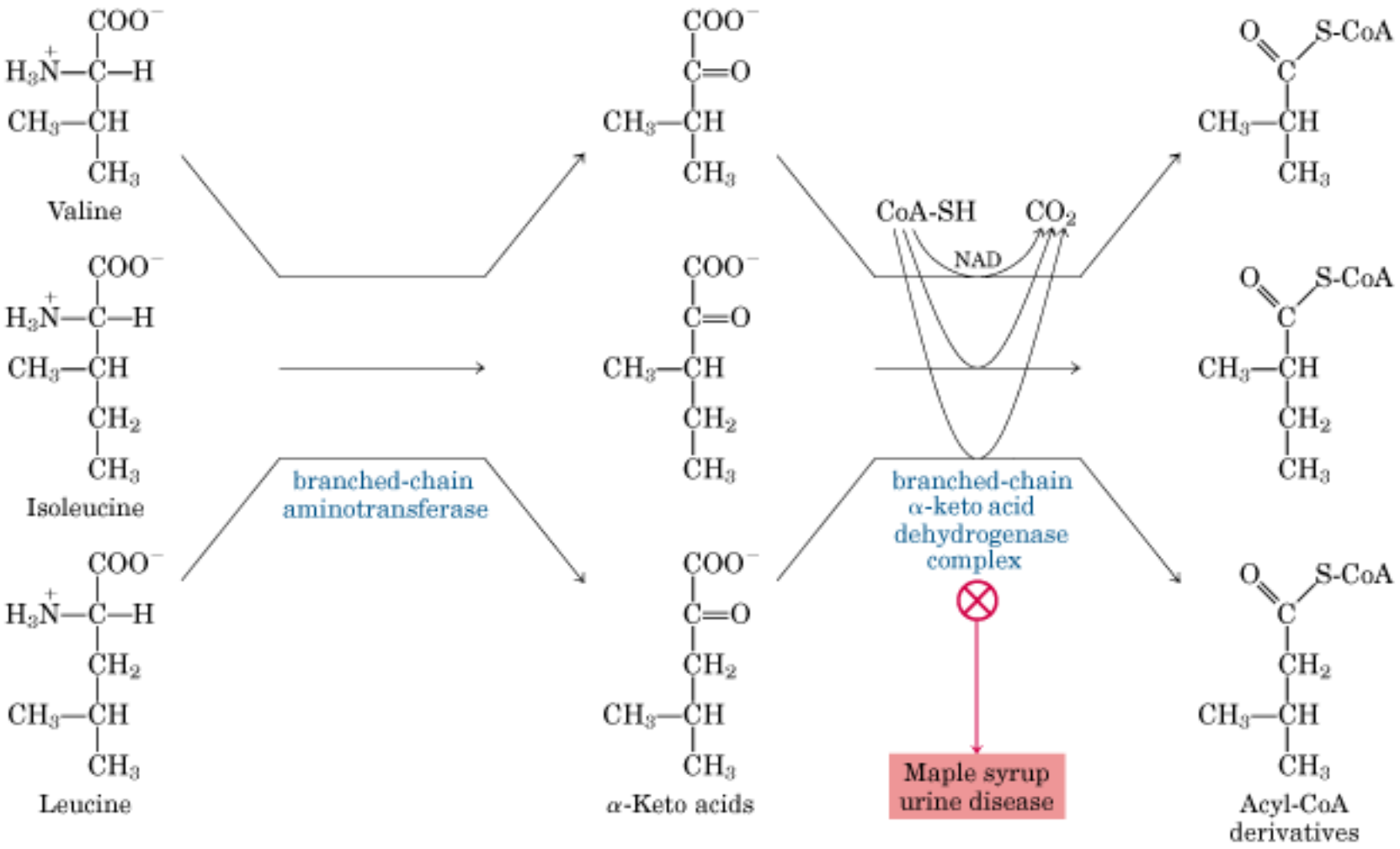
| Nonessential | Essential |
|---|---|
| Alanine | Arginine* |
| Asparagine | Histidine |
| Aspartate | Isoleucine |
| Cysteine | Leucine |
| Glutamate | Lysine |
| Glutamine | Methionine |
| Glycine | Phenylalanine |
| Proline | Threonine |
| Serine | Tryptophan |
| Tyrosine | Valine |

