- Thus far, you have studied various pathways including, Glycolysis, Gluconeogenesis, synthesis and degradation of fatty acids, Pentose phosphate pathway, glycogen synthesis and degradation, Monosaccharides etc. Now we will study the metabolism of amino acids which contribute significantly to the generation of metabolic energy. carnivores 90% herbivores very little.

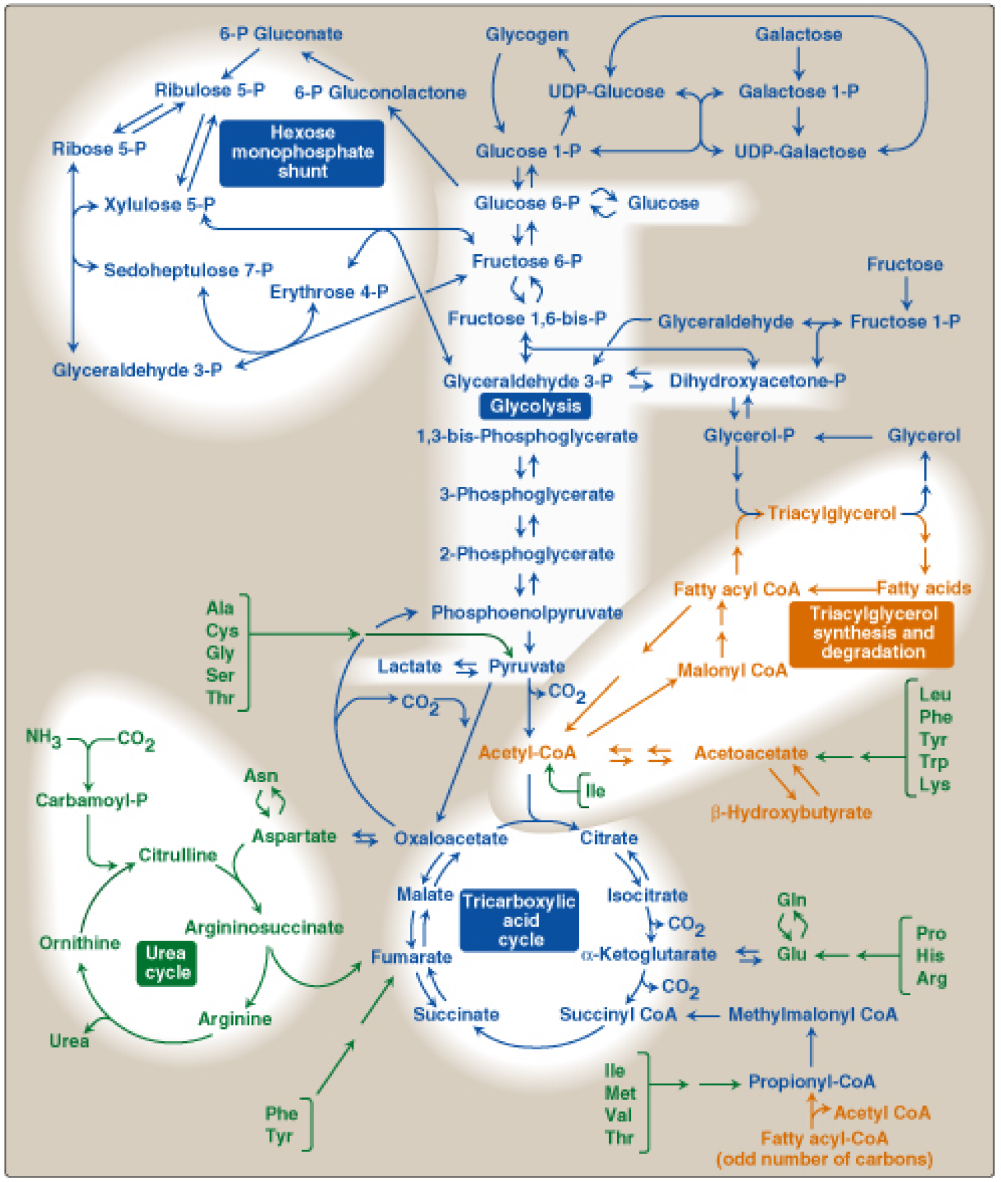
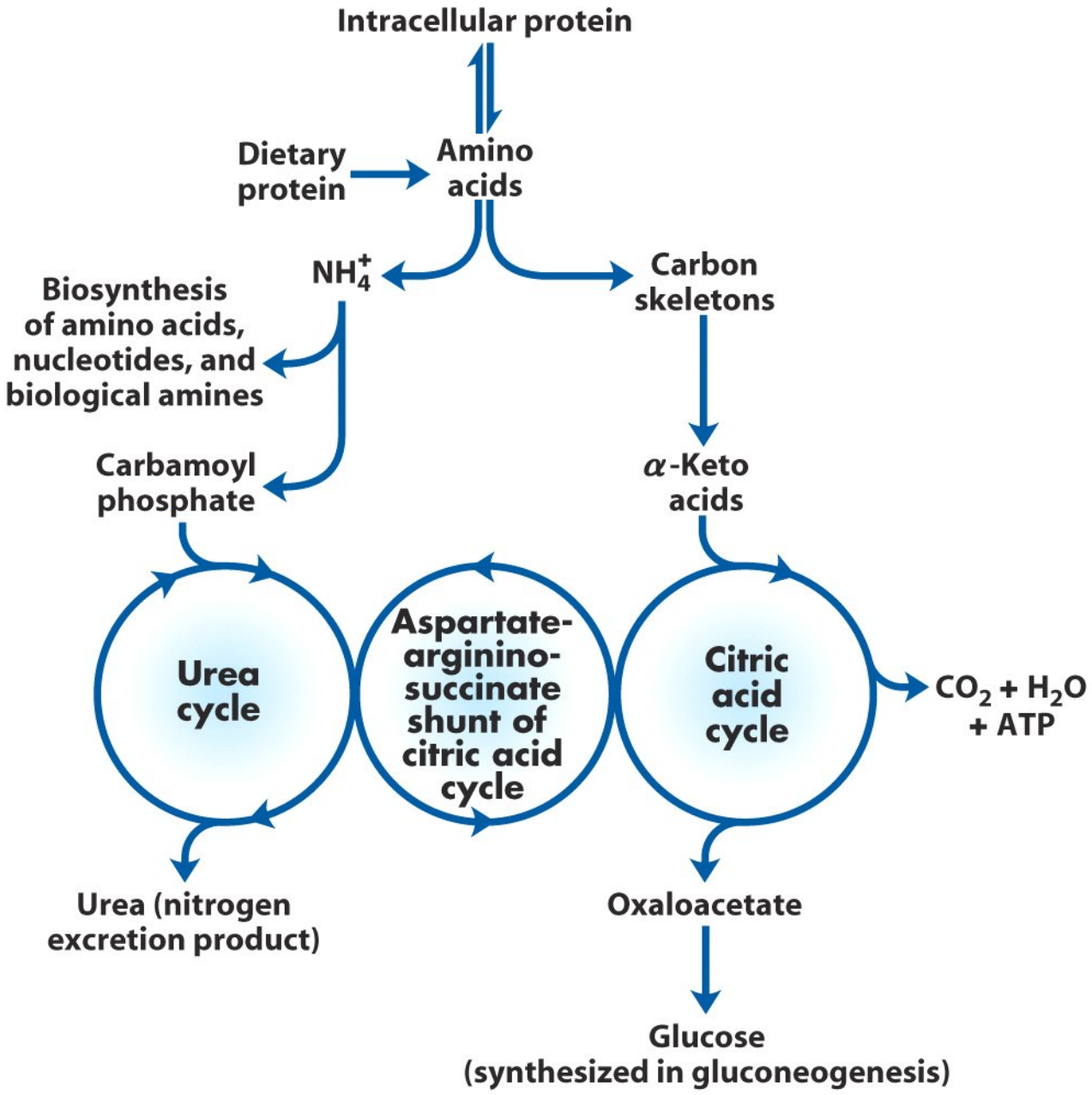
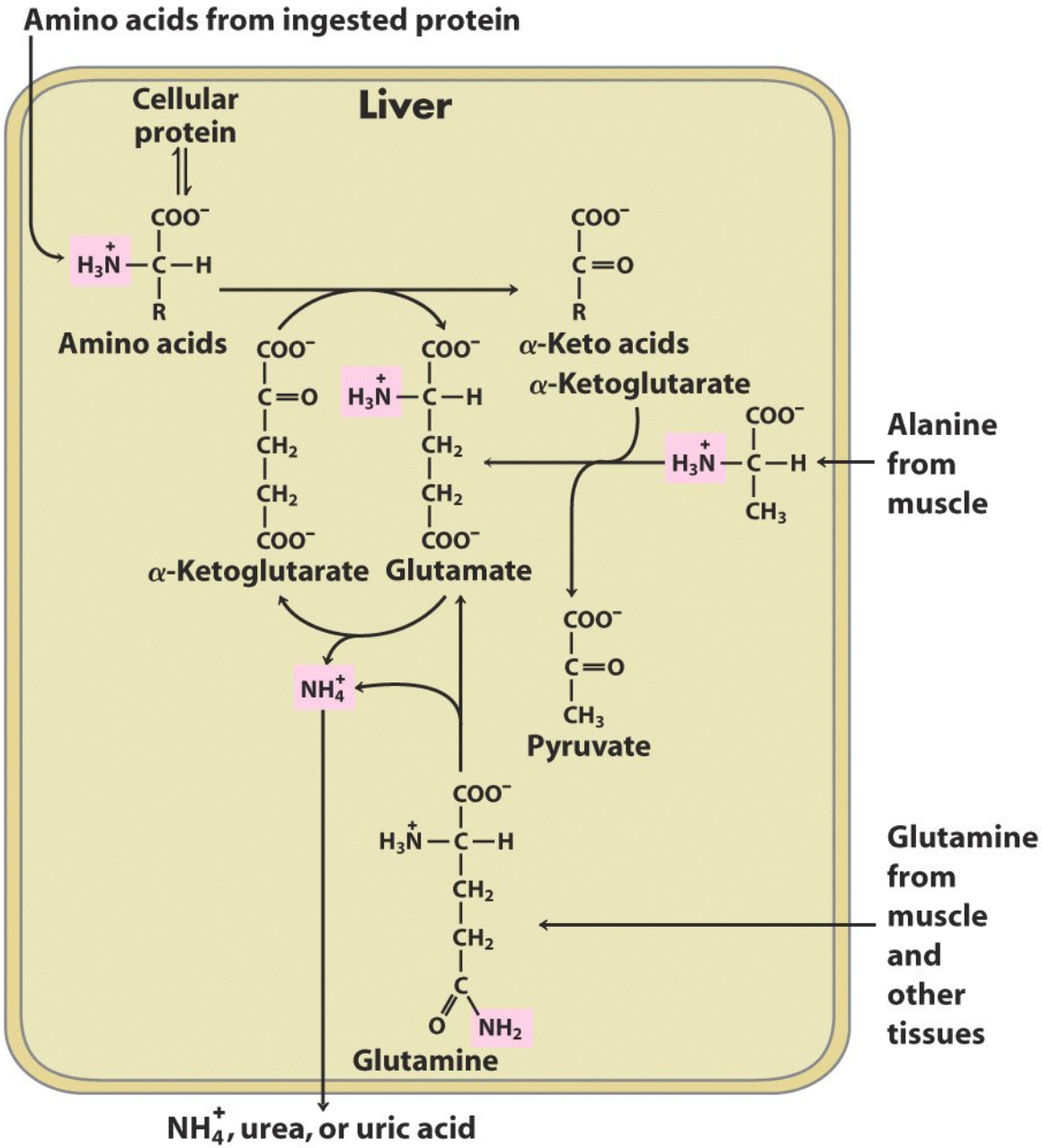
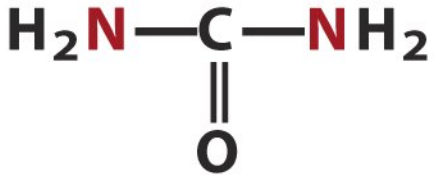


Figure 8.2
Important reactions of intermediary metabolism. Several important pathways to be discussed in later chapters are highlighted. Curved reaction arrows (⟲) indicate forward and reverse reactions that are catalyzed by different enzymes. The straight arrows (⇆) indicate forward and reverse reactions that are catalyzed by the same enzyme. Key: Blue text = intermediates of carbohydrate metabolism; brown text = intermediates of lipid metabolism; green text = intermediates of protein 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 (synthesized in gluconeogenesis)


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

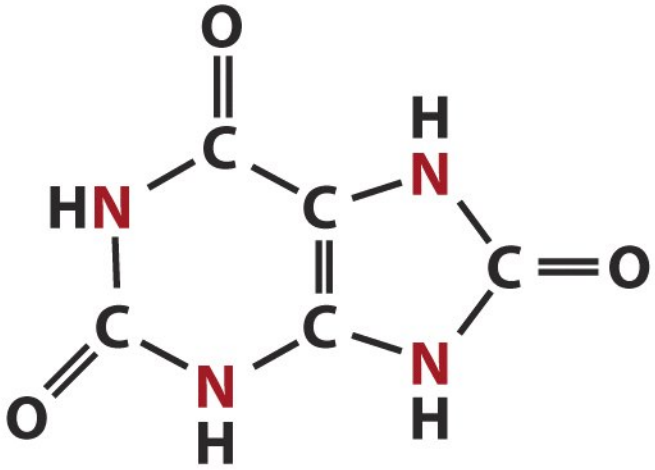
Ammonia (as ammonium ion)



Urea

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

Ureotelic animals: many terrestrial vertebrates; also sharks



Uric acid

Uricotelic animals: birds, reptiles

So lets begin metabolism of amino acids in the dietary protein intake and the enzymes involved in degradation. In humans this occurs in the gastrointestinal tract.

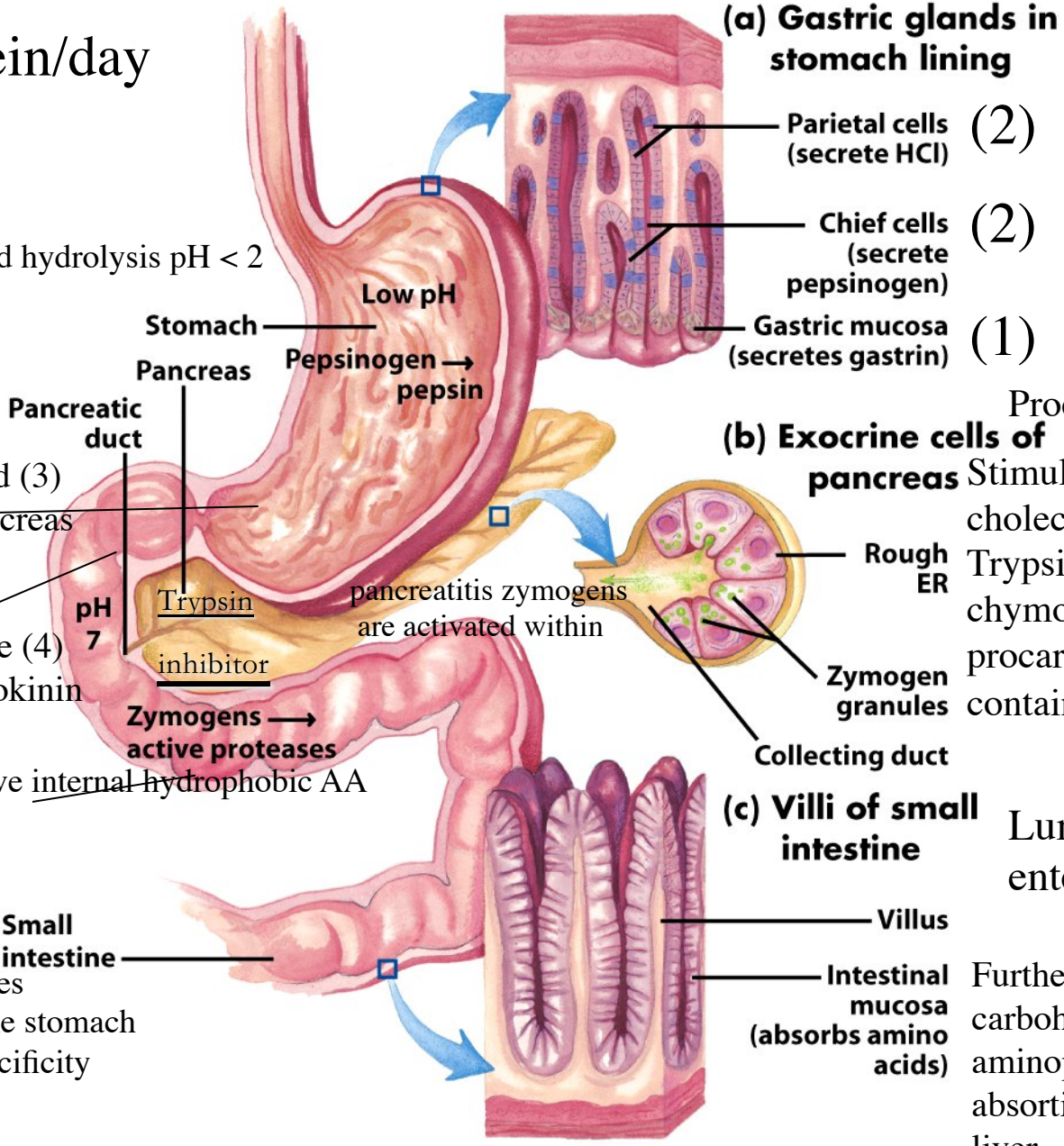
30 g of protein/day

Protein denaturation and hydrolysis pH < 2

Secretin into the blood (3) and stimulated the pancreas to release bicarbonate

amino acids induce the (4) secretion of cholecytokinin

enterepeptidase (6) cleave internal hydrophobic AA converts **trypsin** which activates Trypsinogen, **Chymotrypsinogen**, procarboxypepsidase, and proelastase continues what pepsin started in the stomach different amino acid specificity



(2)

(2)

(1)

Proenzymes (zymogens)

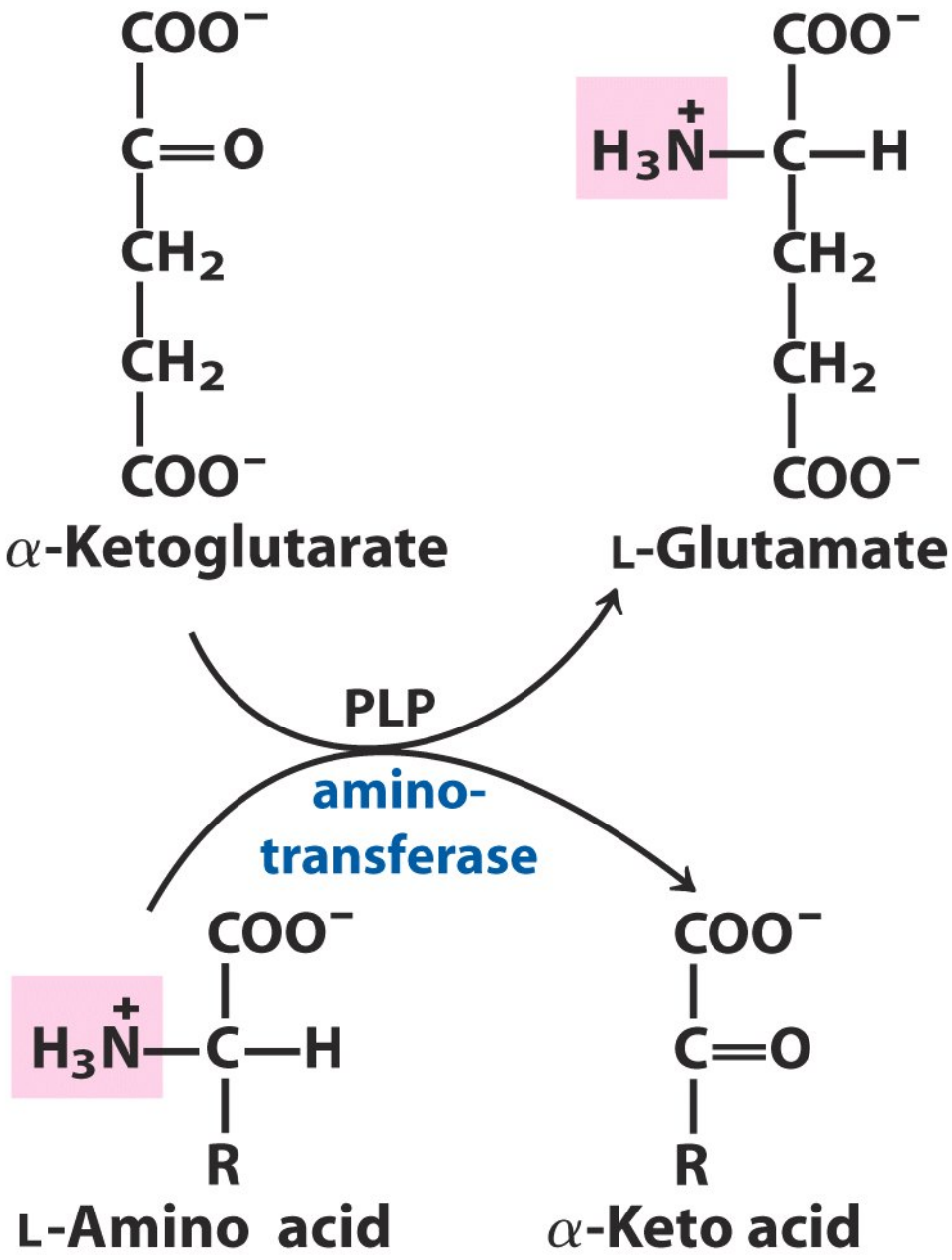
pancreatitis zymogens are activated within

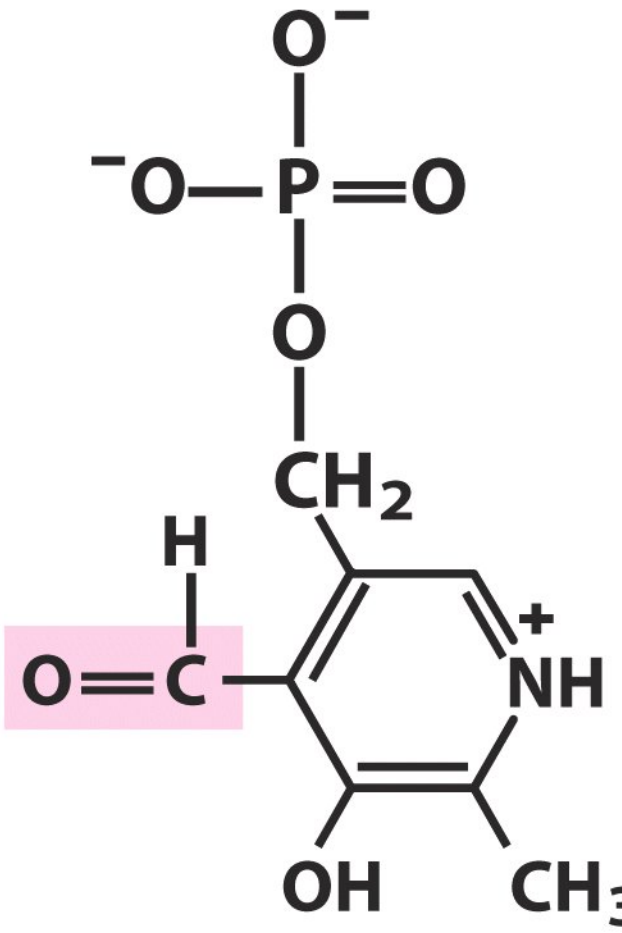
Stimulated by cholecytokinin (5)
Trypsinogen, chymotrypsinogen procarboxypepsidase A&B contain (Zn)

Luminal plasma enterocytes

Further digestion by carbohypeptidase and aminopeptidase (7) absortion and transfer to the liver.