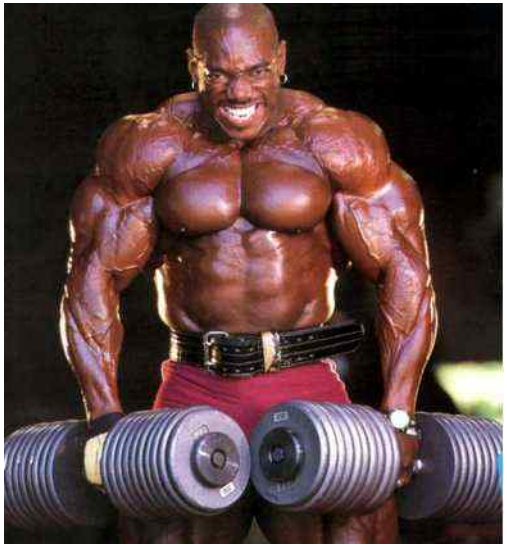
*Essential in young, growing animals but not in adults.


H
OH
$H_2N$
O


H
OH
$H_2N$
O

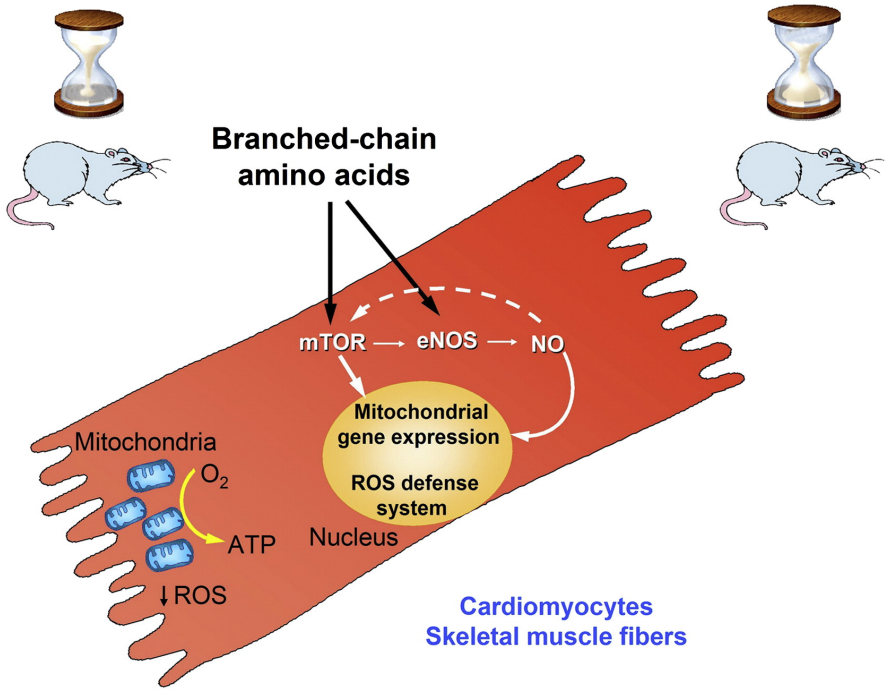

H
H
OH
$H_2N$
O


Valine
Isoleucine
Leucine
branched-chain aminotransferase
α-Keto acids
CoA-SH
CO2
NAD
branched-chain α-keto acid dehydrogenase complex
Maple syrup urine disease
S-CoA
Acyl-CoA derivatives



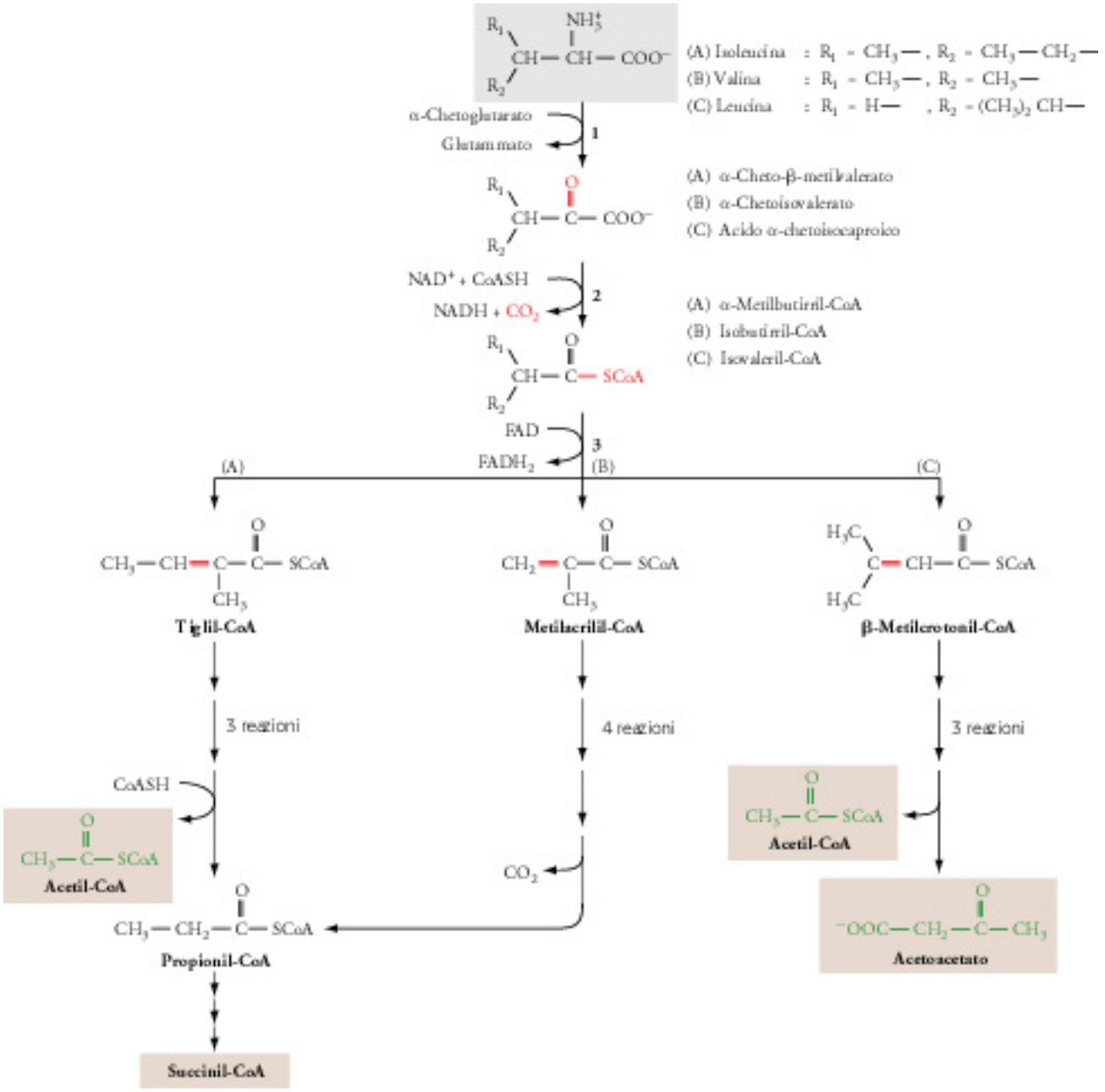

SCITEC NUTRITION
THE MOST ESSENTIAL BCAA
MUSCLE AMINO ACIDS
BCAA
6400
200 TABLETS
DIETARY SUPPLEMENT

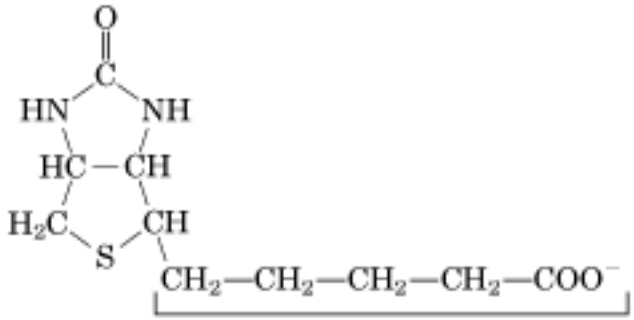
# Branched-Chain Amino Acid Supplementation Promotes Survival and Supports Cardiac and Skeletal Muscle Mitochondrial Biogenesis in Middle-Aged Mice