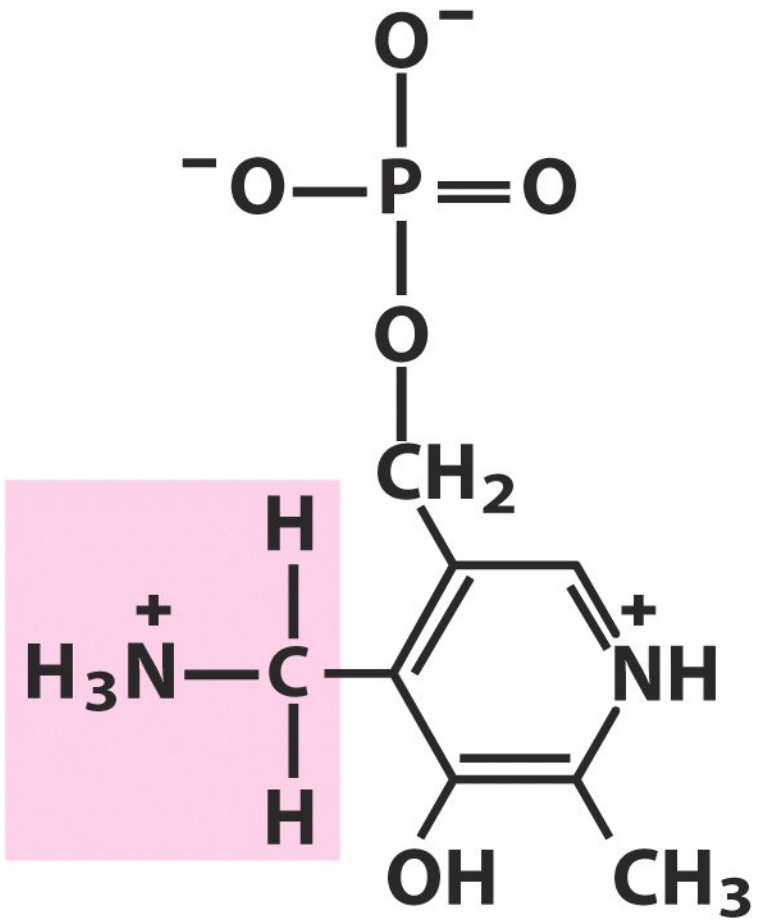
- Once in the liver amino acids are metabolized through the removal of the amino group and consequent formation of the alpha keto acid. The α-amino keep amino acids safe from oxidation. Once removed the N can be incorporated into other molecules or excreted as urea. N can be used for the synthesis of porphyrins, neurotransmitters, hormones, purnes and pyrimidines. The enzymes involved in the removal of the α-amino are called aminotransferases or transaminases.


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



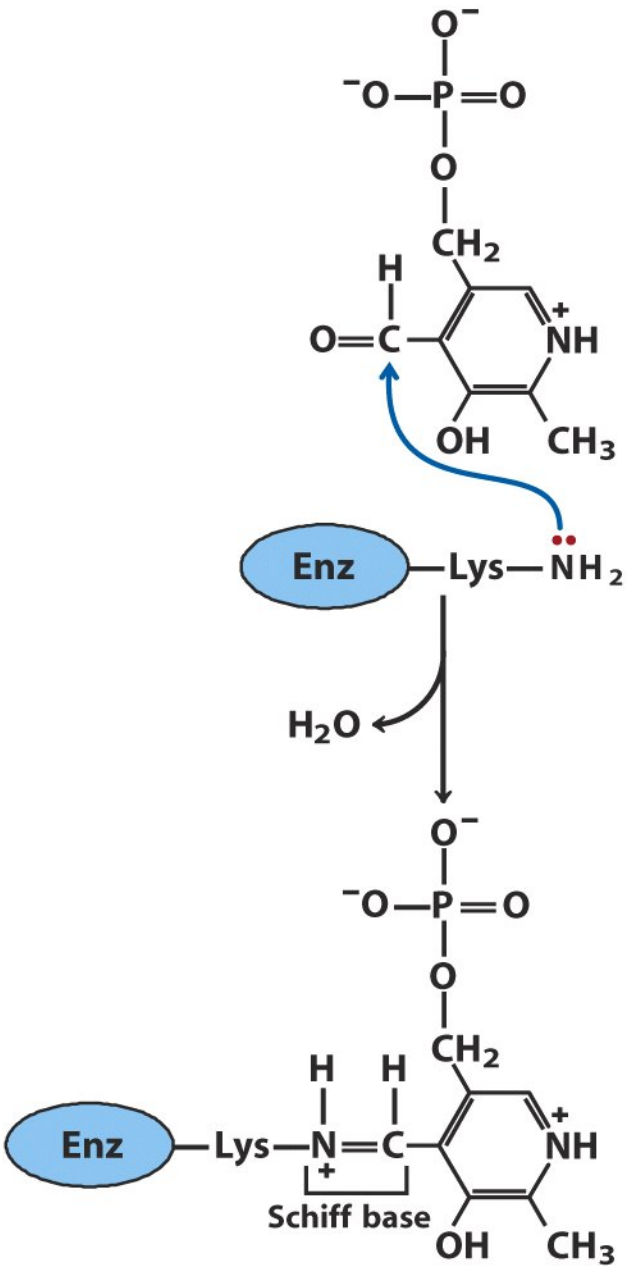
Pyridoxal phosphate (PLP)

Aldehyde form accepts amino groups

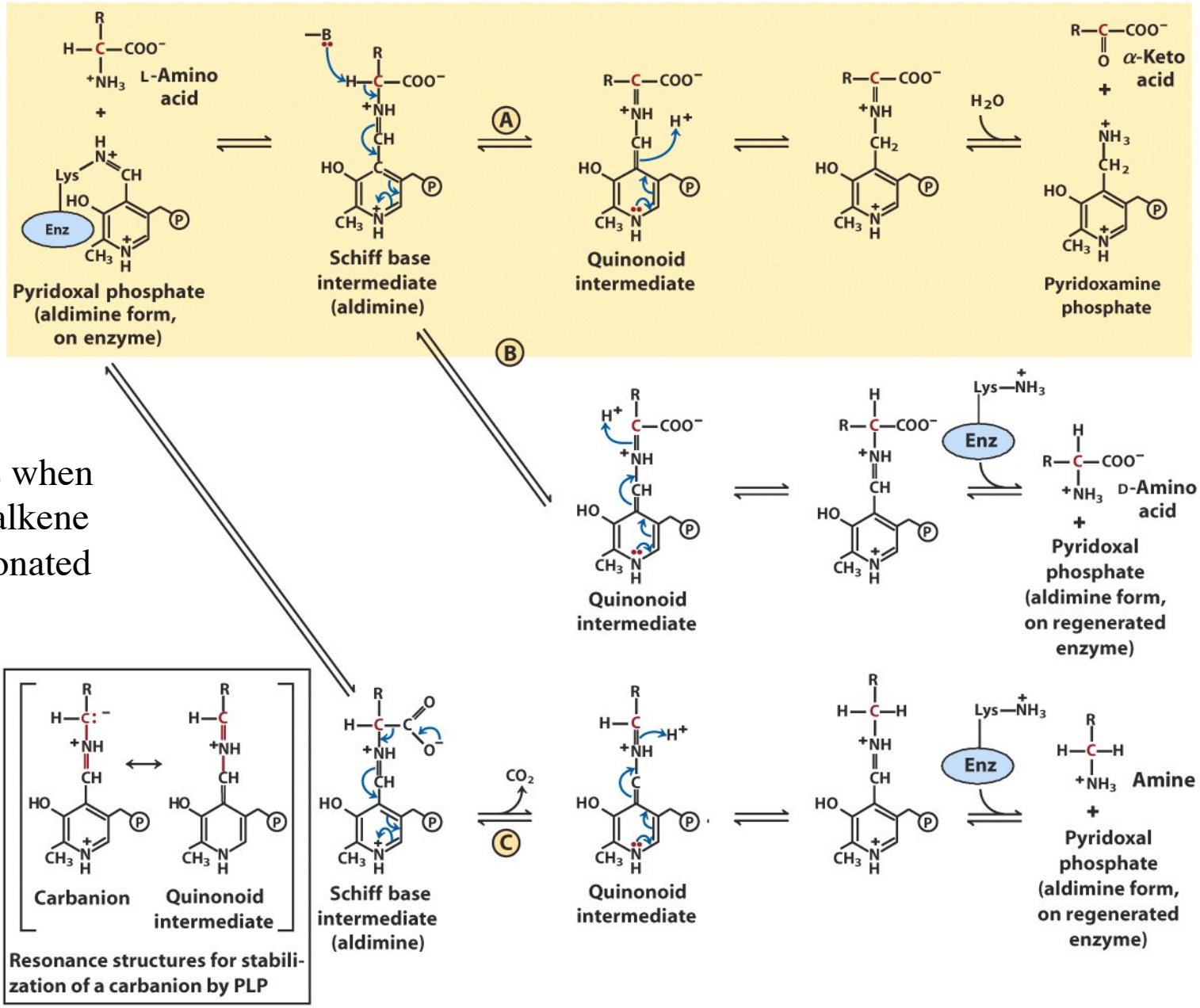


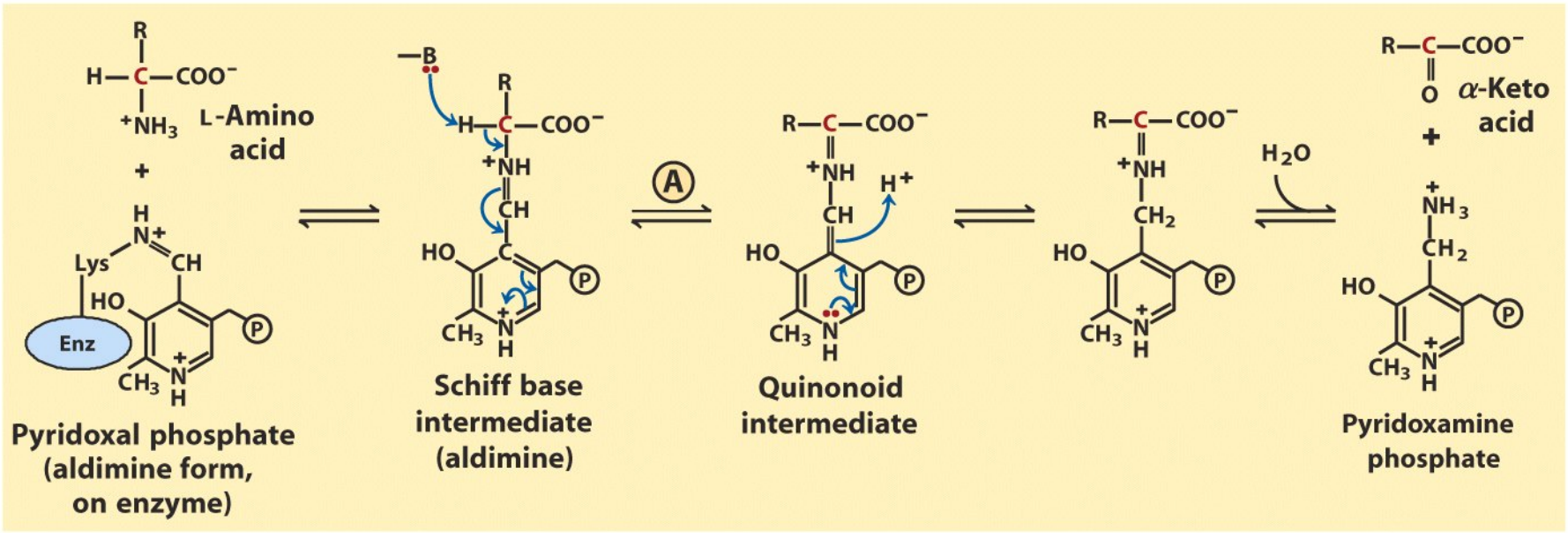
Pyridoxamine phosphate

Aminated form donates to alpha ketoglutarate

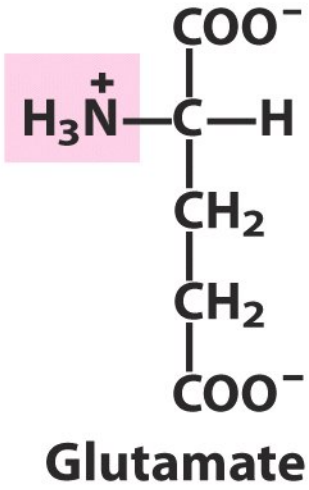

Enz
Lys
NH2
H2O
Enz
Lys
Schiff base
OH
CH3
NH
CH2
O
P
H

Occurs when upper alkene is protonated

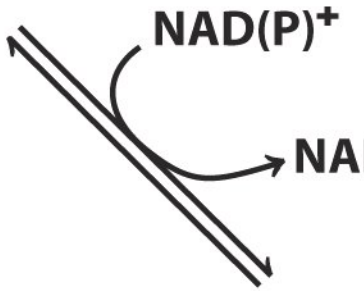



L-Amino acid
Lys
Enz
Pyridoxal phosphate (aldimine form, on enzyme)
Schiff base intermediate (aldimine)
A
Quinonoid intermediate
H2O
α-Keto acid
Pyridoxamine phosphate

oxidative deamination

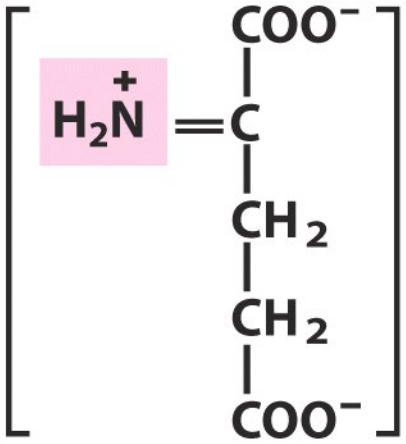


Glutamate

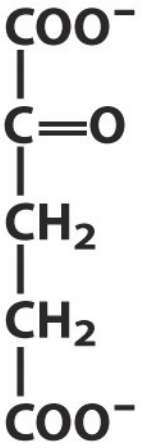


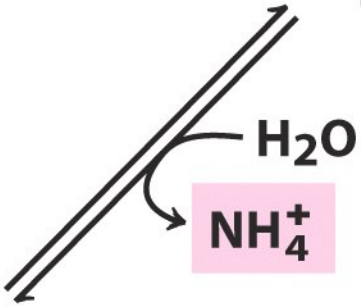
L-glutamate dehydrogenase (+ADP, - GTP)

mutations on the GTP binding site in humans cause hyperinsulinism-hyperammonemia



Glutamate is transfered to the mitochondria in liver where it releases ammonia

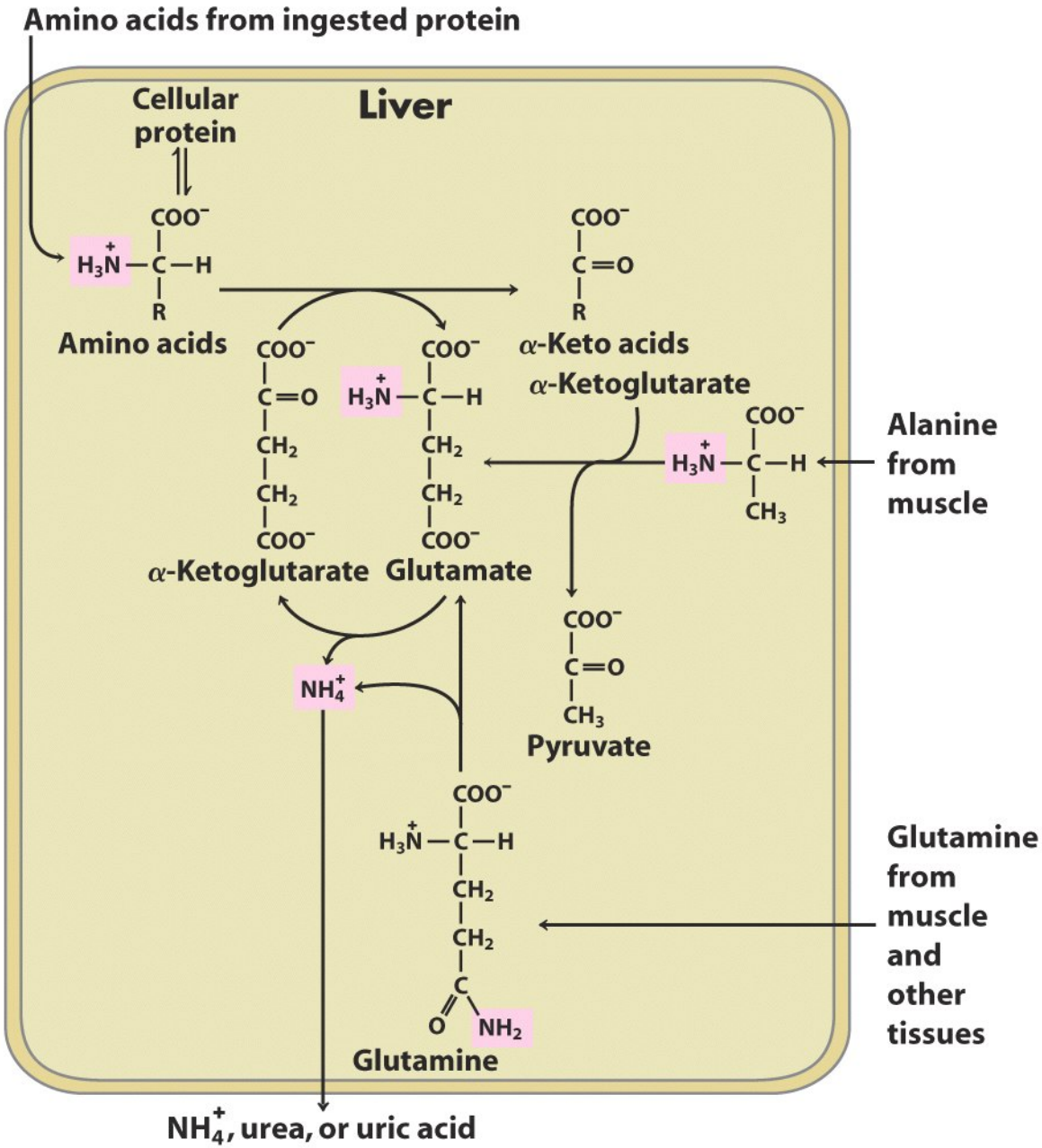




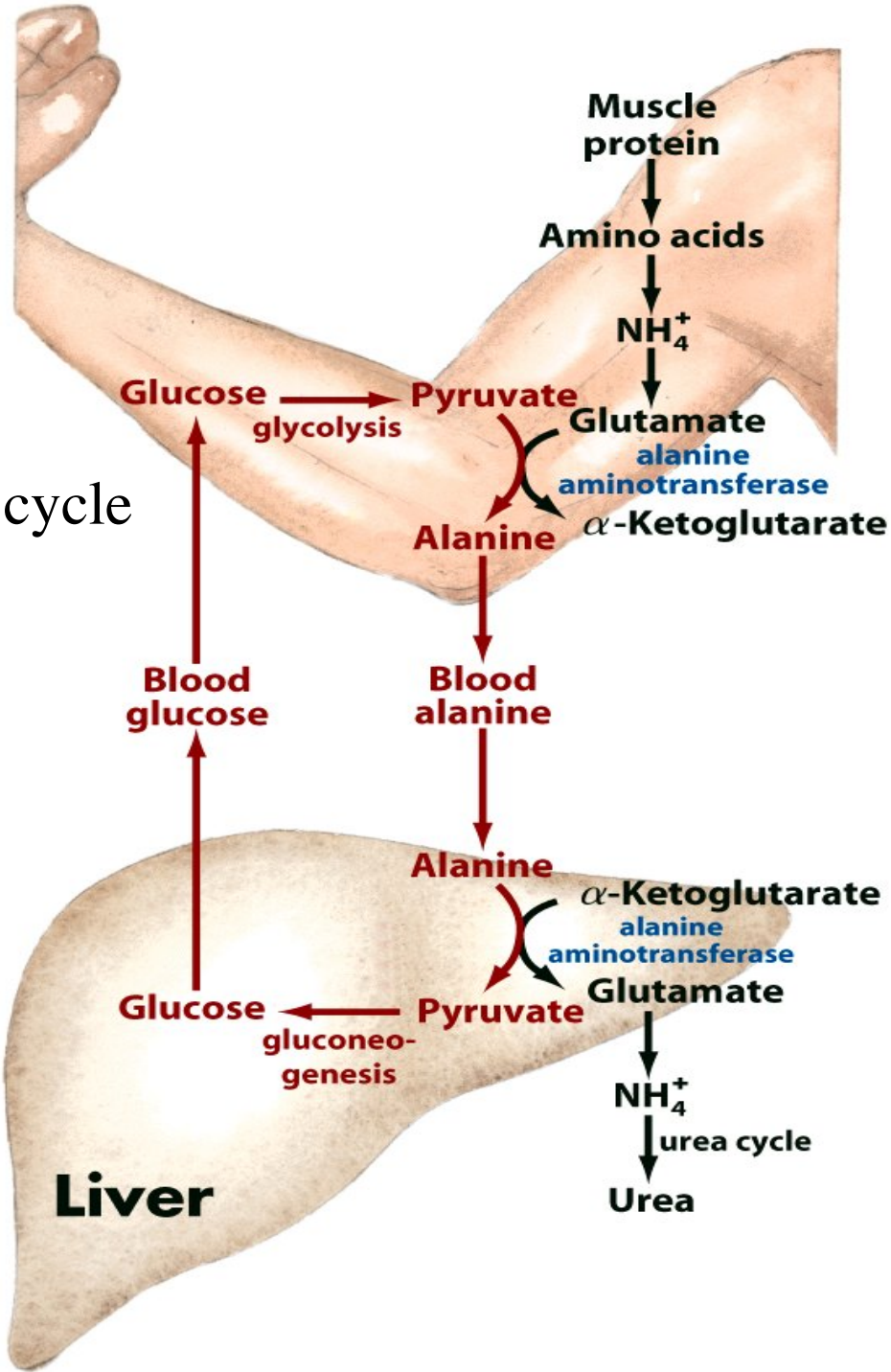
α-Ketoglutarate

Ammonia is toxic to animal tissues (can cause edema in the brain) High levels of Glutamine (osmolarity) low levels of glutamate (- neurotransmiters). and the blood levels are regulated. It is converted to nontoxic forms before exported from extrahepatic tissues. Transported to liver and kidneys. It is transported to the liver in two forms

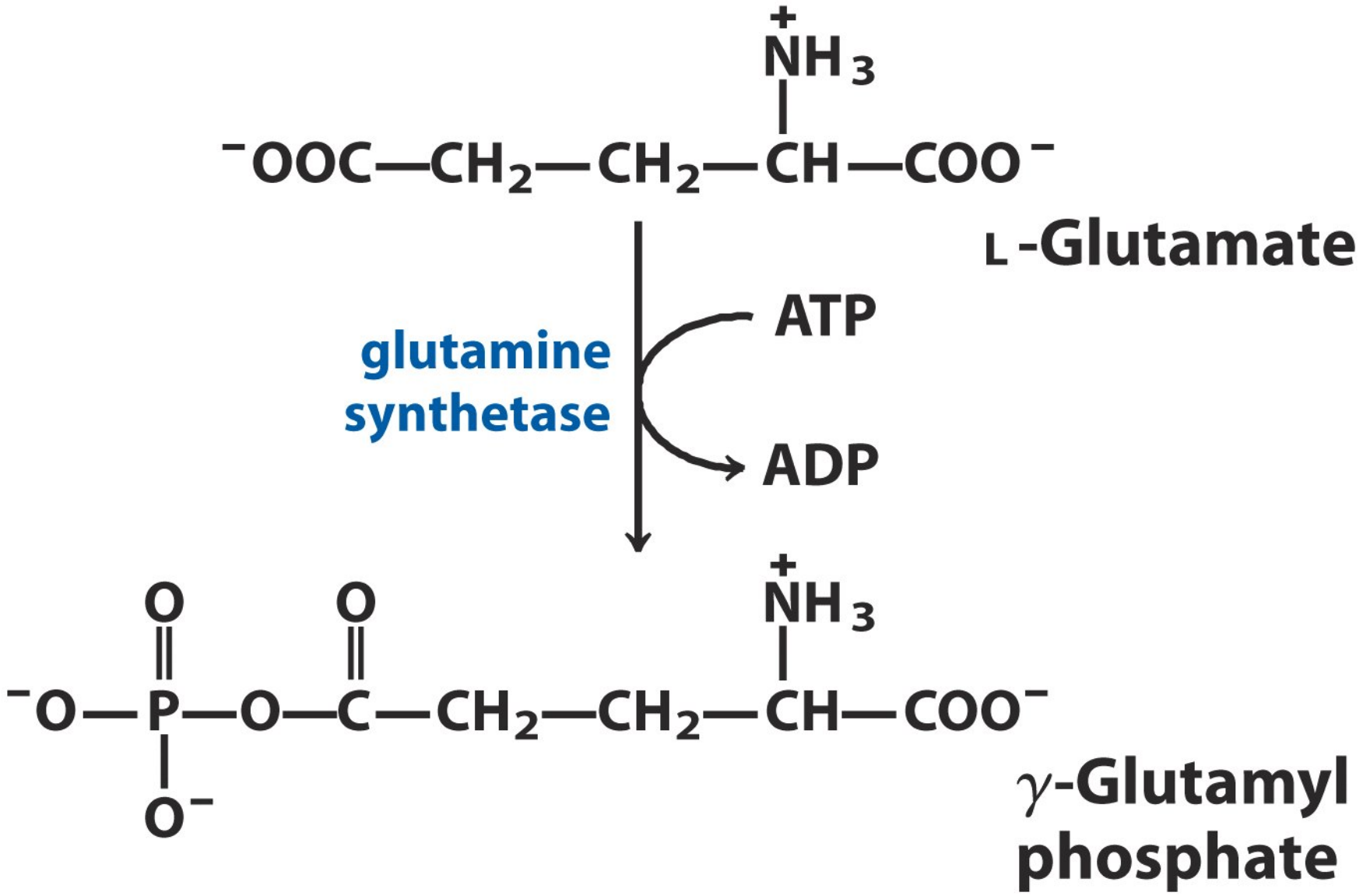
- Ammonia toxicity, comatose conditions
- cerebral edema (increase brain water content) increase cranial pressure
- speculations centers in ATP depletion
- increase in glutamate dehydrogenase increase ammonia leads to increase glutamine (glutamine synthetase) which acts as an osmotic solute in brain astrocytes leading to swelling. depletion of glutamate and derivative gama aminobutyrate (GABA) are important neurotransmitters so there could also be a depletion of neurotransmitters.

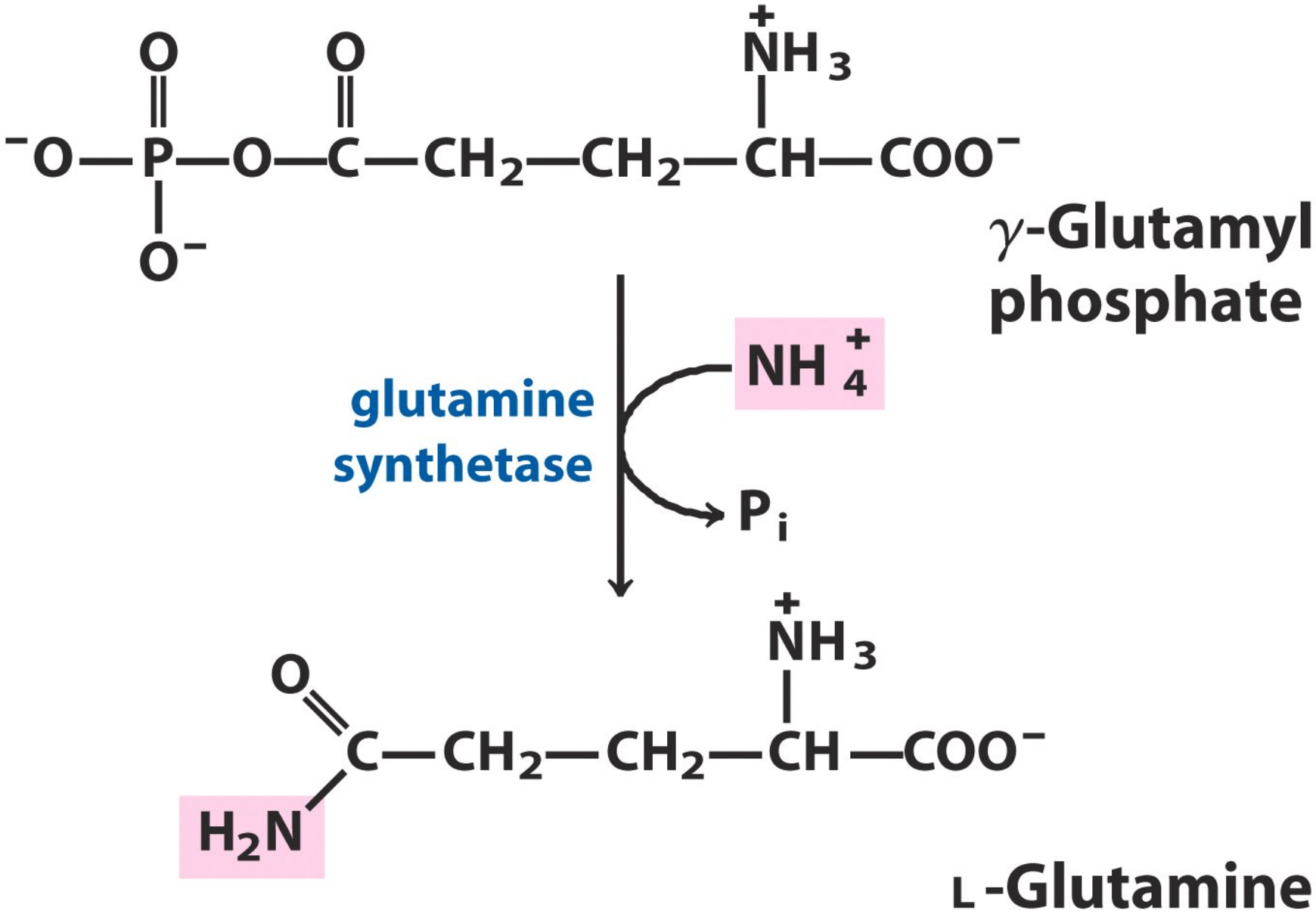

Amino acids from ingested protein
Liver
Cellular protein
Amino acids
α-Keto acids
α-Ketoglutarate
Alanine from muscle
α-Ketoglutarate
Glutamate
Pyruvate
Glutamine from muscle and other tissues
Glutamine
NH4+, urea, or uric acid

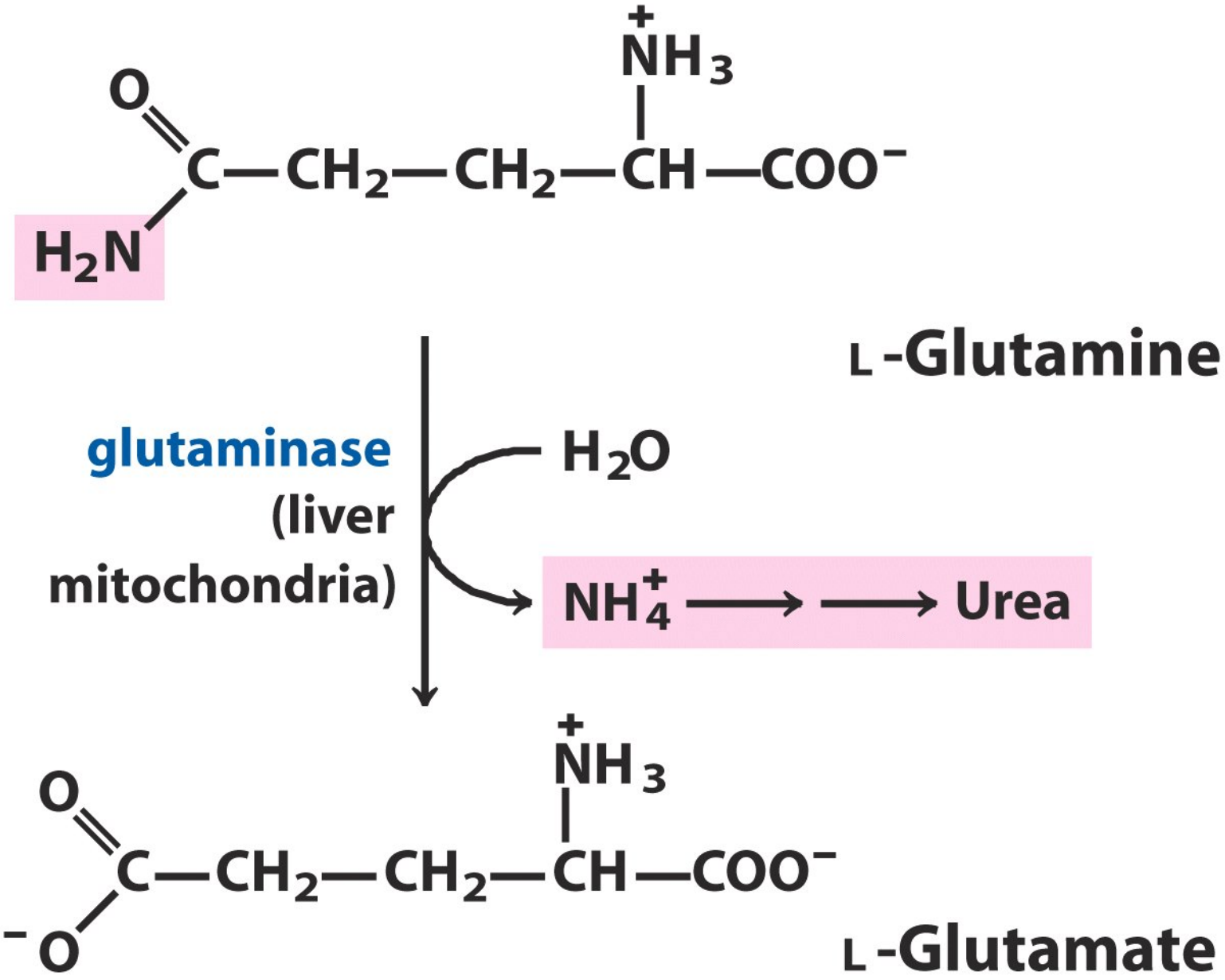
glucose-alanine cycle

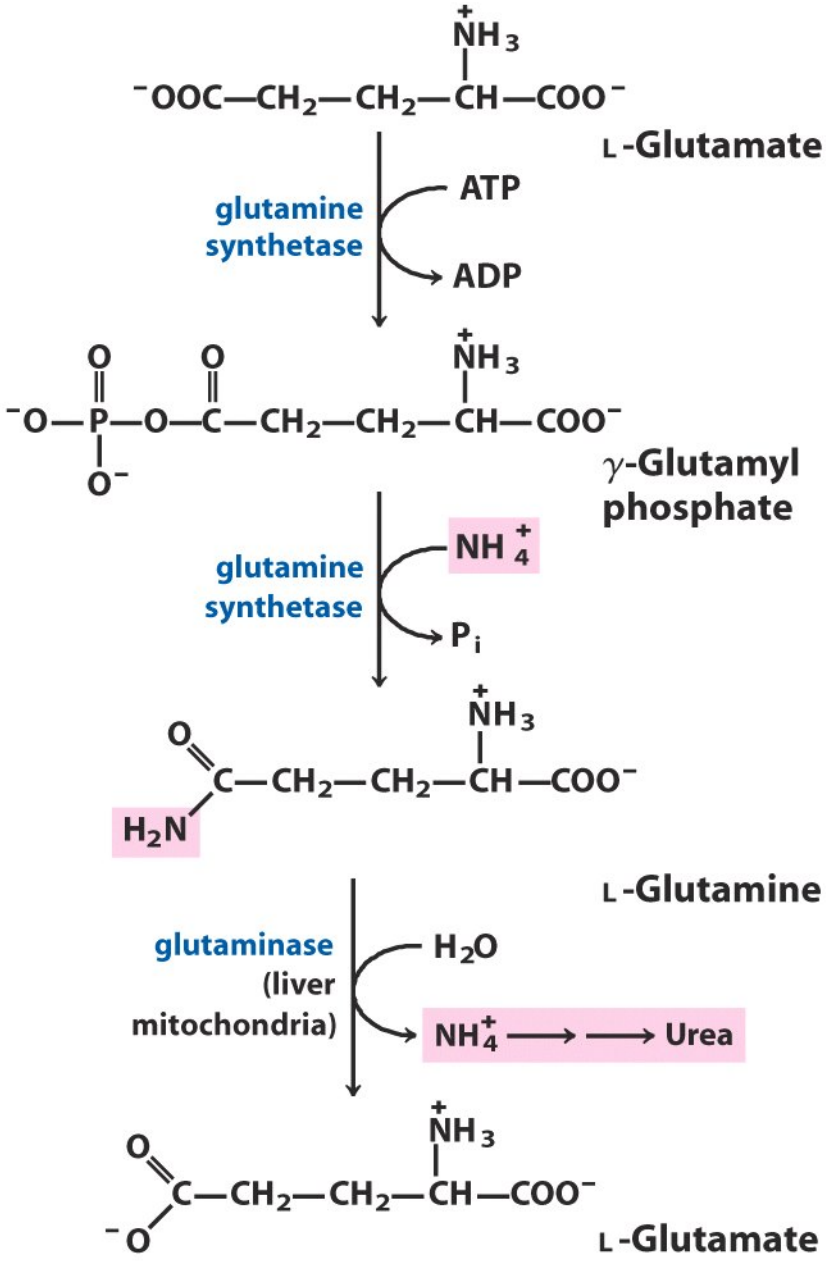


Assays for tissue damage ALT (SGPT) and AST (SGOT) after heart attacks creatine kinase (SCK) and liver damage


+
NH3
⁻OOC—CH2—CH2—CH—COO⁻
L-Glutamate
glutamine synthetase
ATP
ADP
O
O
+
NH3
⁻O—P—O—C—CH2—CH2—CH—COO⁻
O⁻
γ-Glutamyl phosphate

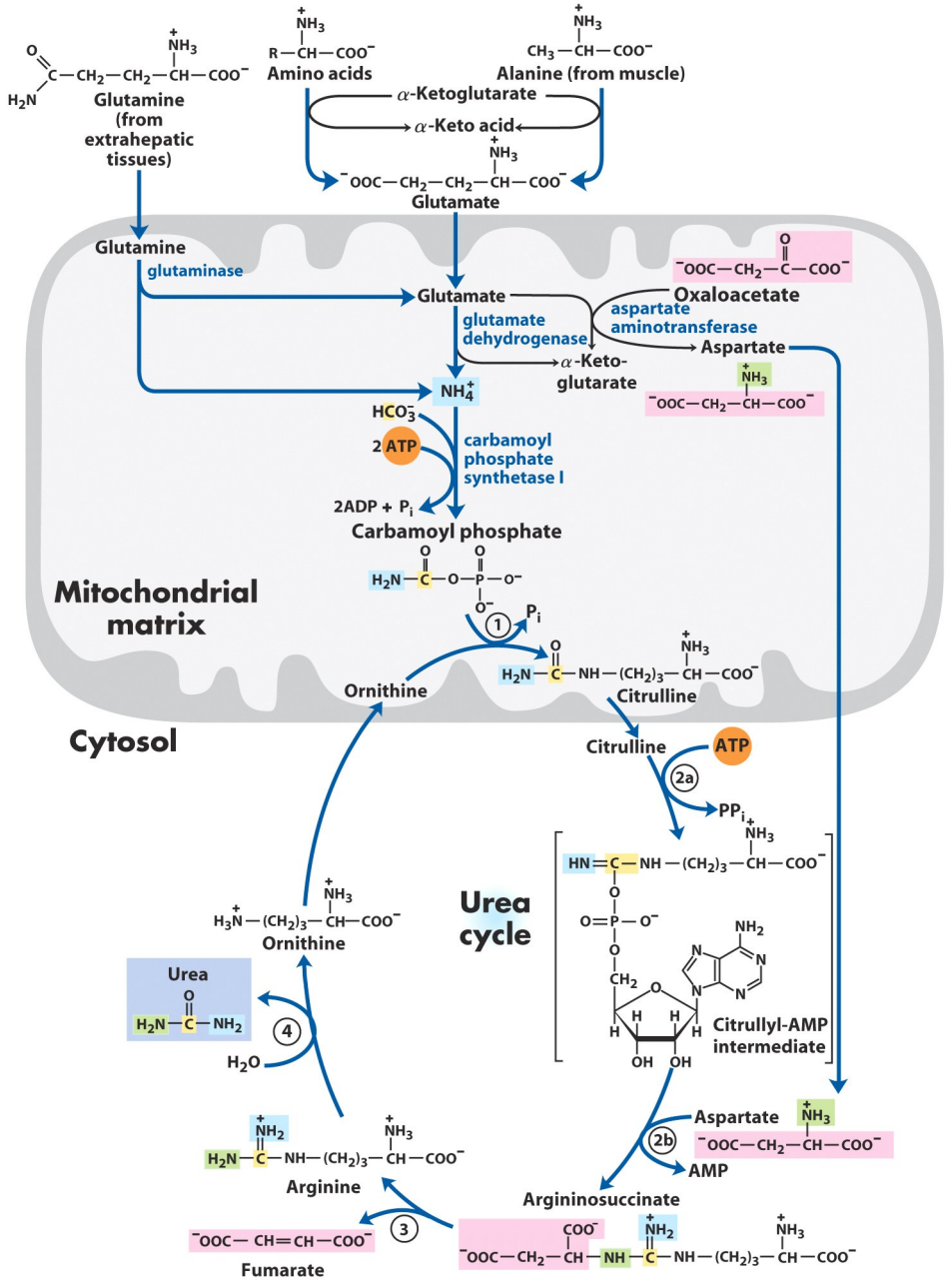

γ-Glutamyl phosphate
glutamine synthetase
NH 4 +
Pi
L-Glutamine

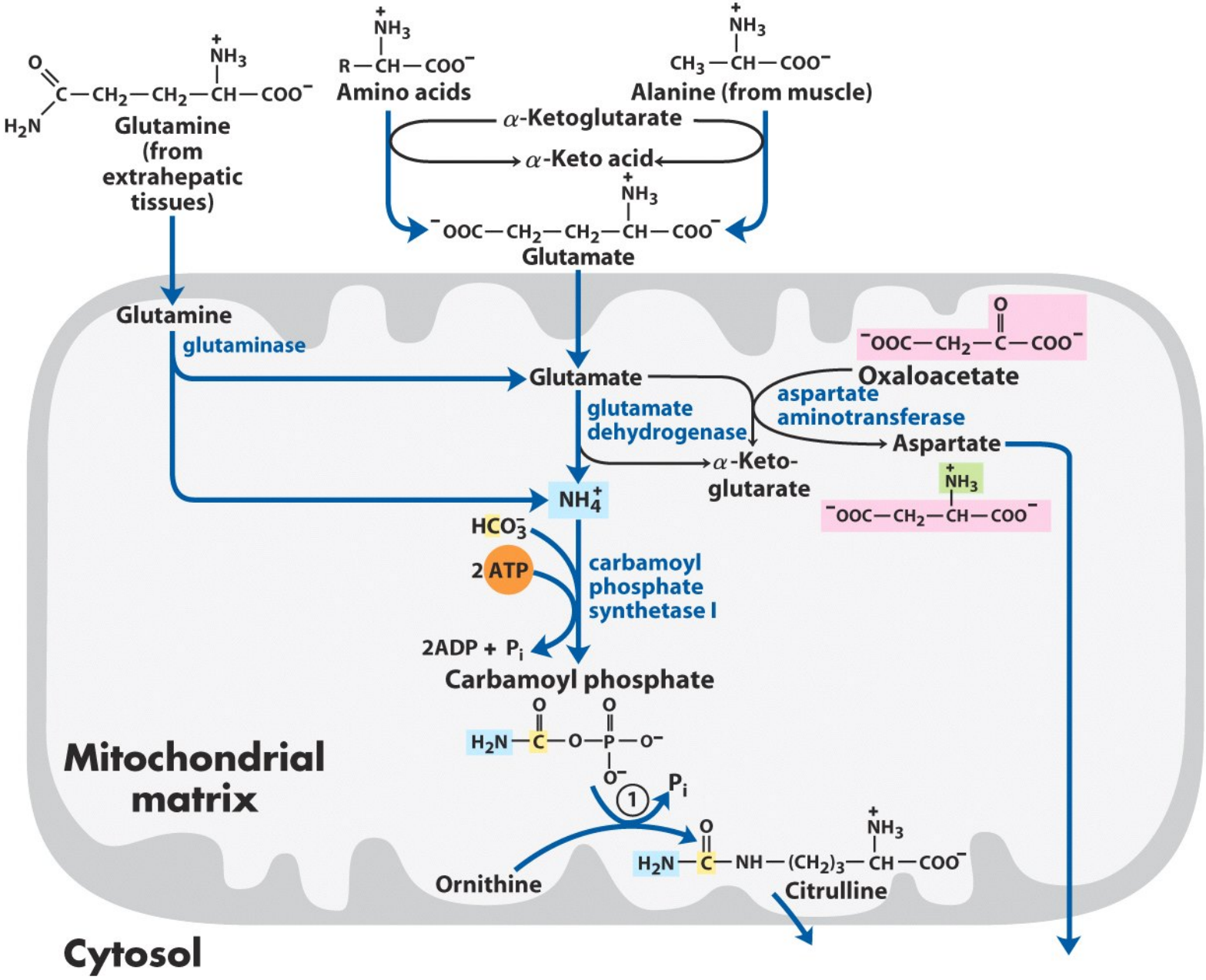

NH3+
O
C—CH2—CH2—CH—COO−
H2N
L-Glutamine
glutaminase
(liver
mitochondria)
H2O
NH4+ ⟶ ⟶ Urea
NH3+
O
C—CH2—CH2—CH—COO−
−O
L-Glutamate