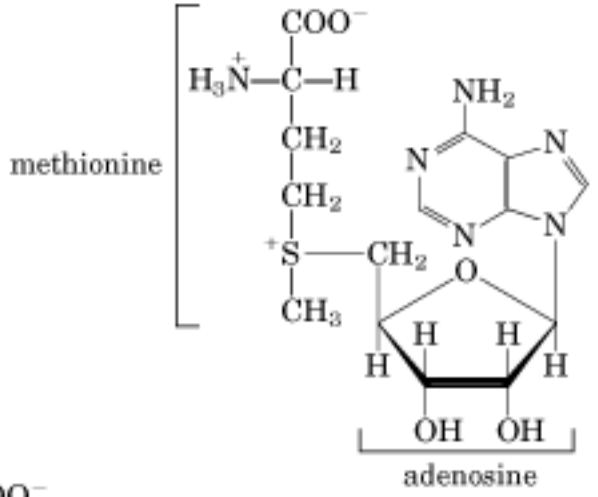

## Highlights

► BCAAem supplementation increases the average life span of male mice ► BCAAem activates mTOR and eNOS signaling pathways ► BCAAem increases mitochondrial biogenesis and ROS defense system in middle-aged mice ► BCAAem supplementation improves age-related muscle deficits

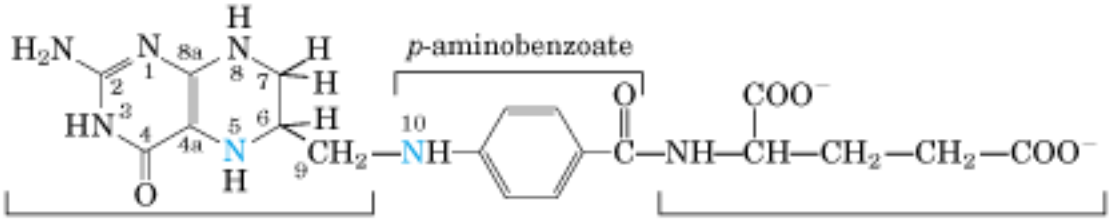

(A) Isoleucina : R1 = CH3—, R2 = CH3—CH2—
(B) Valina : R1 = CH3—, R2 = CH3—
(C) Leucina : R1 = H—, R2 = (CH3)2 CH—
α-Chetoglutarato
Glutammato
1
(A) α-Cheto-β-metilvalerato
(B) α-Chetoisovalerato
(C) Acido α-chetoisocaproico
NAD+ + CoASH
NADH + CO2
2
(A) α-Metilbutiril-CoA
(B) Isobutiril-CoA
(C) Isovaleril-CoA
FAD
FADH2
3
(A)
(B)
(C)
Tiglil-CoA
Metilacrilil-CoA
β-Metilcrotonil-CoA
3 reazioni
4 reazioni
3 reazioni
CoASH
Acetil-CoA
CO2
Acetil-CoA
Propionil-CoA
Acetoacetato
Succinil-CoA



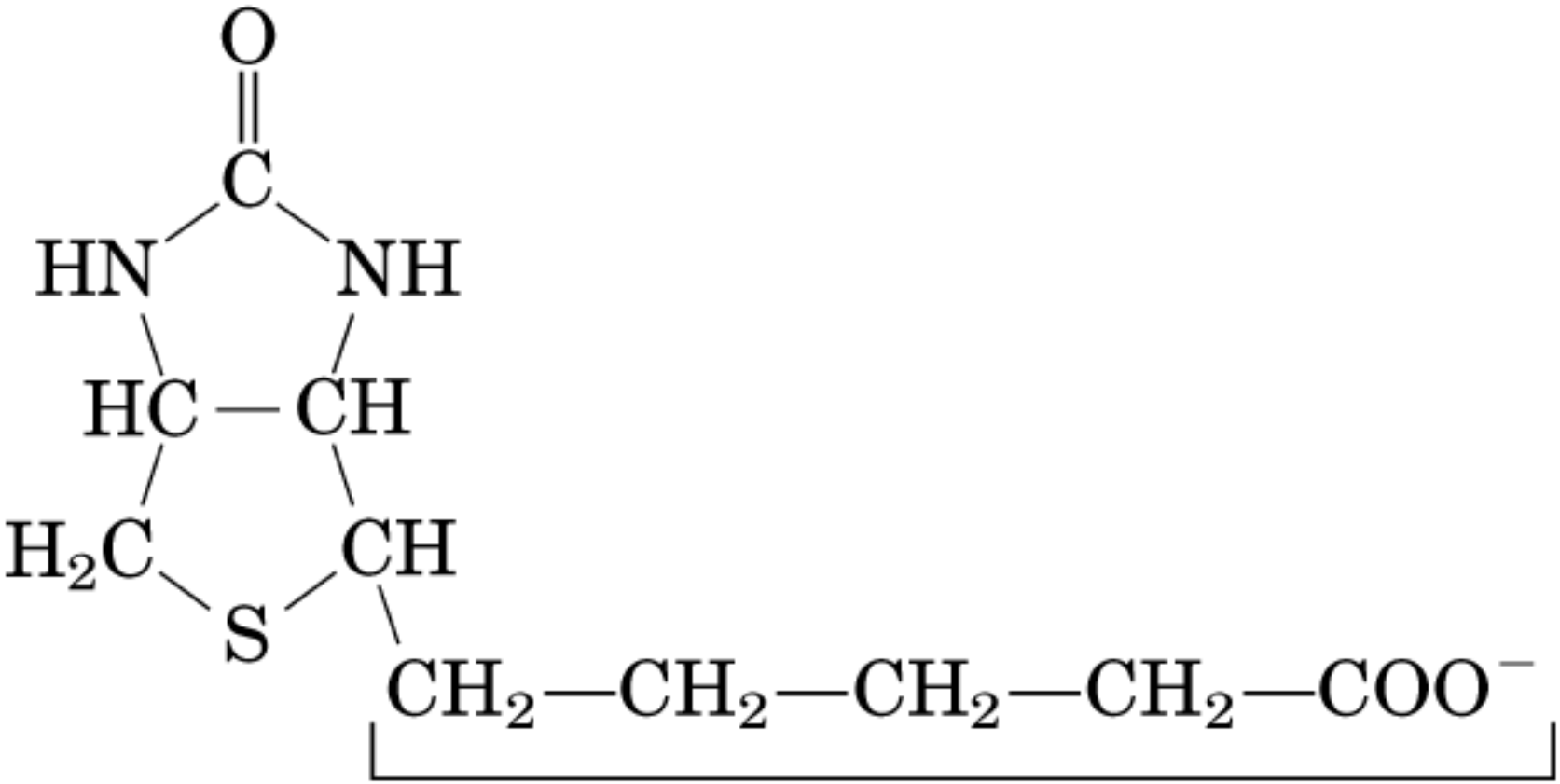

Biotin



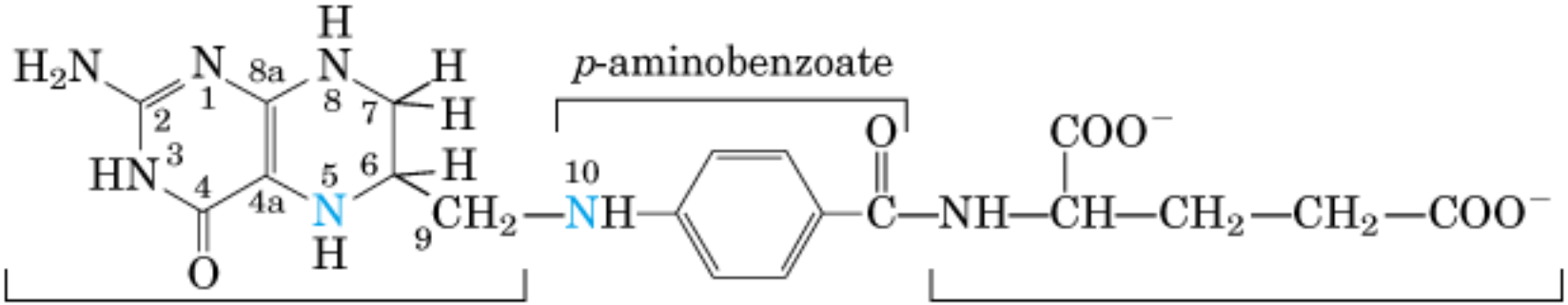

*S*-Adenosylmethionine (adoMet)