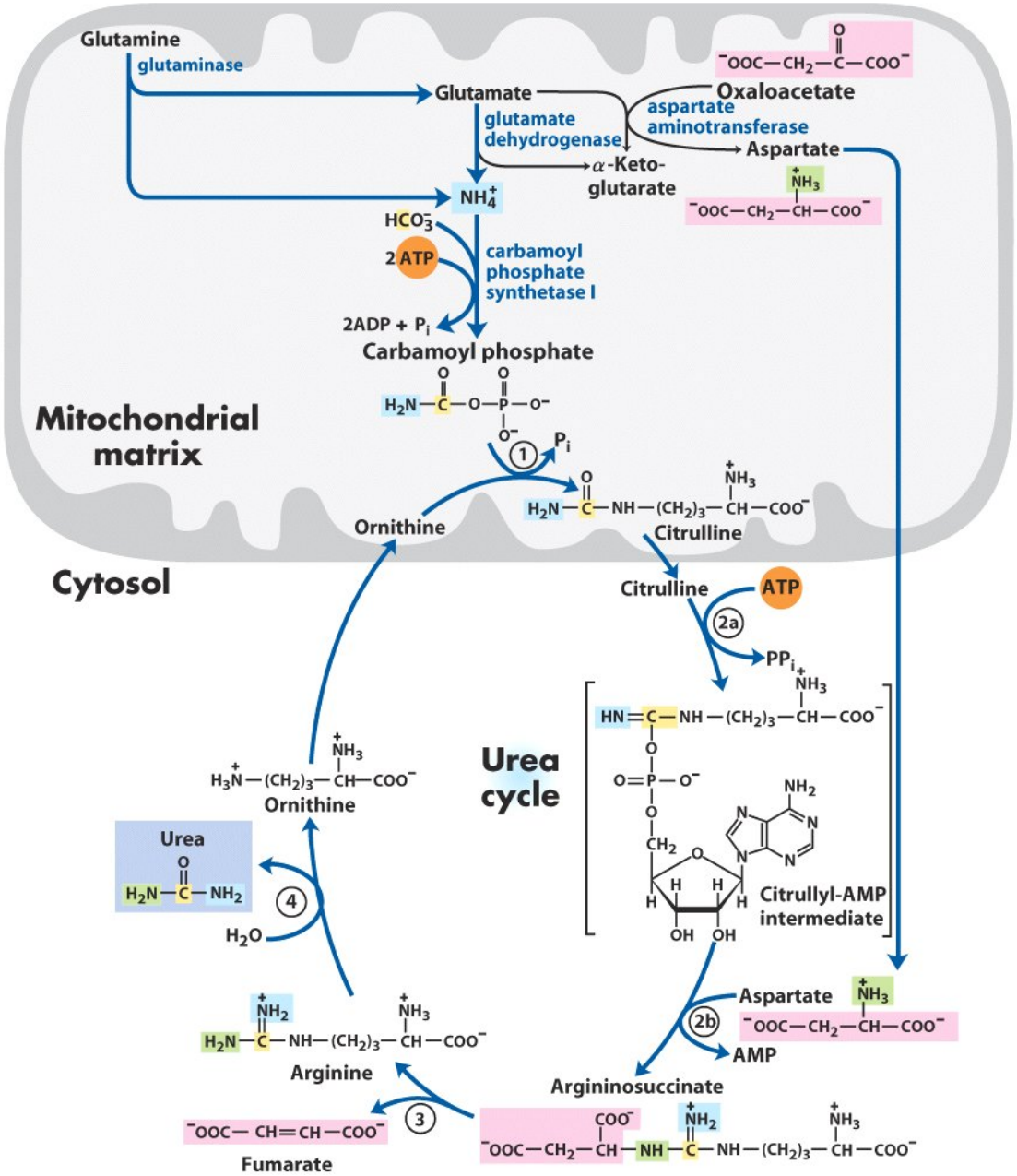

L-Glutamate
glutamine synthetase
ATP
ADP
γ-Glutamyl phosphate
glutamine synthetase
NH4+
Pi
L-Glutamine
glutaminase (liver mitochondria)
H2O
NH4+ → → Urea
L-Glutamate

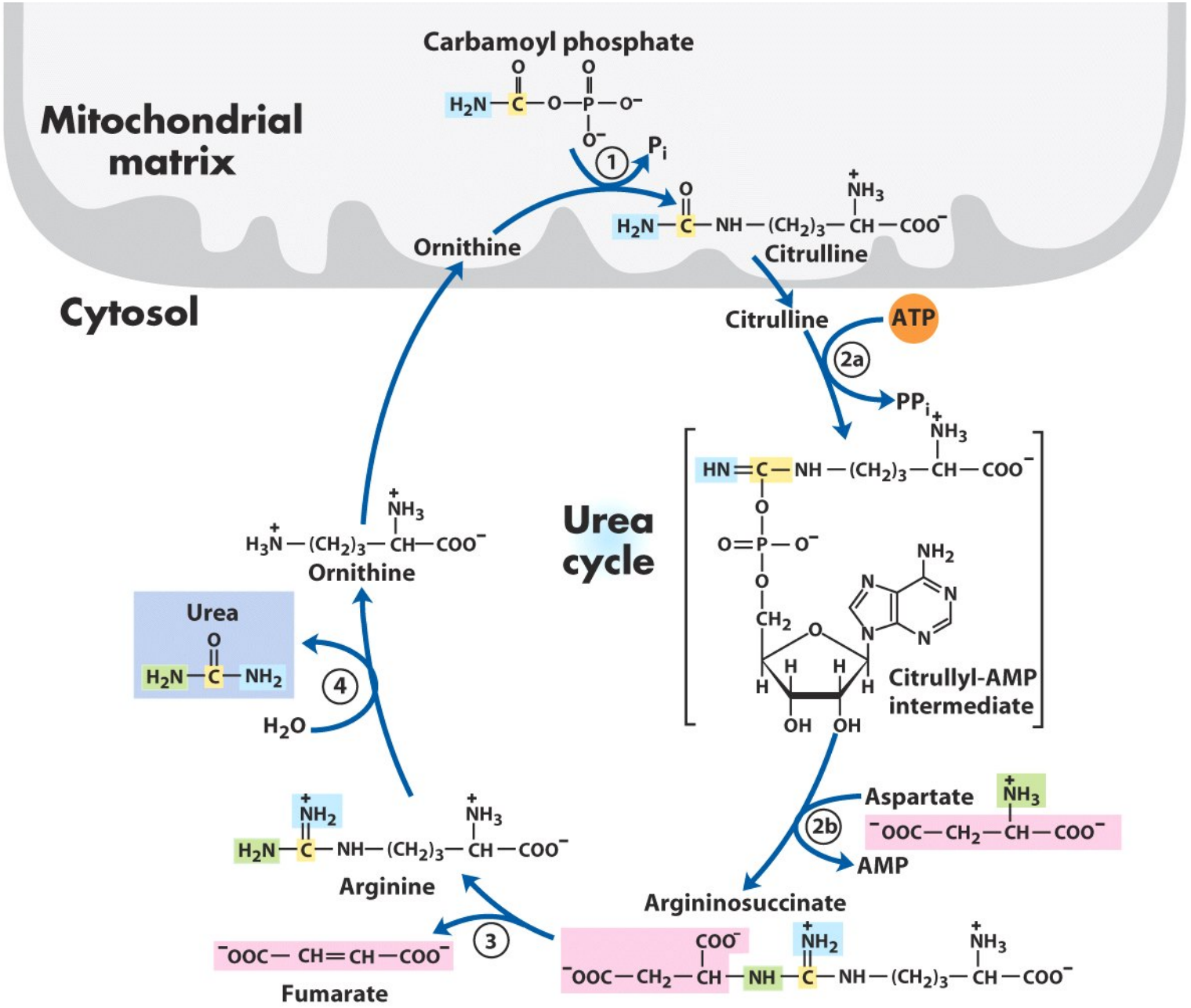
- Nitrogen excretion and the Urea Cycle

- Urea is produced from ammonia in five enzymatic steps (the cycle has 4) it begins inside the mitochondria. Two non-coding amino acids are very important in the cycle. Ornithine and citrulline


Glutamine (from extrahepatic tissues)
Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamate
Glutamine
glutaminase
Glutamate
Oxaloacetate
aspartate aminotransferase
Aspartate
glutamate dehydrogenase
α-Keto-glutarate
NH4+
HCO3−
2 ATP
carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Mitochondrial matrix
Pi
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Argininosuccinate
Arginine
3
Fumarate
Ornithine
Urea
4
H2O


Glutamine
(from
extrahepatic
tissues)
Amino acids
Alanine (from muscle)
α-Ketoglutarate
α-Keto acid
Glutamate
Glutamine
glutaminase
Glutamate
Oxaloacetate
aspartate
aminotransferase
Aspartate
glutamate
dehydrogenase
α-Keto-
glutarate
NH4+
HCO3−
2 ATP
carbamoyl
phosphate
synthetase I
2ADP + Pi
Carbamoyl phosphate
Mitochondrial
matrix
Pi
1
Ornithine
Citrulline
Cytosol


Glutamine
glutaminase
Glutamate
glutamate dehydrogenase
α-Keto-glutarate
Oxaloacetate
aspartate aminotransferase
Aspartate
NH4+
HCO3−
2 ATP
carbamoyl phosphate synthetase I
2ADP + Pi
Carbamoyl phosphate
Mitochondrial matrix
Pi
1
Ornithine
Citrulline
Cytosol
Citrulline
ATP
2a
PPi
Urea cycle
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Argininosuccinate
3
Fumarate
Arginine
Urea
4
H2O
Ornithine


Mitochondrial matrix
Cytosol
Carbamoyl phosphate
Ornithine
Citrulline
Citrulline
ATP
Urea cycle
Citrullyl-AMP intermediate
Aspartate
AMP
Argininosuccinate
Fumarate
Arginine
Ornithine
Urea
H_2O
1
2a
2b
3
4

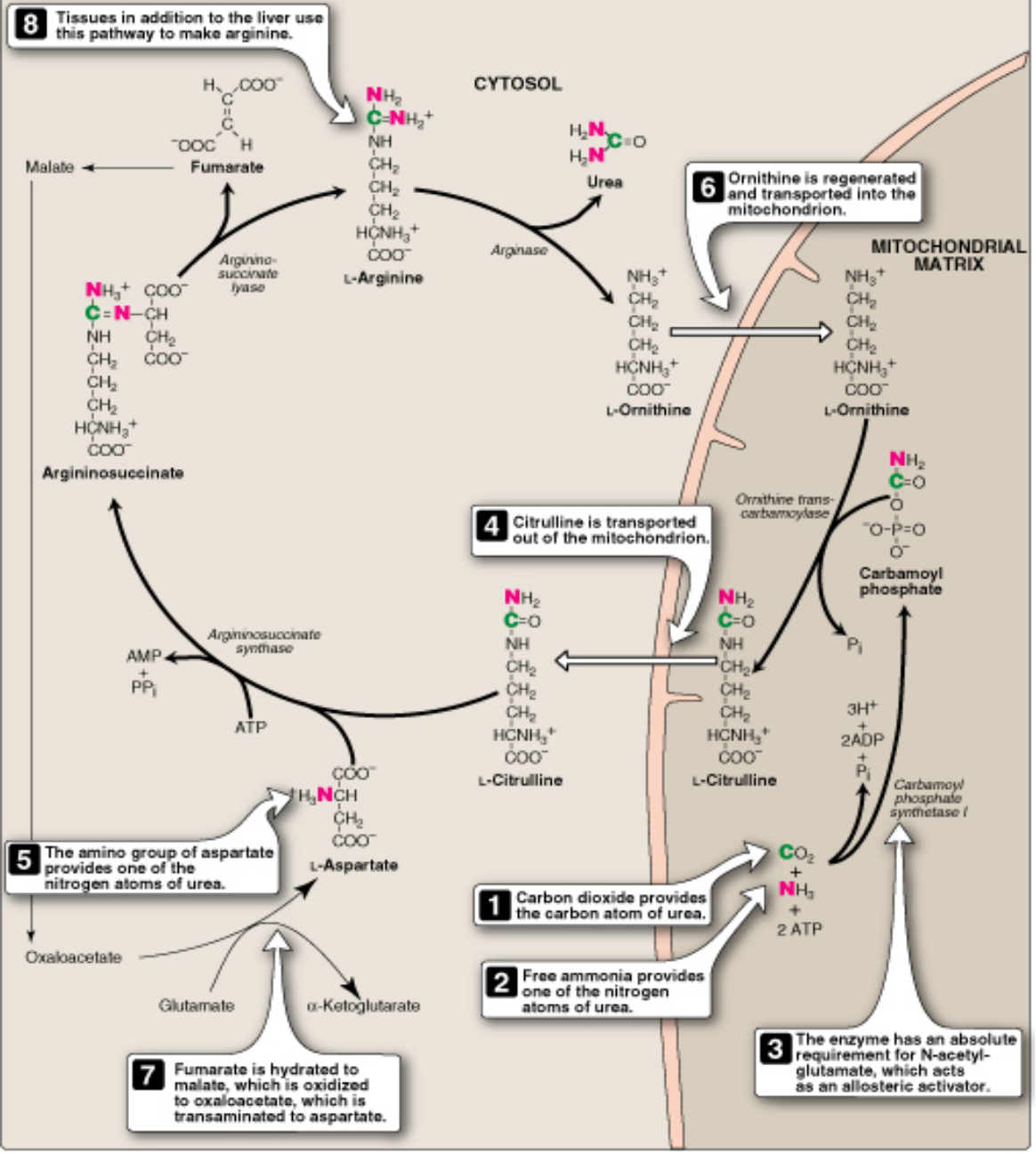
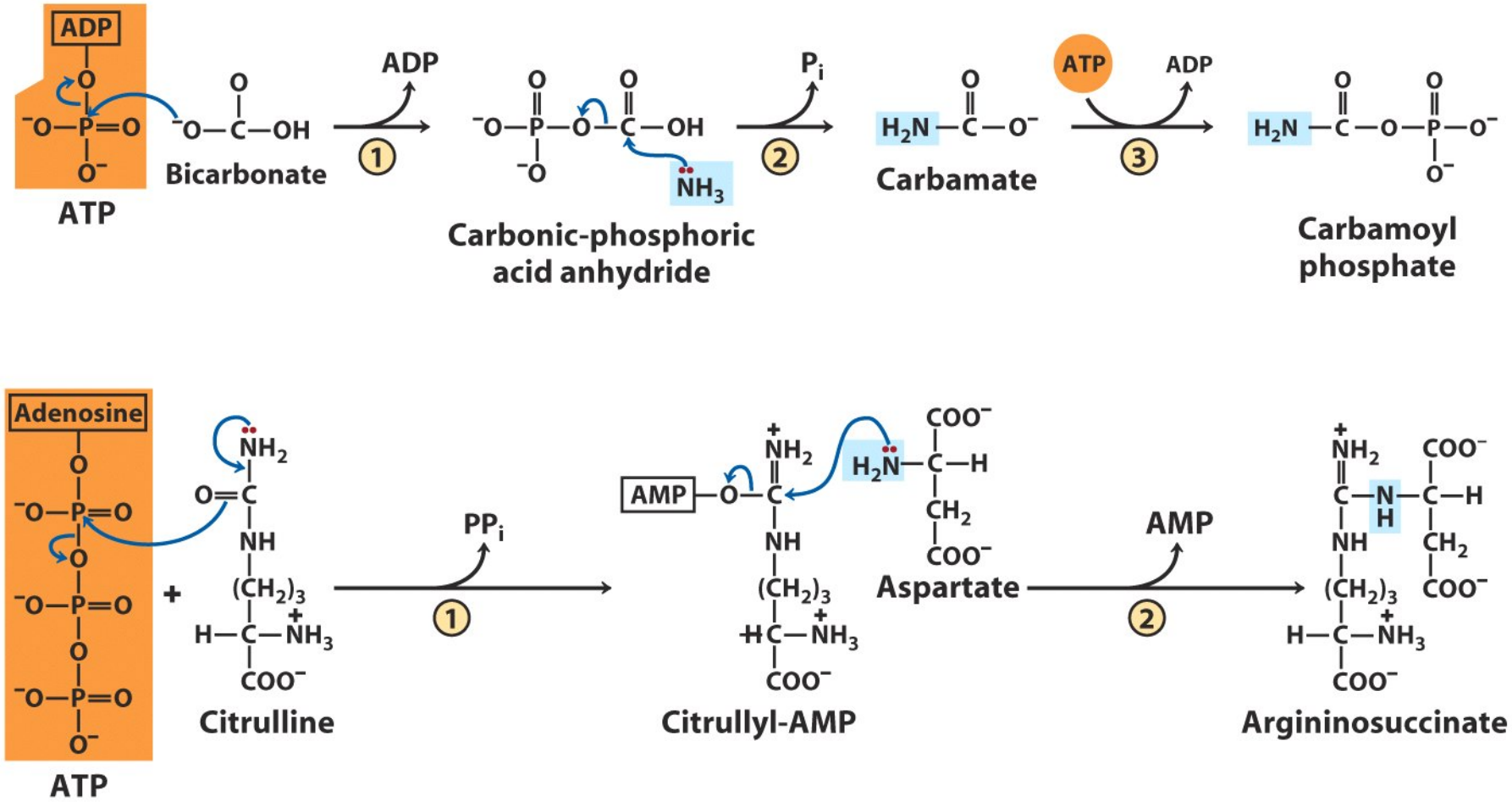
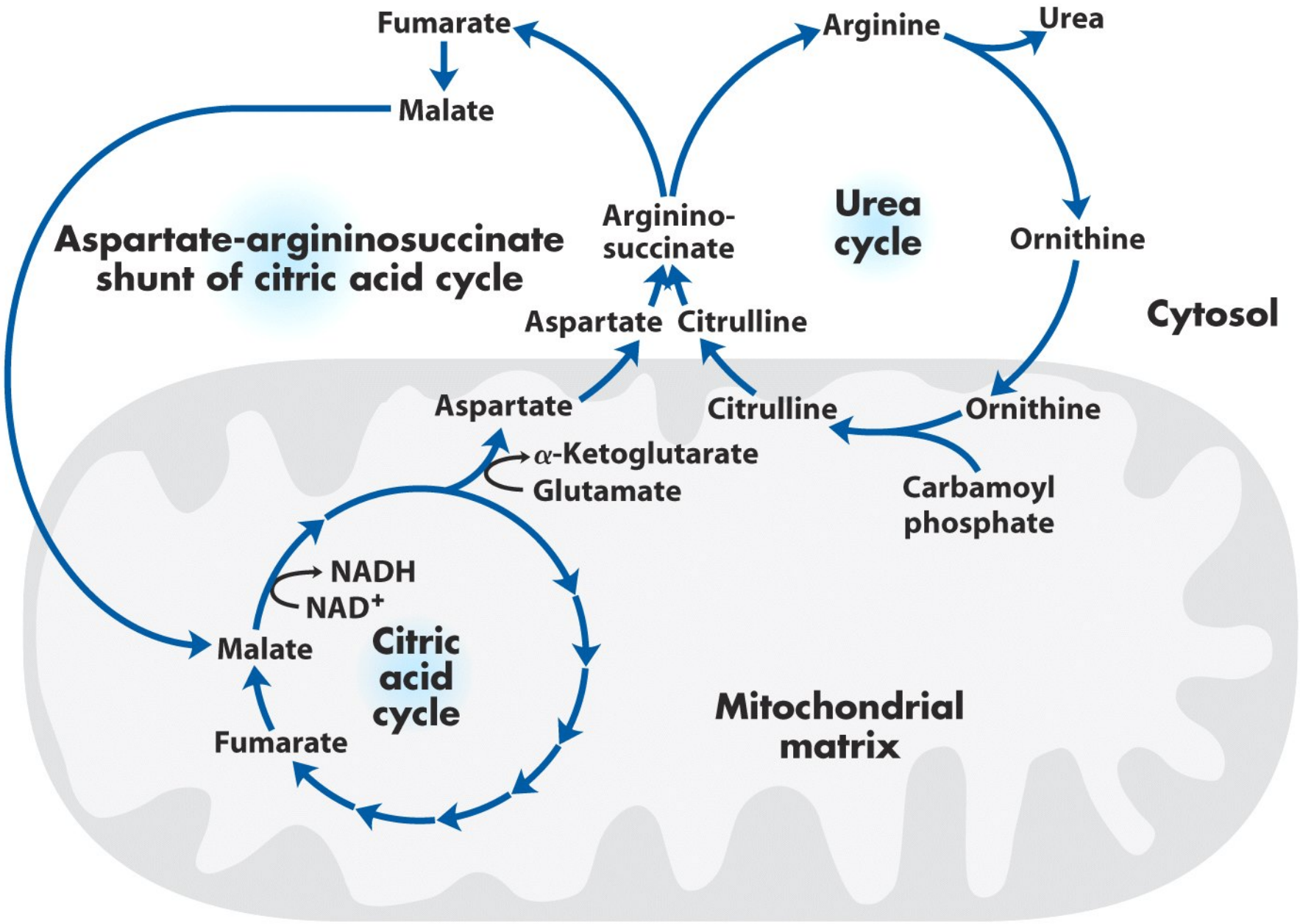
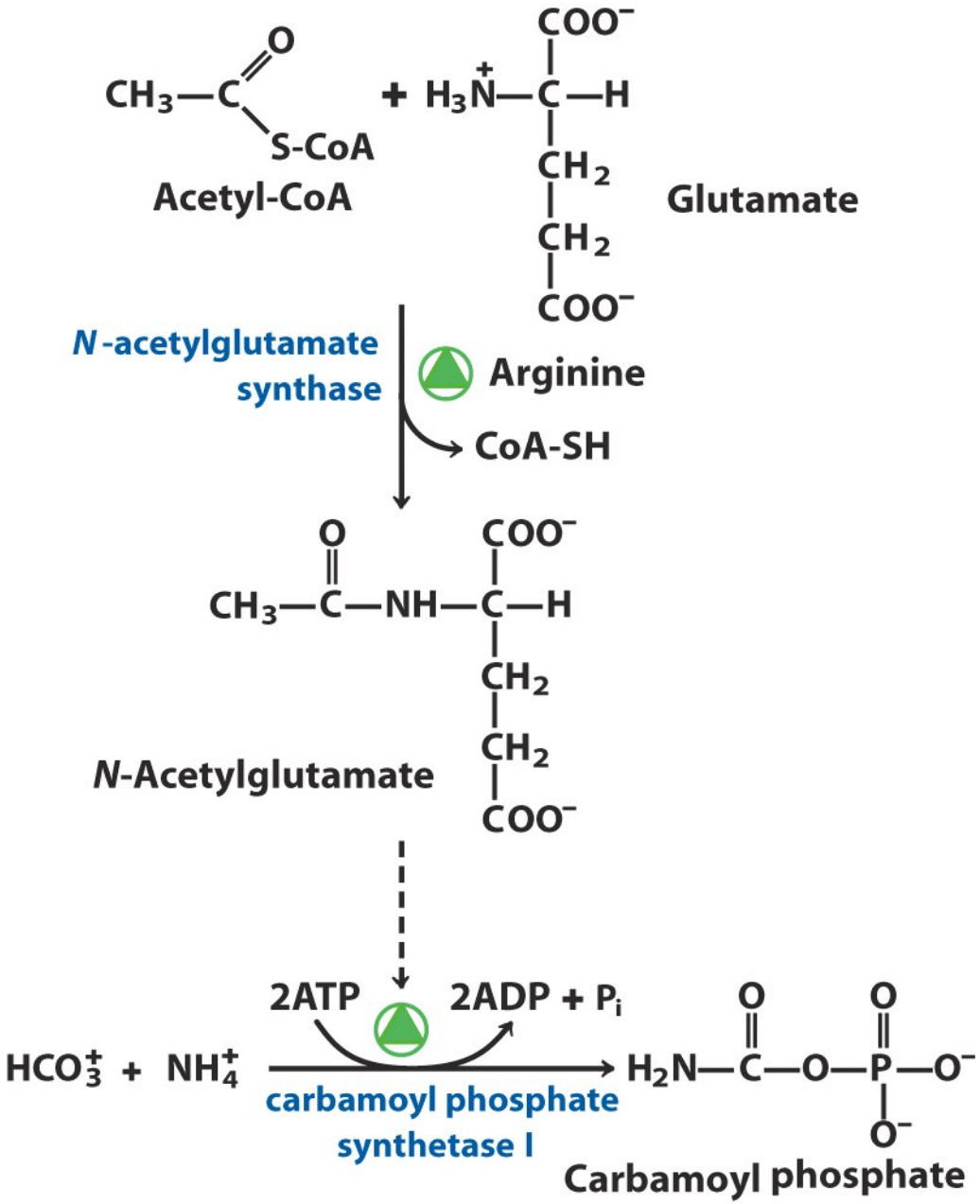