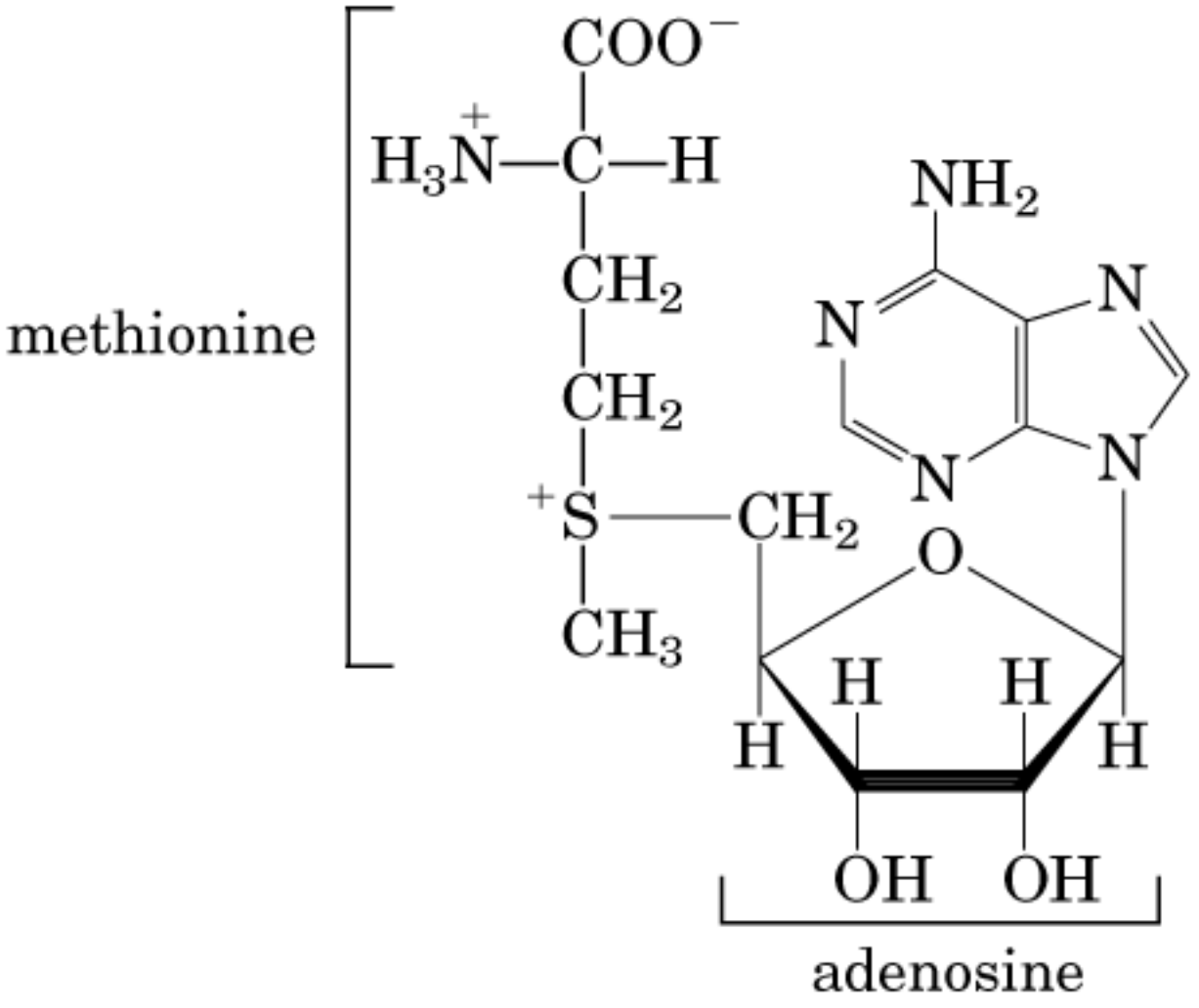

Tetrahydrofolate ($H_4$ folate)