Figure 19.14
Reactions of the urea cycle.

Reactions of the Urea cycle The formation of carbamoyl phosphate (CO_2 provides the Carbon for Urea and free ammonia provides one of the nitrogen atoms of urea forming the previous compound Carbamoyl phosphate synthetase 1) uses an ATP. This step requires N-acetylglutamate as activator of the enzyme. Carbamoyl phosphate synthetase 2 does not require the activator and is used in biosynthesis of pyrimidines. Citrulline is then formed from L-Ornithine (2)ornithine transcarbamoylase). Ornithine is regenerated in each cycle similar to oxaloacetate. The formation of citrulline liberates an inorganic phosphate. Notice that these rxs occur in mitochondria. Arginosuccinate is then synthesized from aspartate in the cytosol as it condenses with citrulline(3)Arginosuccinate synthetase, the amino group of aspartate provides 2nd nitrogen of Urea. Cleavage of arginosuccinate to yield Arginine & fumarate (4) arginosuccinate lyase). Arginine is the precursor of urea, fumarate is hydrated to malate (TCA)


ADP
ATP
Bicarbonate
ADP
1
Carbonic-phosphoric acid anhydride
Pi
2
Carbamate
ATP
ADP
3
Carbamoyl phosphate
Adenosine
ATP
Citrulline
PPi
1
AMP
Citrullyl-AMP
Aspartate
AMP
2
Argininosuccinate


Fumarate
Arginine
Urea
Malate
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


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

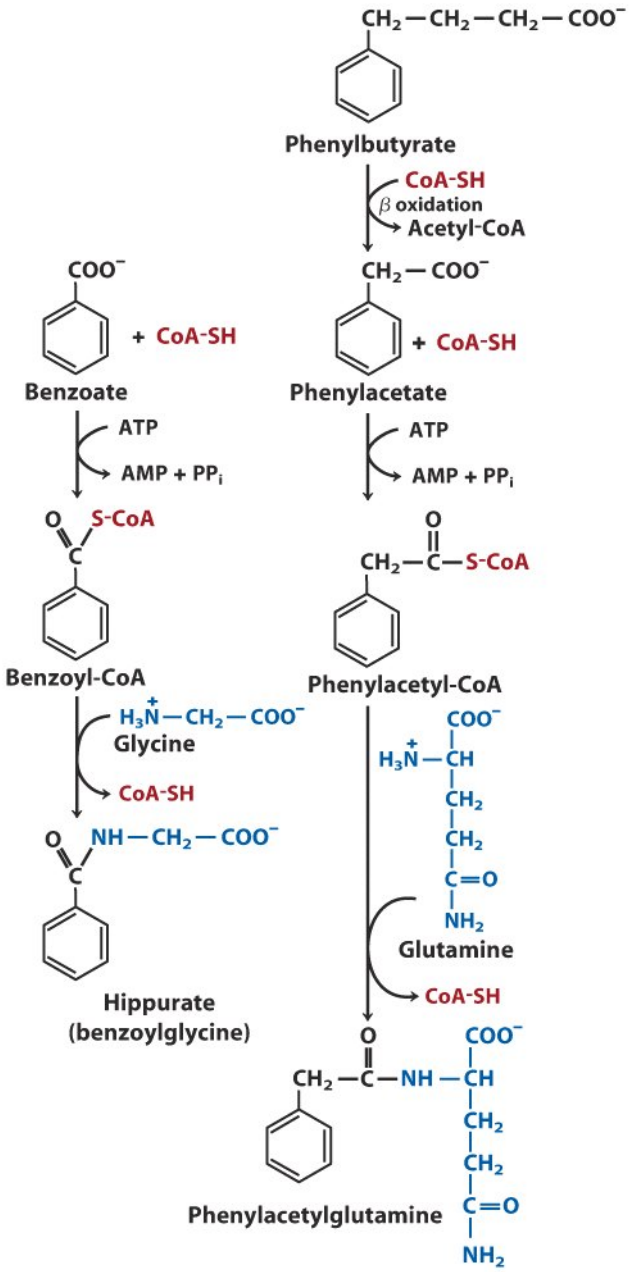
- Genetic defects in the urea cycle can be life threatening. The absence of urea cycle enzymes result in hyperammonemia or build up of one or more cycle intermediate. Most of the urea cycle steps are irreversible. The only reversible step is by argininosuccinate lyase (argininosuccinase)
- protein -free diet is not a treatment option since many amino acids are essential and needed in the diet.

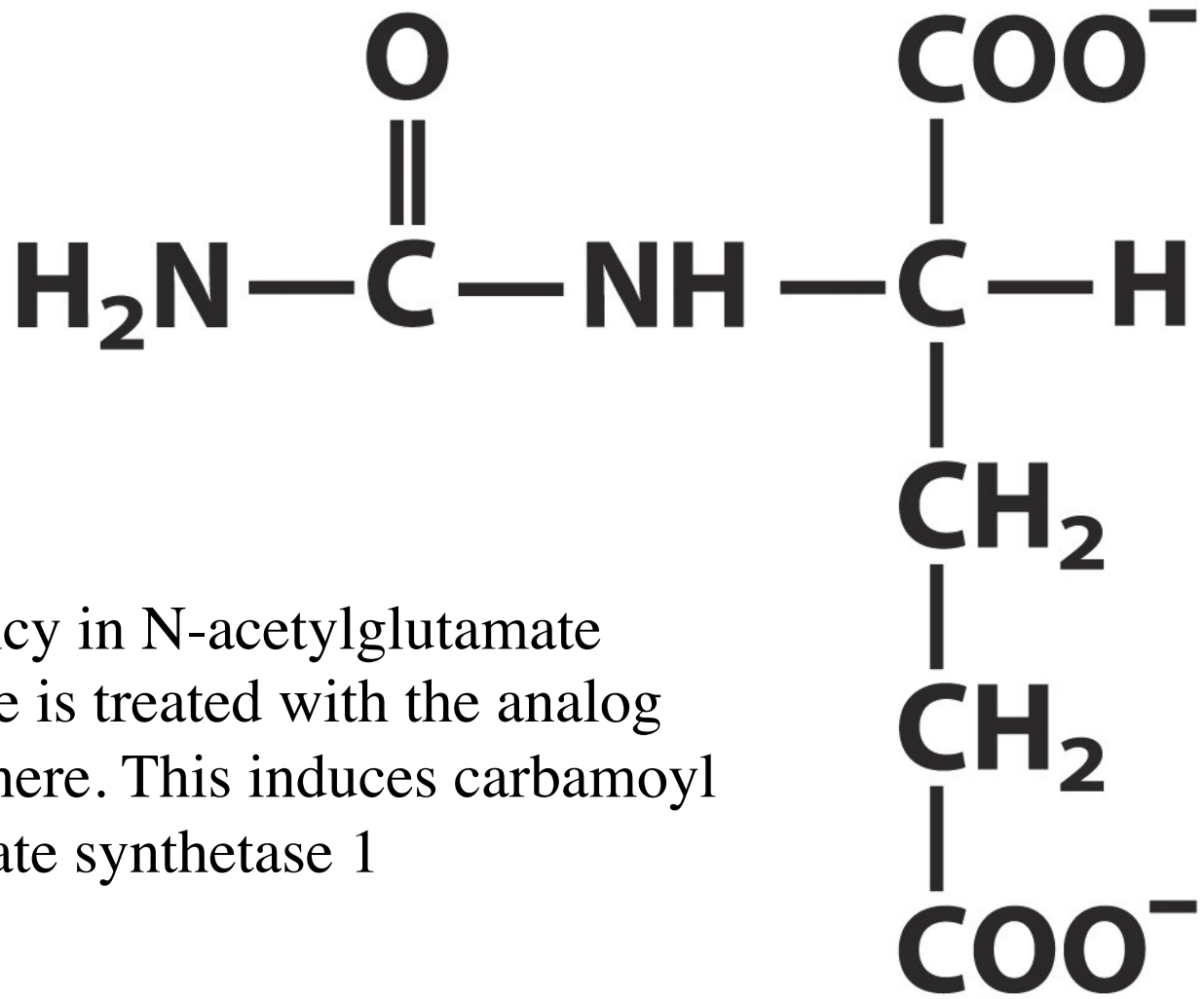
TABLE 18–1 Nonessential and Essential Amino Acids for Humans and the Albino Rat

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

*Required to some degree in young, growing animals, and/or sometimes during illness.

- Treatment for urea cycle defects
- aromatic acids benzoate or phenylbutyrate can help lower ammonia levels
- carbamoyl glutamate

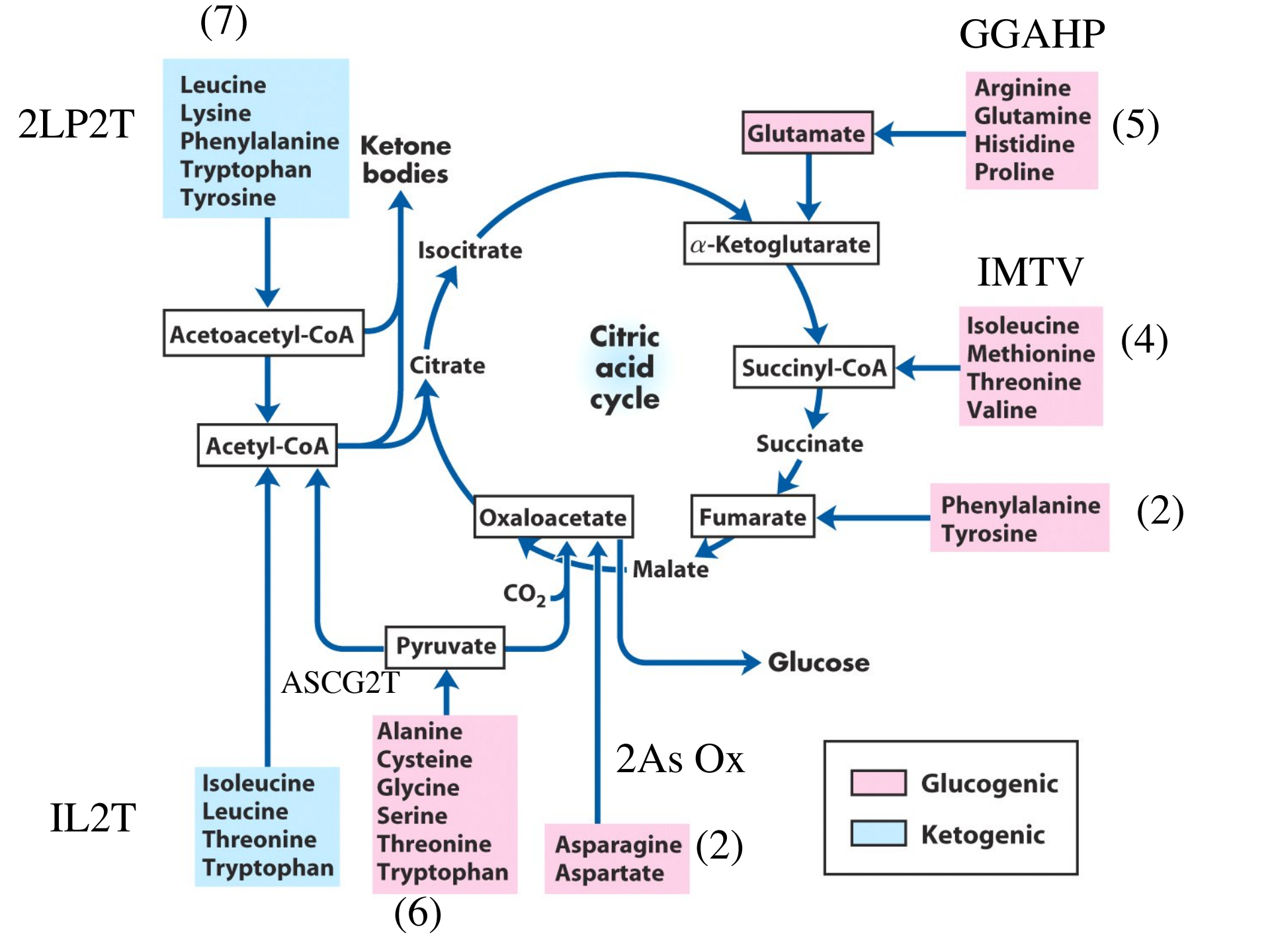

Phenylbutyrate
CoA-SH
β oxidation
Acetyl-CoA
Benzoate
+ CoA-SH
Phenylacetate
+ CoA-SH
ATP
AMP + PPi
ATP
AMP + PPi
Benzoyl-CoA
Phenylacetyl-CoA
Glycine
CoA-SH
Glutamine
CoA-SH
Hippurate
(benzoylglycine)
Phenylacetylglutamine



deficiency in N-acetylglutamate synthase is treated with the analog shown here. This induces carbamoyl phosphate synthetase 1

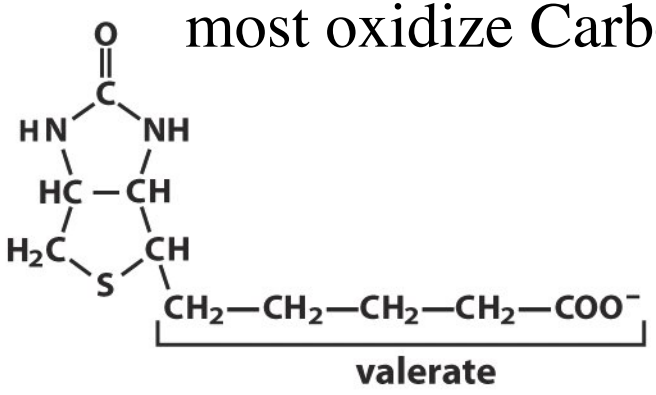
Carbamoyl glutamate

Pathways of amino acid degradation will concentrate on nonessential amino acids.

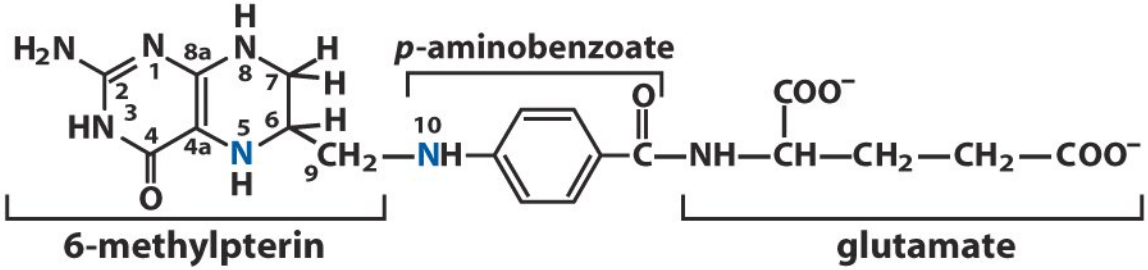

(7)
GGAHP
2LP2T
Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Arginine
Glutamine
Histidine
Proline
(5)
Glutamate
Isocitrate
α-Ketoglutarate
IMTV
Acetoacetyl-CoA
Citric acid cycle
Isoleucine
Methionine
Threonine
Valine
(4)
Citrate
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
(2)
Malate
CO2
Pyruvate
Glucose
ASCG2T
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan
2As Ox
Isoleucine
Leucine
Threonine
Tryptophan
IL2T
Asparagine
Aspartate
(2)
(6)
Glucogenic
Ketogenic

- Several cofactors in enzymes involved in catabolism of amino acids
- transaminations (PLP)
- one carbon transfer (biotin, tetrahydrofolate(H_4 folate) S-adenosylmethionine

most oxidize Carbon

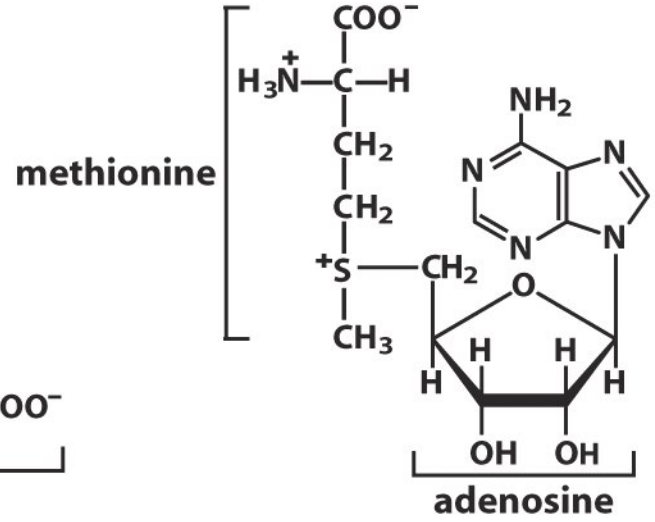


Biotin



Tetrahydrofolate (H_4 folate)

intermediate



S-Adenosylmethionine (adoMet)

methyl groups

6 amino acids degraded to Pyruvate (ASCG2T)

alanine

glycine

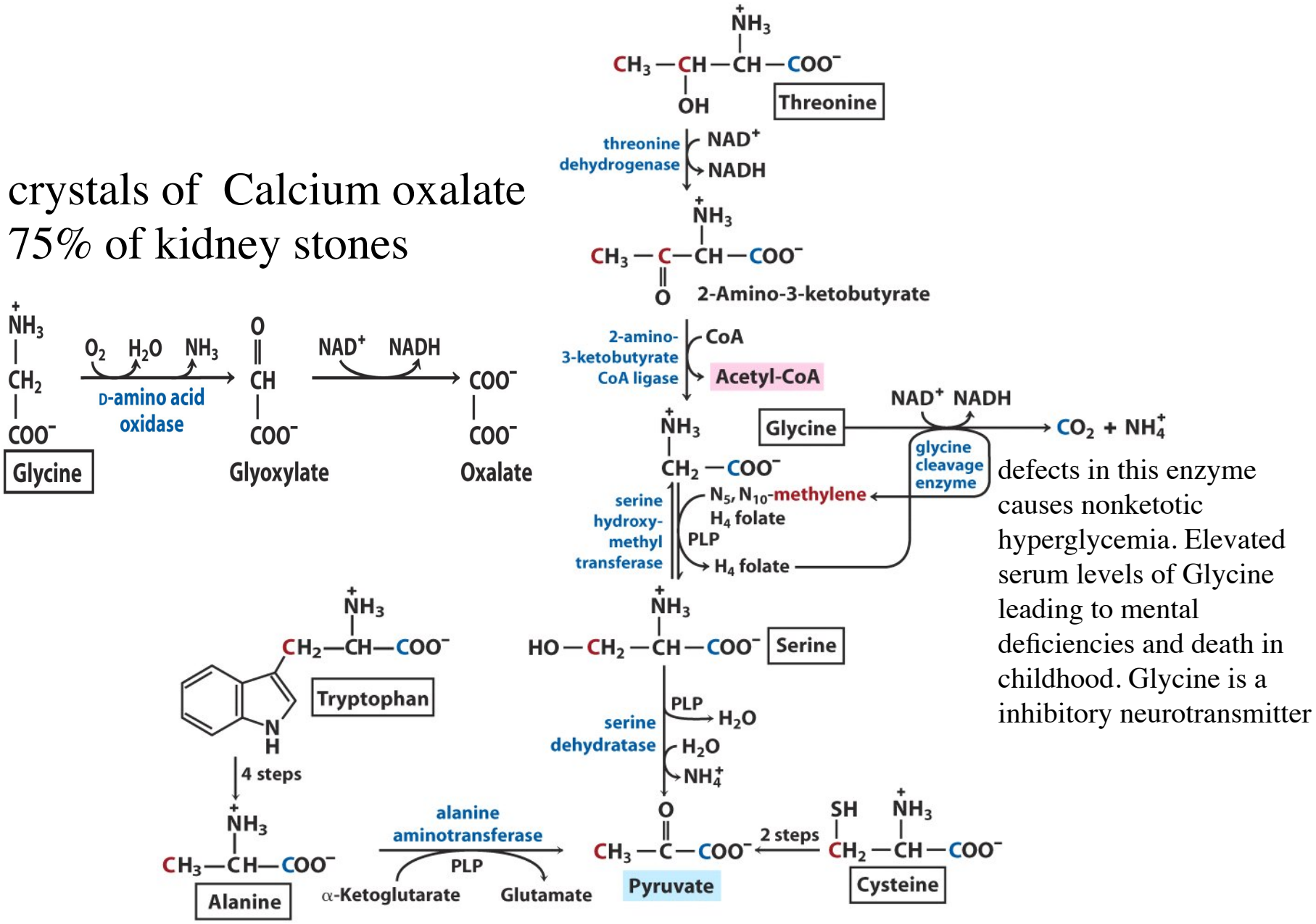
serine

cysteine

tryptophan

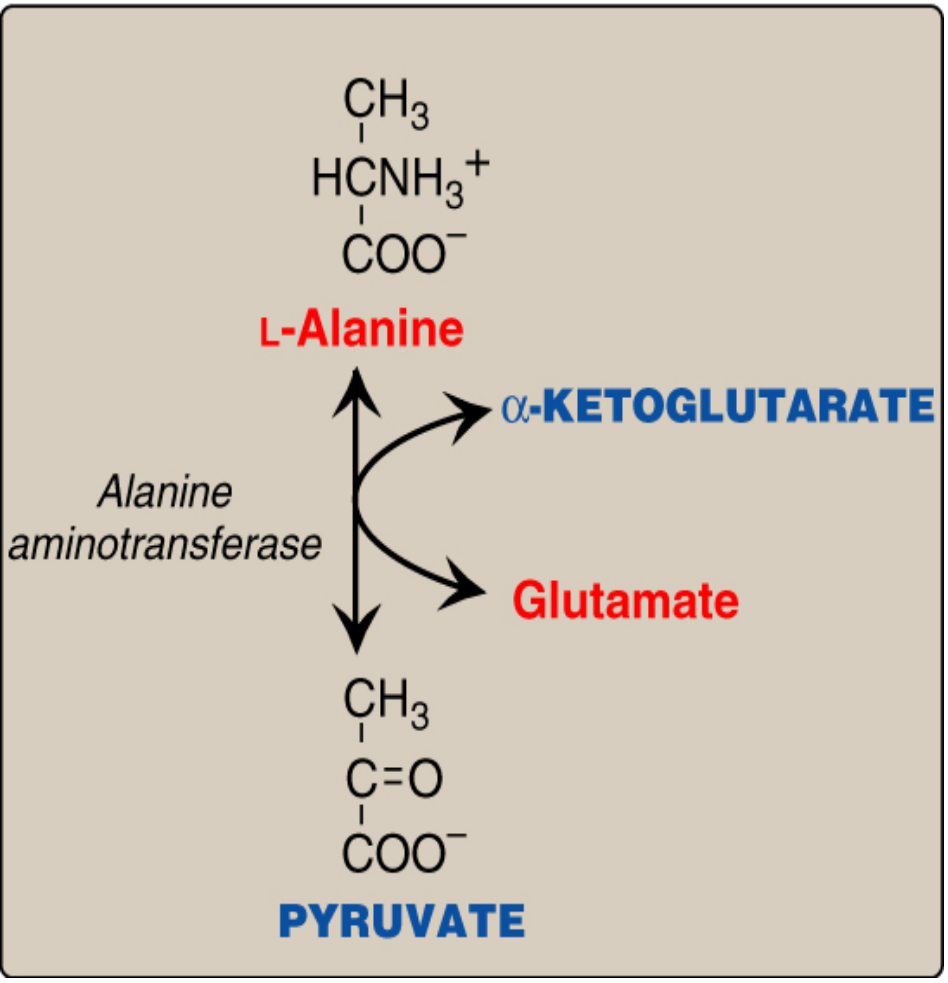
threonine

crystals of Calcium oxalate
75% of kidney stones

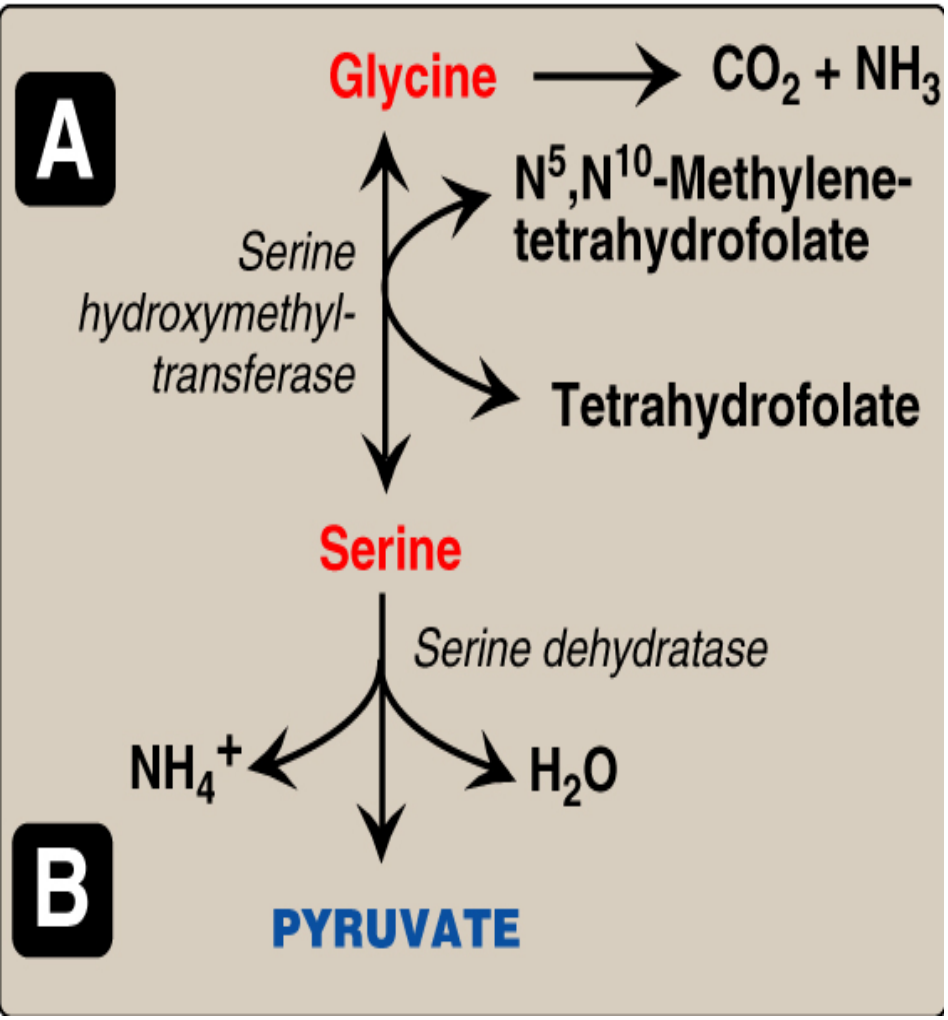


defects in this enzyme causes nonketotic hyperglycemia. Elevated serum levels of Glycine leading to mental deficiencies and death in childhood. Glycine is a inhibitory neurotransmitter

Amino acids that form pyruvate

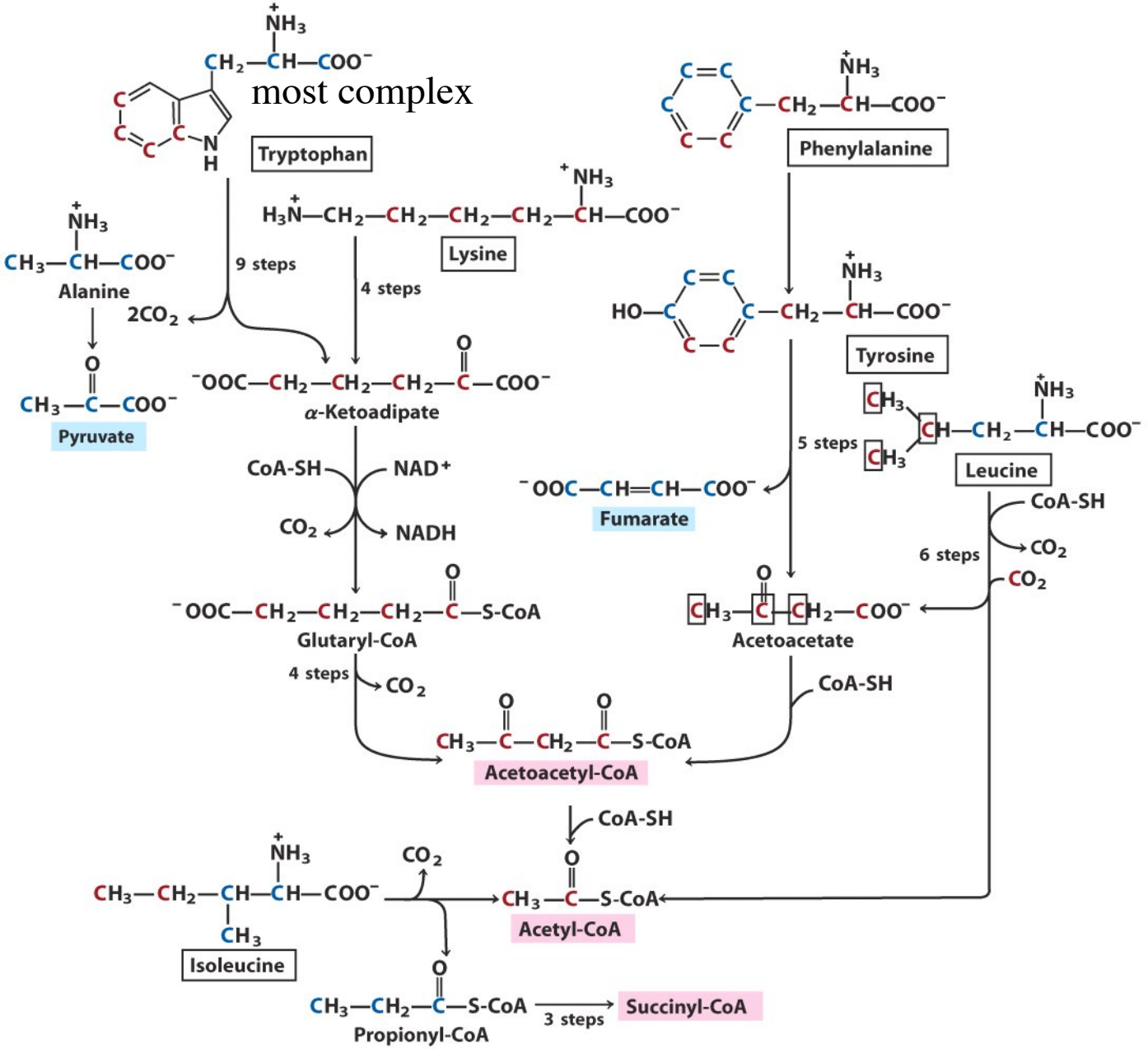


- Alanine loses its amino group by transamination to form pyruvate.

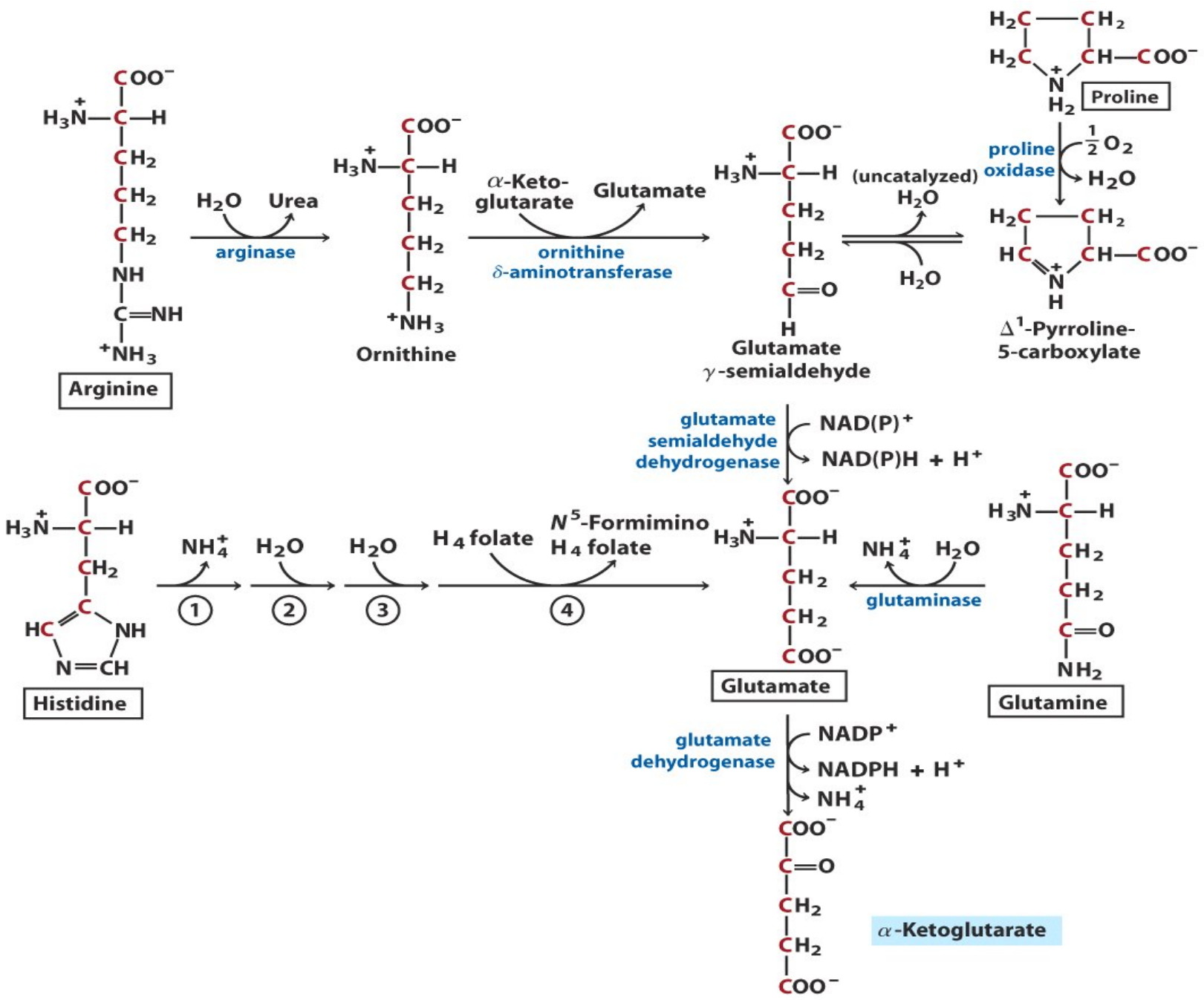


- Serine can be converted to glycine and N^5, N^{10}-methylenetetrahydrofolate. Serine can also be converted to pyruvate by serine dehydratase.
- Glycine can either be converted to serine by addition of a methylene group from N^5,N^{10}-methylenetetrahydrofolic acid, or oxidized to CO_2 and NH_4^+

- Seven amino acids degraded to acetyl CoA IP2L3T
- tryptophan, lysine, phenylalanine, tyrosine, leucine isoleucine and threonine.


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

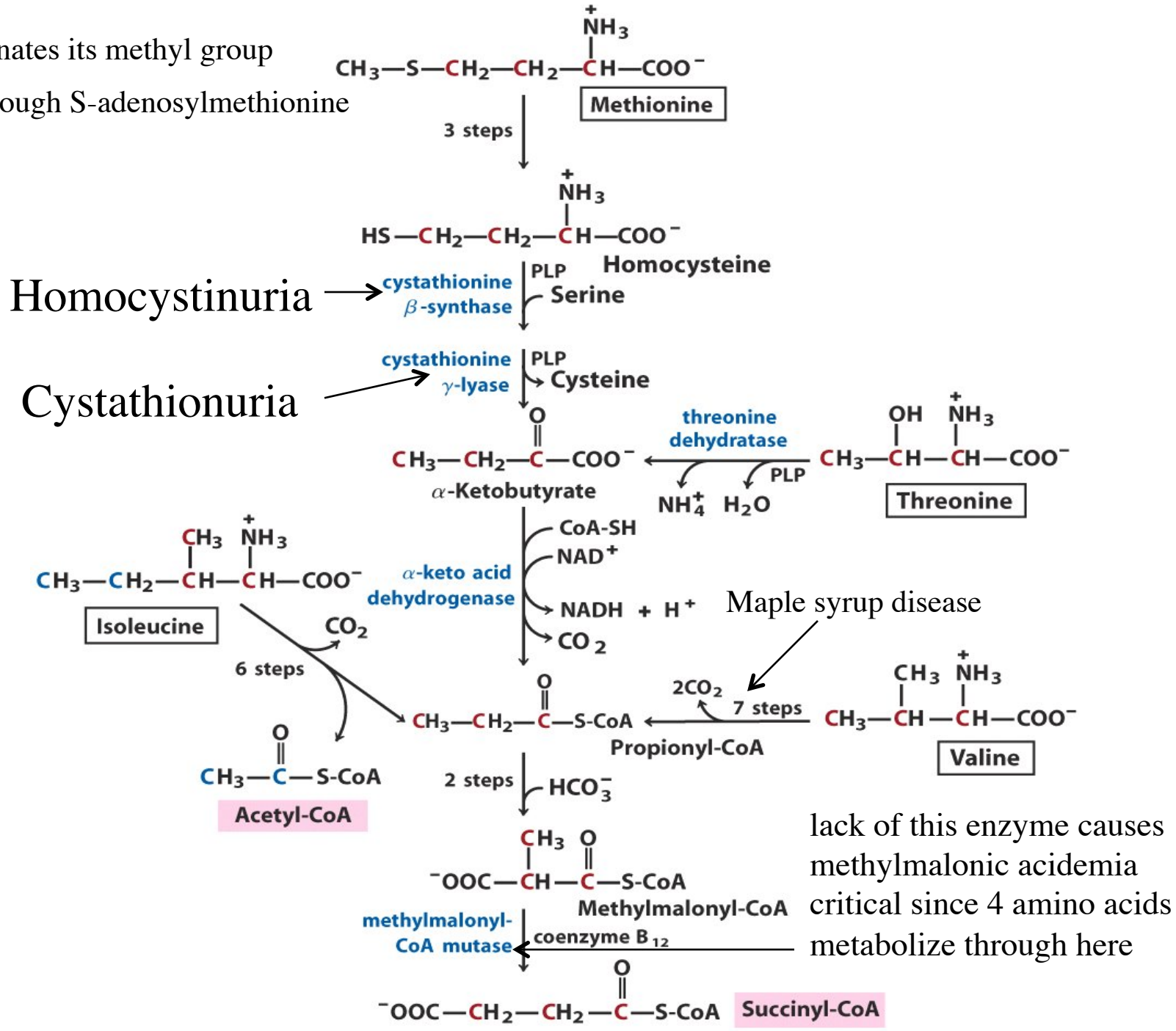
- Five amino acids converted to alpha ketoglutarate GGAHP
- glutamate, glutamine, arginine, histidine and Proline


Arginine
H_2O
Urea
arginase
Ornithine
α-Keto-glutarate
Glutamate
ornithine δ-aminotransferase
Glutamate γ-semialdehyde
(uncatalyzed)
H_2O
H_2O
Proline
proline oxidase
$\frac{1}{2}O_2$
H_2O
Δ^1-Pyrroline-5-carboxylate
glutamate semialdehyde dehydrogenase
$NAD(P)^+$
$NAD(P)H + H^+$
Histidine
NH_4^+
H_2O
H_2O
H_4 folate
N^5-Formimino H_4 folate
1
2
3
4
Glutamate
NH_4^+
H_2O
glutaminase
Glutamine
glutamate dehydrogenase
$NADP^+$
$NADPH + H^+$
NH_4^+
α-Ketoglutarate