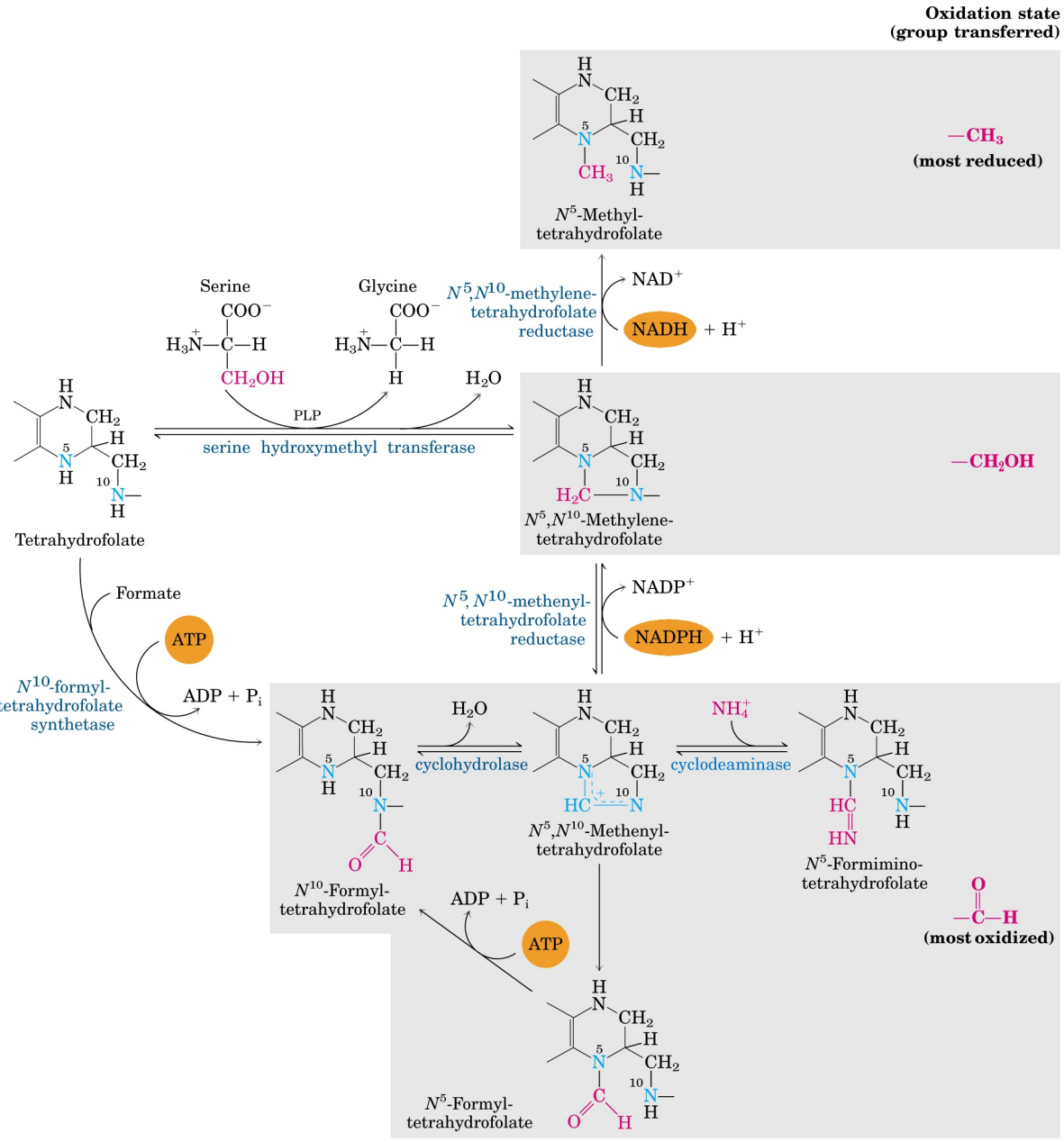

Biotin

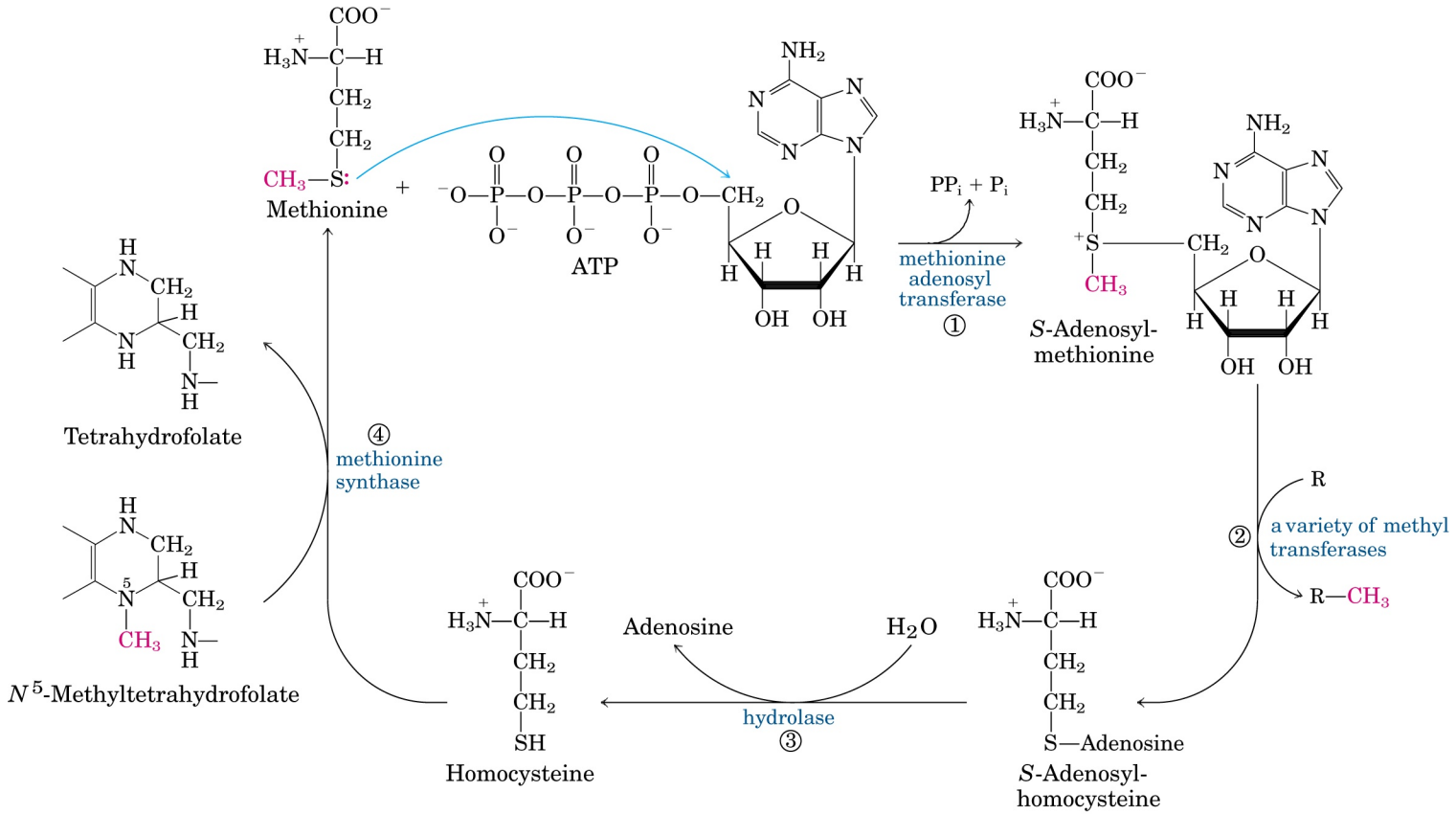



Tetrahydrofolate ($H_4$ folate)




*S*-Adenosylmethionine (adoMet)


Oxidation state
(group transferred)
$N^5$-Methyl-
tetrahydrofolate
—CH3
(most reduced)
Serine
Glycine
$N^5,N^{10}$-methylene-
tetrahydrofolate
reductase
NAD+
NADH + H+
PLP
H2O
serine hydroxymethyl transferase
Tetrahydrofolate
$N^5,N^{10}$-Methylene-
tetrahydrofolate
—CH2OH
Formate
ATP
ADP + Pi
$N^{10}$-formyl-
tetrahydrofolate
synthetase
$N^5,N^{10}$-methenyl-
tetrahydrofolate
reductase
NADP+
NADPH + H+
H2O
cyclohydrolase
NH4+
cyclodeaminase
$N^{10}$-Formyl-
tetrahydrofolate
$N^5,N^{10}$-Methenyl-
tetrahydrofolate
$N^5$-Formimino-
tetrahydrofolate
—C—H
(most oxidized)
ADP + Pi
ATP
$N^5$-Formyl-
tetrahydrofolate


Methionine
ATP
PPi + Pi
methionine adenosyl transferase
①
S-Adenosyl-methionine
②
a variety of methyl transferases
R
R—CH3
S-Adenosyl-homocysteine
hydrolase
③
Adenosine
H2O
Homocysteine
④
methionine synthase
Tetrahydrofolate
N5-Methyltetrahydrofolate