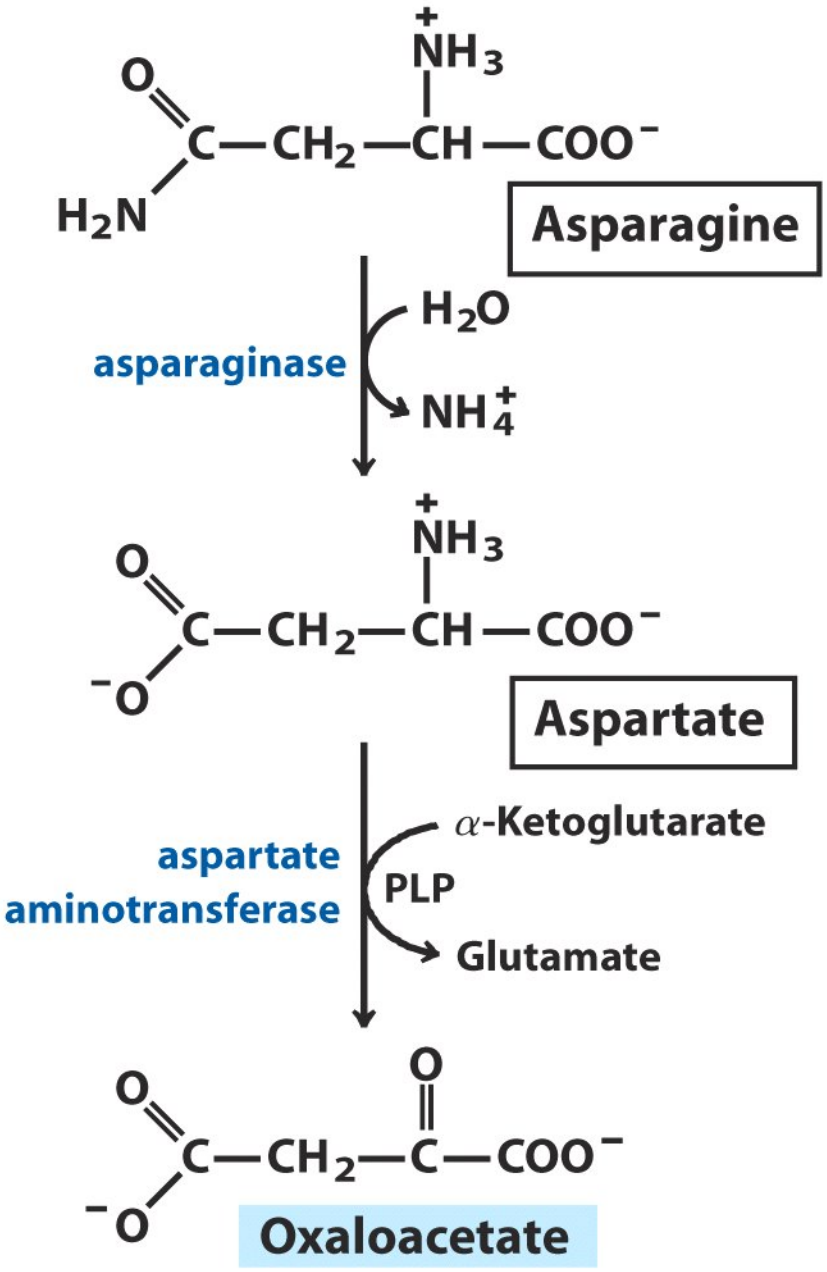
- Four amino acids converted to succinyl CoA. (IMTV)
- isoleucine, methionine, threonine and Valine

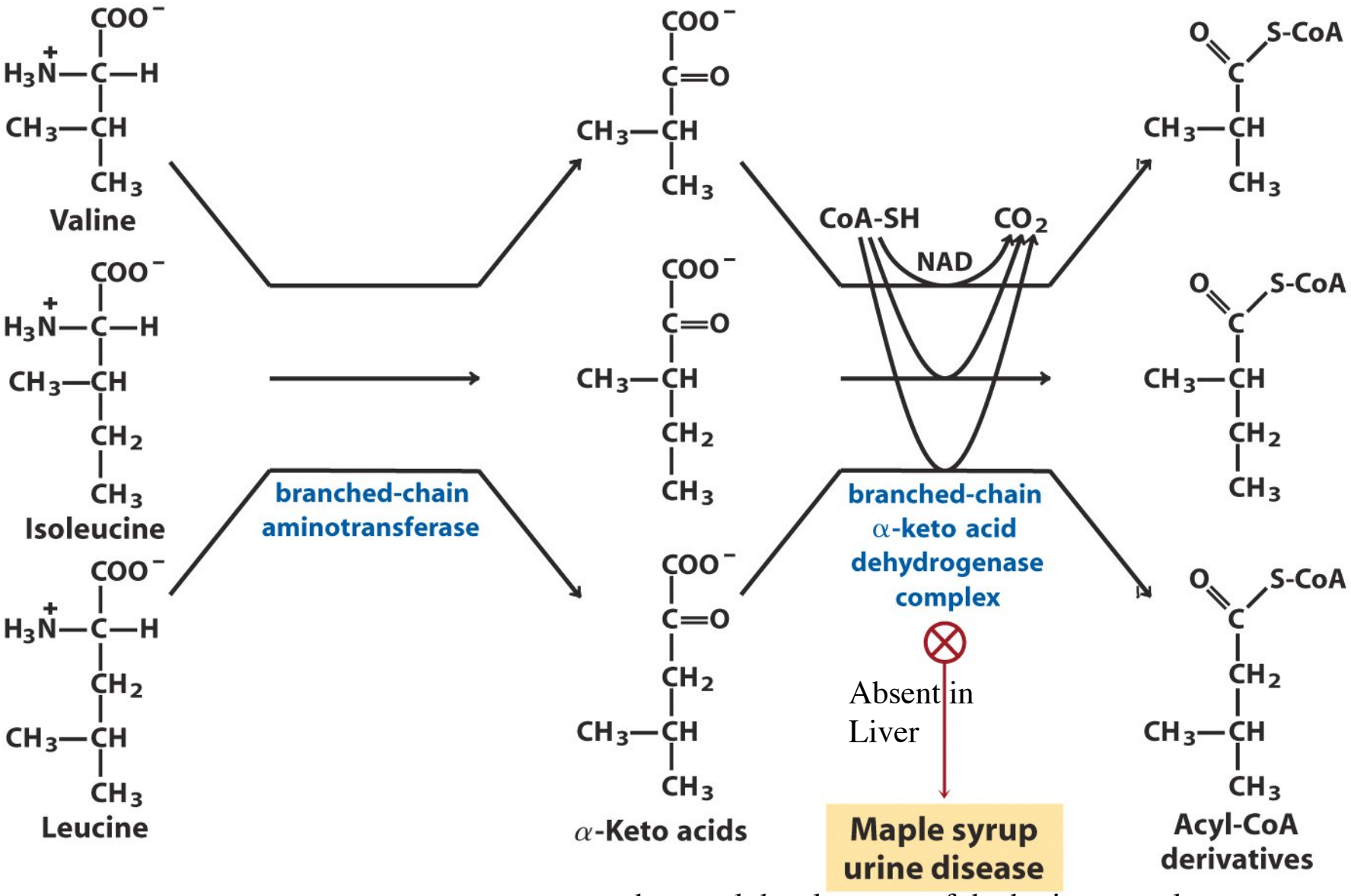
donates its methyl group

through S-adenosylmethionine



lack of this enzyme causes methylmalonic acidemia critical since 4 amino acids metabolize through here


Asparagine
asparaginase
H_2O
NH_4^+
Aspartate
aspartate
aminotransferase
α-Ketoglutarate
PLP
Glutamate
Oxaloacetate



abnormal development of the brain, mental retardation and death in infants. Needs rigid diet

- Human genetic disorders affecting amino acid catabolism

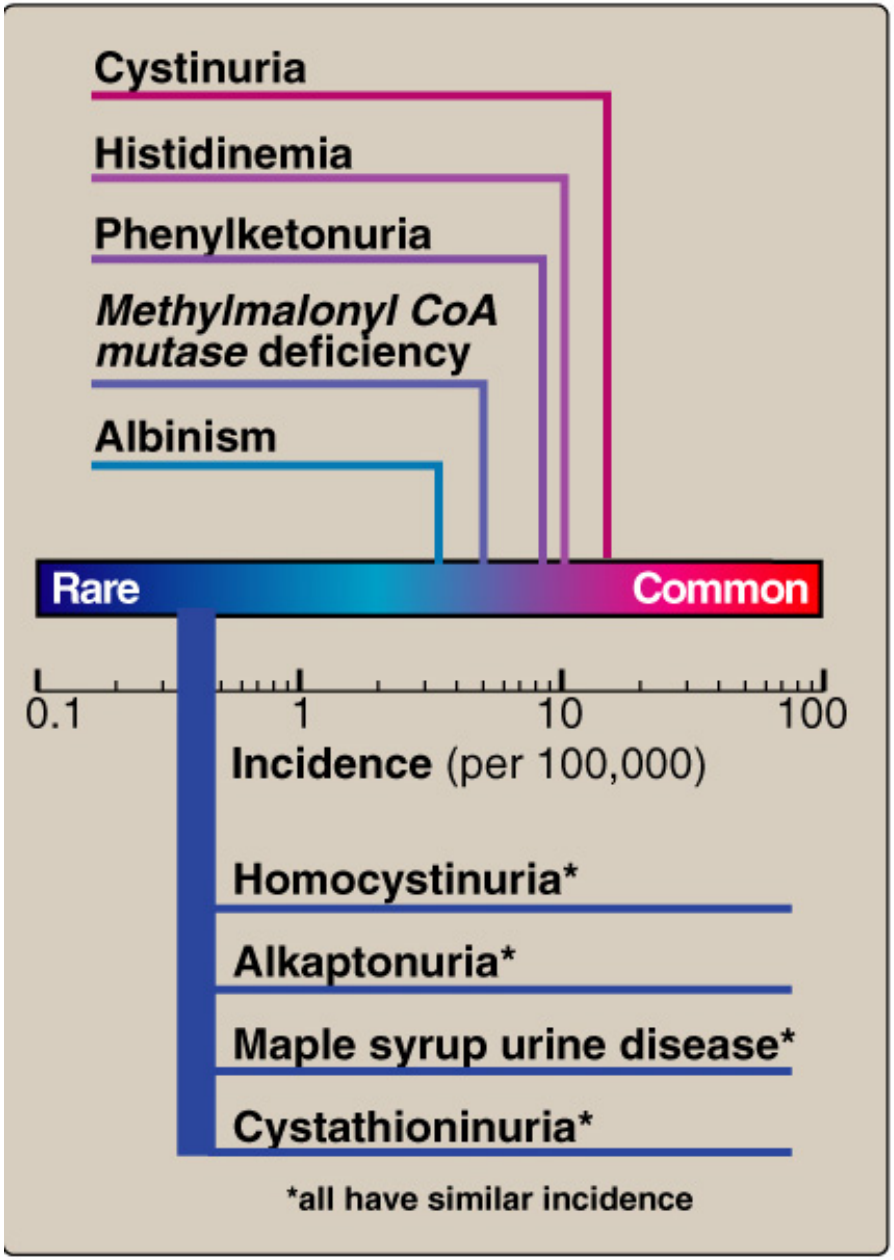


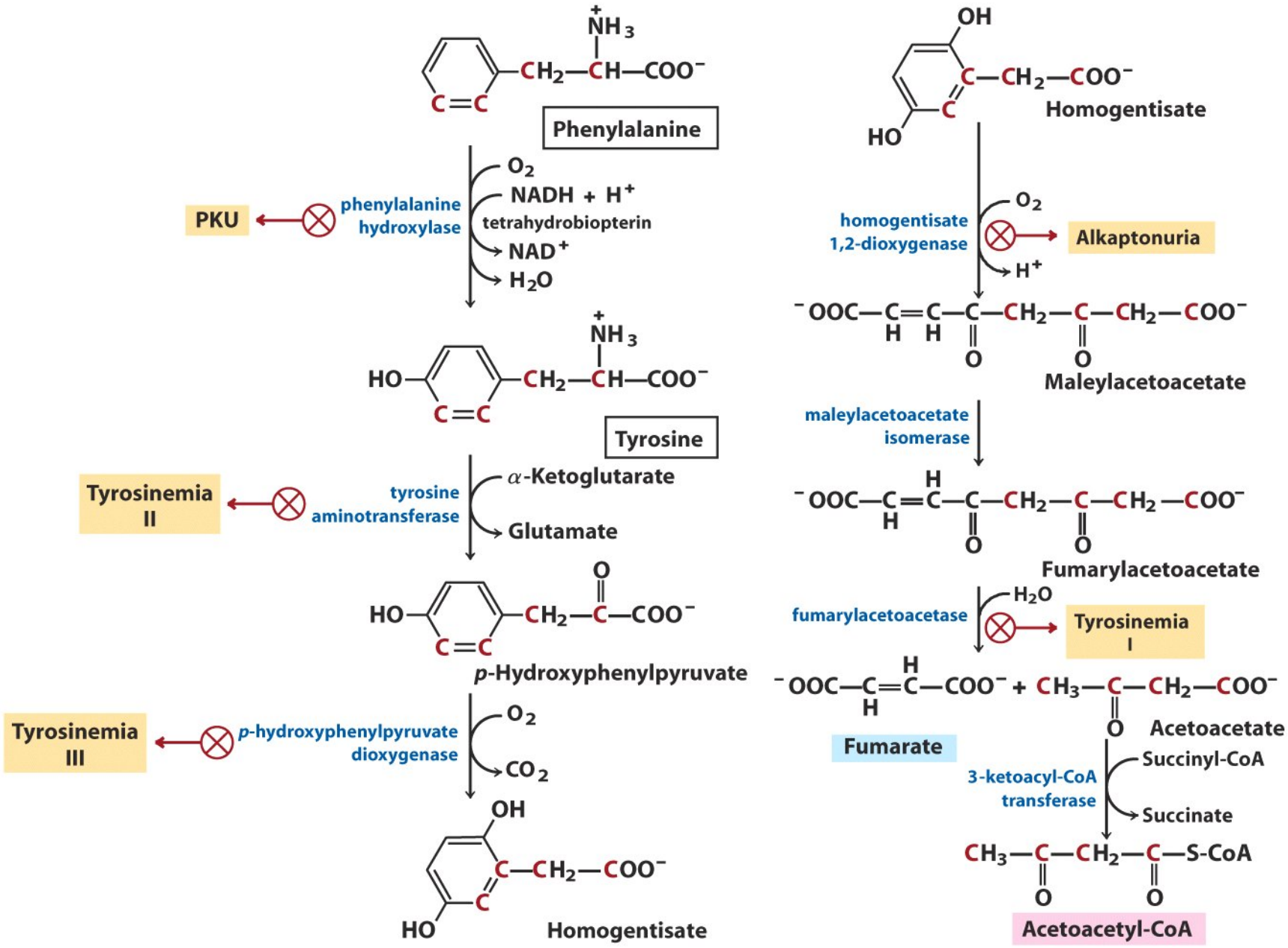
Figure 20.13
Incidence of inherited diseases of amino acid metabolism. [Note: Cystinuria is the most common genetic error of amino acid transport.]

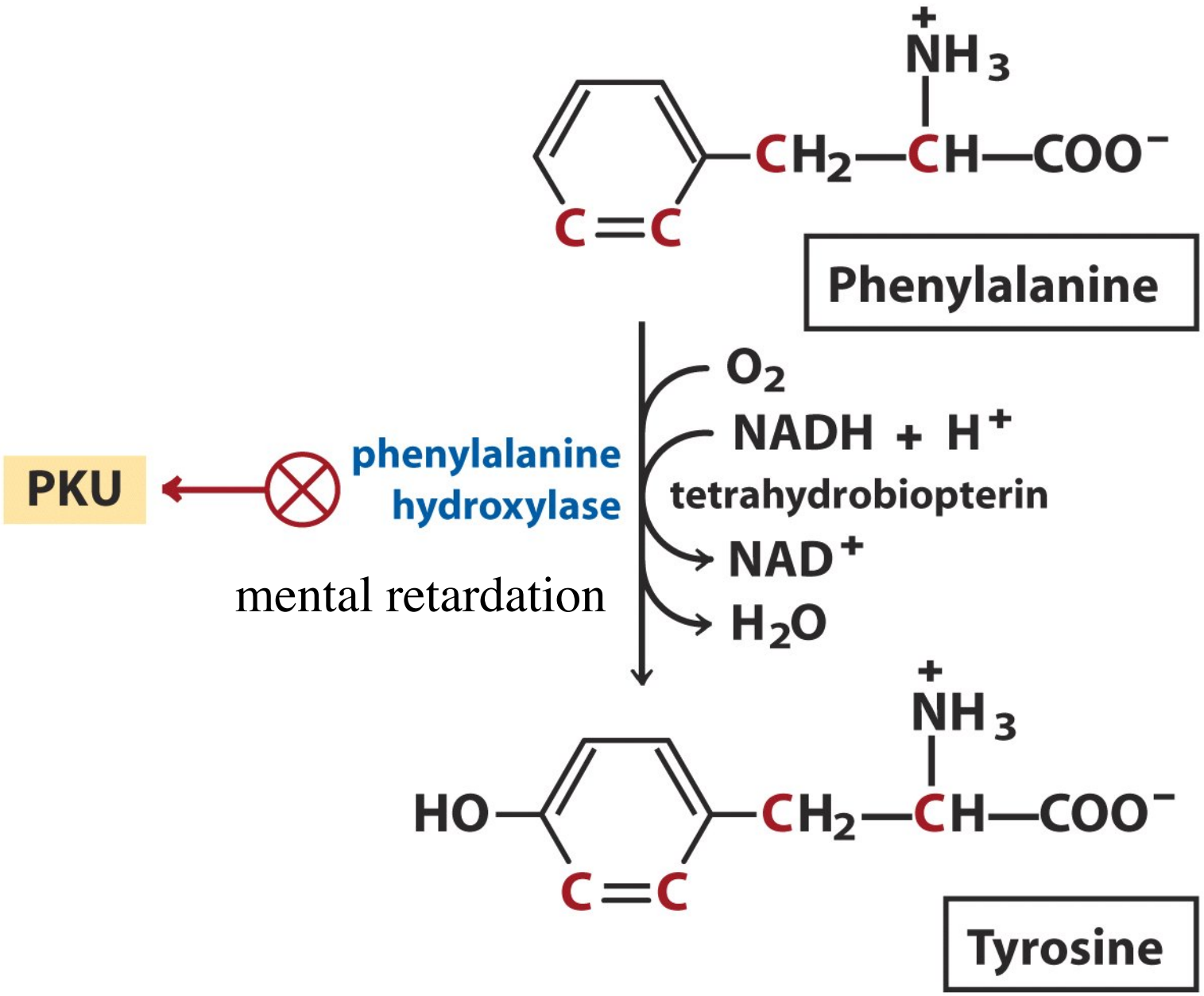
Metabolic defects in amino acid metabolism

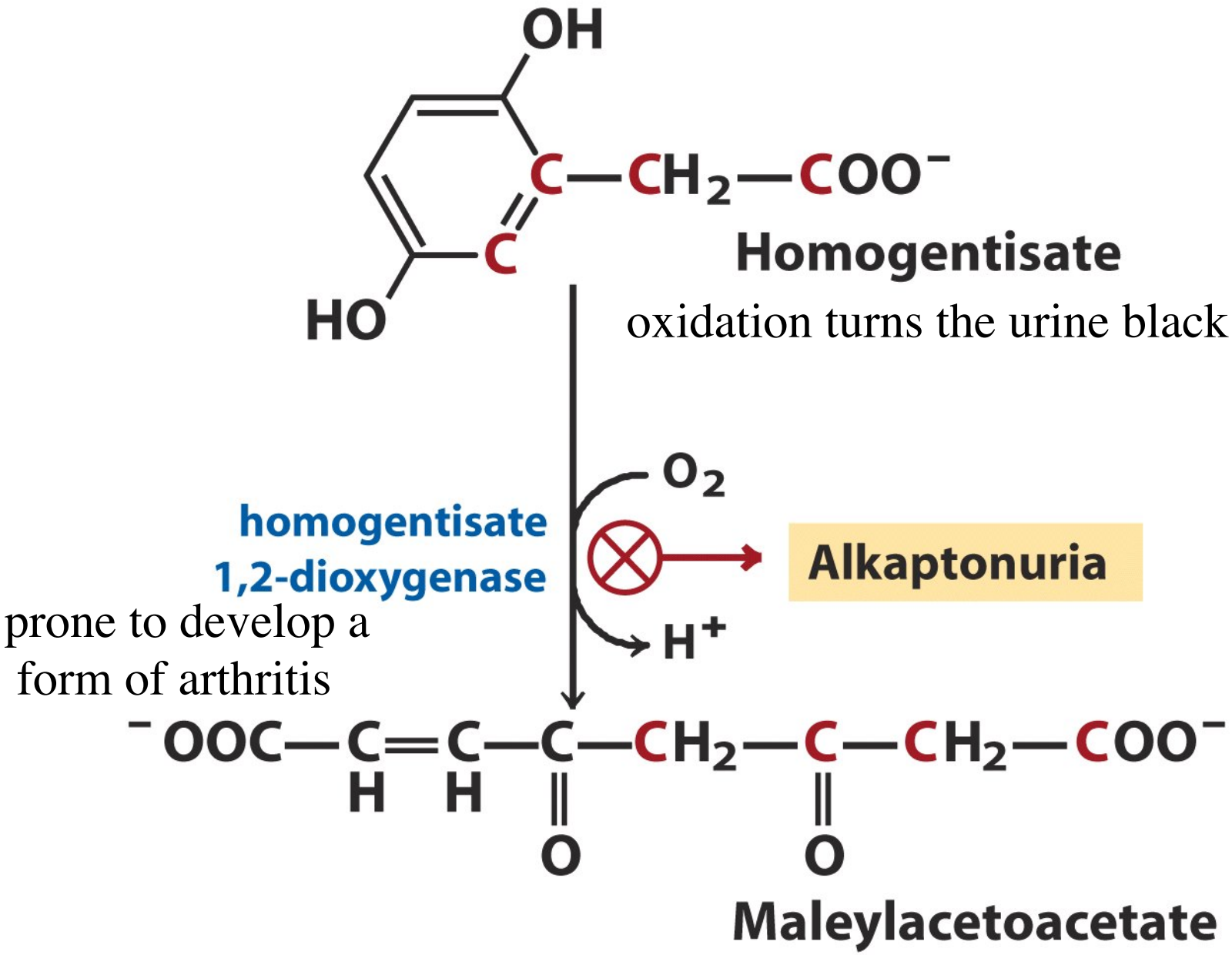
Caused by mutant genes resulting in abnormal proteins, total lost or partial deficiency (more often). Can result in mental retardation or developmental abnormalities. As much as fifty disorders have been described but are rare (why?) 1:250,000 however, we expect this number to increase (why?). These are some of the most commonly encountered diseases with the incidences in most populations. Phenylketonuria, maple syrup urine disease, albinism, homocystinuria and alkaptonuria.

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-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


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 1,2-dioxygenase
Alkaptonuria
O2
H+
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
H2O
Tyrosinemia I
Fumarate
Acetoacetate
3-ketoacyl-CoA transferase
Succinyl-CoA
Succinate
Acetoacetyl-CoA


NH3
CH2—CH—COO−
C=C
Phenylalanine
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
PKU
phenylalanine hydroxylase
mental retardation
HO
NH3
CH2—CH—COO−
C=C
Tyrosine


OH
C—CH2—COO⁻
C
HO
Homogentisate
oxidation turns the urine black
O2
homogentisate
1,2-dioxygenase
Alkaptonuria
H+
prone to develop a
form of arthritis
⁻OOC—C=C—C—CH2—C—CH2—COO⁻
H H O O
Maleylacetoacetate

Phenylketonuria (PKU)

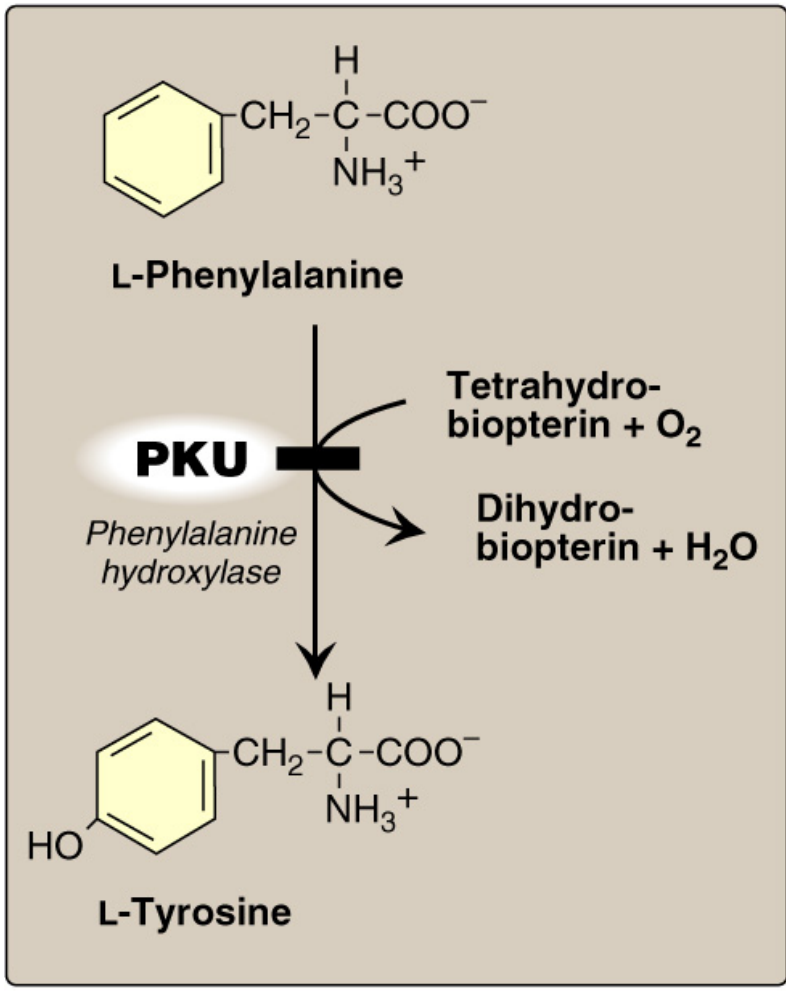


Figure 20.15
A deficiency in *phenylalanine hydroxylase* results in the disease phenylketonuria (PKU).

- Caused by a deficiency in phenylalanine hydroxylase 1:11,000. Hyperphenylalaninemia deficiency in enzymes involved in synthesis of the coenzyme tetrahydrobiopterin BH_4

Hyperphenylalaninemia

- Dihydrobiopterin (BH_4) synthetase
- Dihydrobiopterin (BH_4) reductase
- They are very important in synthesis of neurotransmitters, serotonin and catecolamines, dietary restriction of phenylalanine does not reverse CNS effects replacement therapy with BH_4 and 5-hydroxytryptophan and DOPA (sueño?)

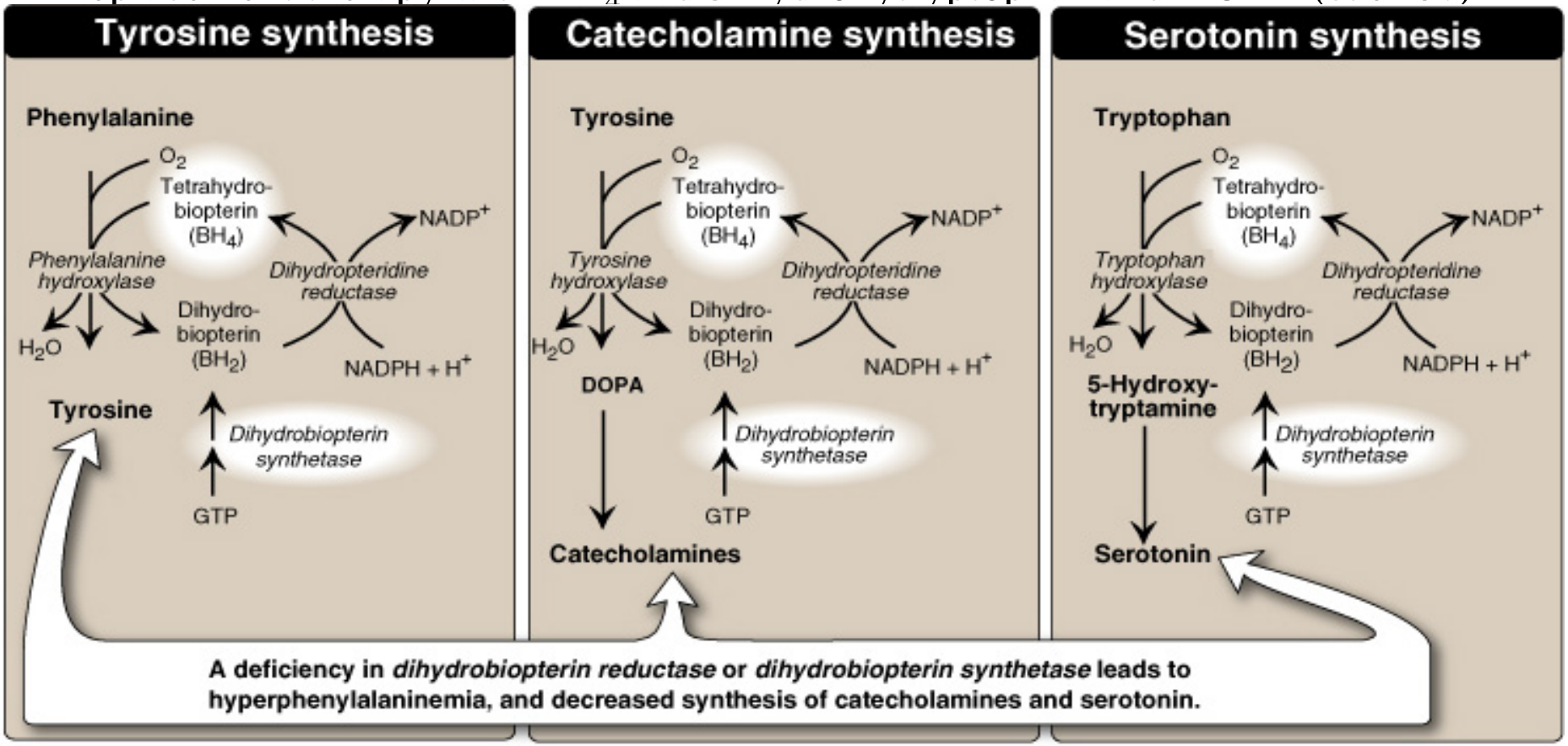


Figure 20.16
Biosynthetic reactions involving amino acids and tetrahydrobiopterin.

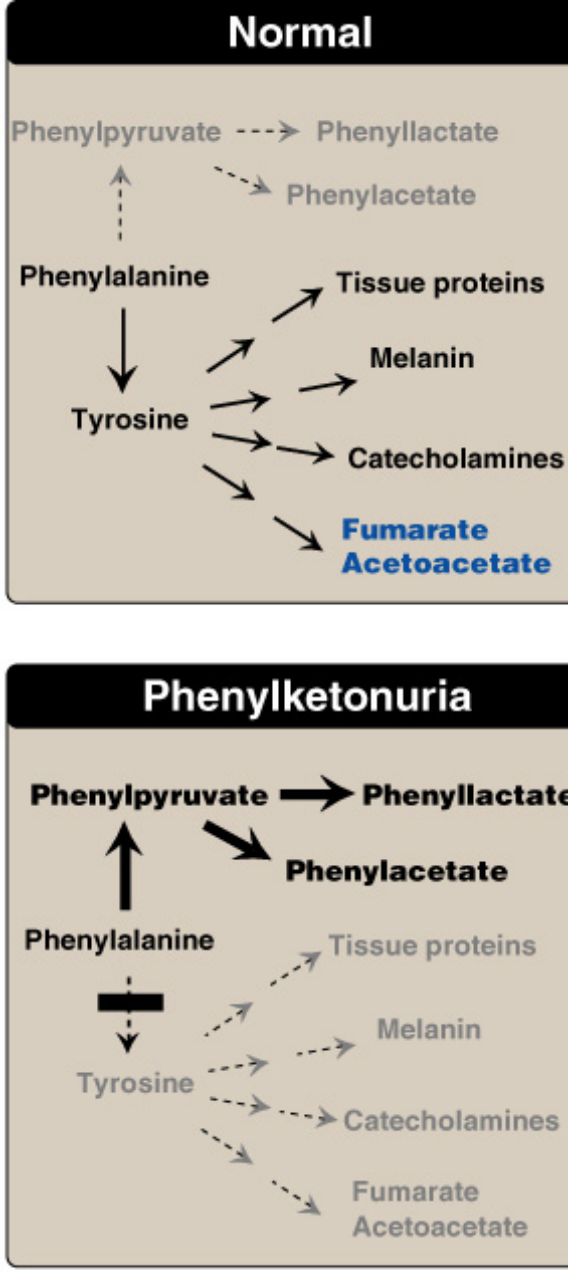


Figure 20.17
Pathways of phenylalanine metabolism in normal individuals and in patients with phenylketonuria.

Characteristics of PKU

- Elevated phenylalanine (tissue, plasma, and urine. Phenylpyruvate, Phenyllactate and Phenylacetate also elevated when normally not . Musty (hongo) odor urine.
- Mental retardation failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, failure to grow. IQ below 50.

- Hypopigmentation deficiency in pigmentation (fair hair, light skin and blue eyes) due to hydroxyation of Tyrosine to melanin which is inhibited by high levels of phenylalanine

Intellectual ability in untreated PKU patients of different ages.

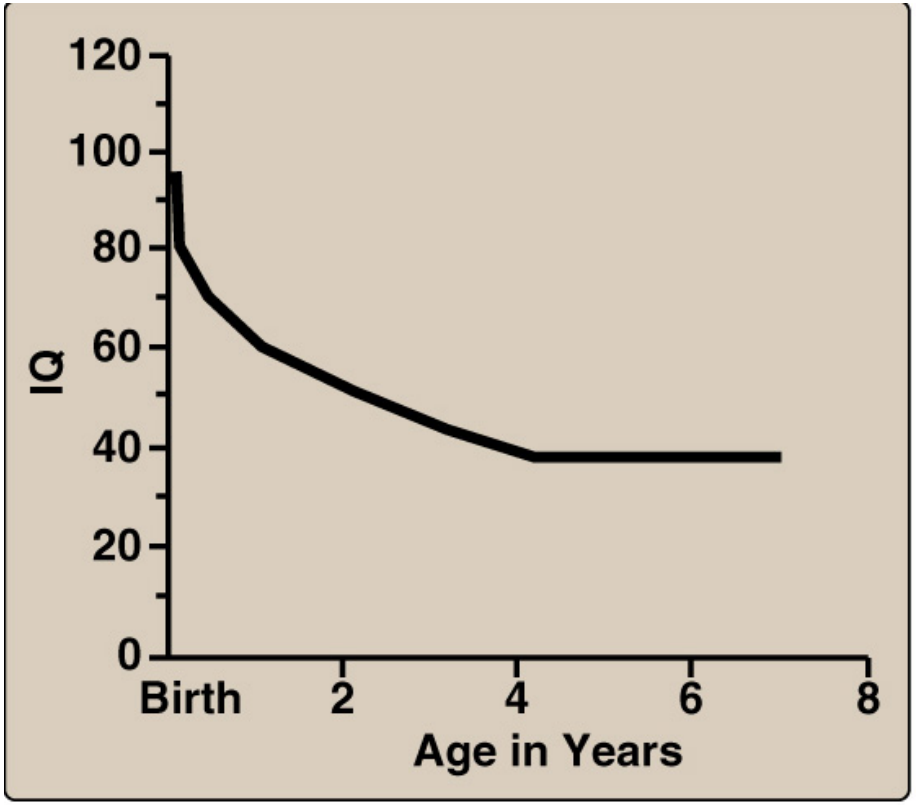


Figure 20.18
Typical intellectual ability in untreated PKU patients of different ages.

Treatment must start within7-10 days of life to prevent retardation

- Maternal PKU syndrome causes microcephaly, mental retardation and congenital heart abnormalities.
- 40 different mutations of the gene phenylalanine hydrohylase 6-10 are causes of PKU.
- Feeding synthetic amino acid preparations low in phenylalanine, with natural foods fruits, vegetables & certain cereals.

Changes in IQ scores after discontinuaton of low-phenylalanine diet in patients with PKU

Synthetic formula with limited ammounts of leucine,isoleucine and valine.

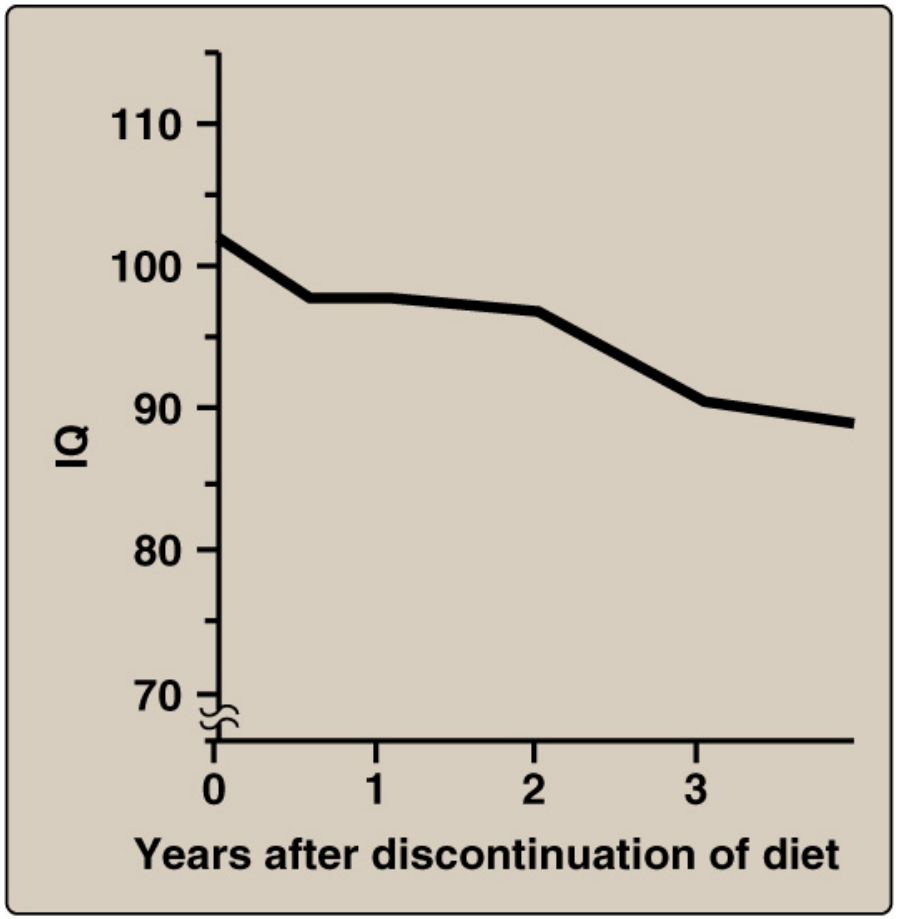
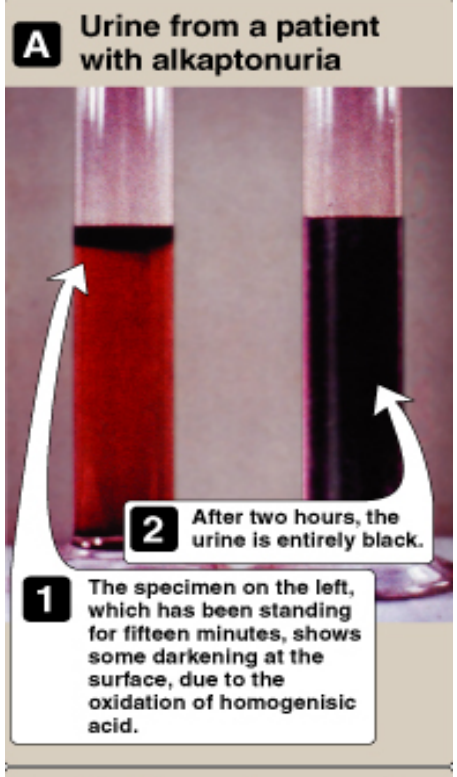
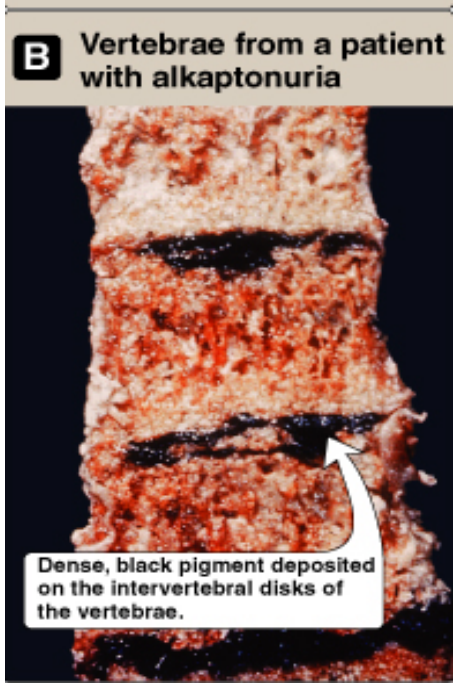


Figure 20.19
Changes in IQ scores after discontinuation of low-phenylalanine diet in patients with phenylketonuria.

- Life long restriction of dietary phenylalanine is recommended
- Maple syrup urine disease (MSUD) recessive disorder deficiency in the branched-chain α-ketoacid dehydrogenase enzyme that decarboxylates leucine, isoleucine and valine these amino acids and their α-ketoacids accumulate in blood with toxic effects that interferes with brain function. Feeding problems, vomiting, dehydration, severe metabolic acidosis and maple syrup odor. Mental retardation, phsical disability and death.

Alkaptonuria

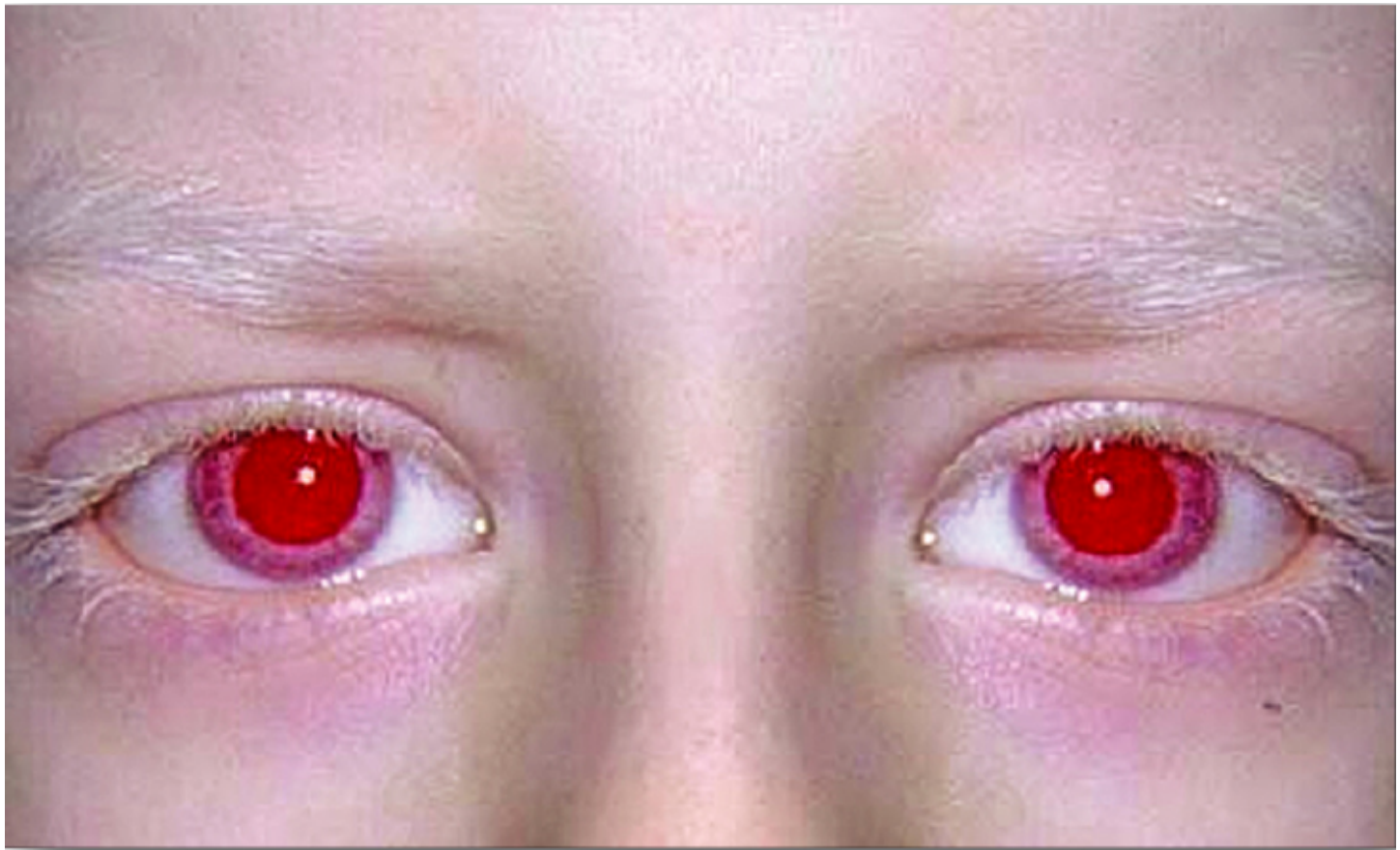




- Rare metabolic disease involving the deficiency in homogentisic acid oxidase, resulting in accumulation of homogentisic acid (degradative pathway of tyrosine) Symptoms
- Homogentisic aciduria (high levels of this acid in urine gives it a dark color upon standing (Fig. A)
- Large joint arthritis
- Pigmentation of cartilage (Fig. B)asymptomatic until age of forty
- Diets low in protein recommended although no treatment as such

Albinism

A group of conditions with a defect of in tyrosine metabolism in a deficiency in the production of melanin. This suggest that melanin production depends on this pathway and other pathways are not available. Autosomal recessive, autosomal dominant and X-linked. Photophobia, they sunburn easily and do not tan.



Homocystinuria

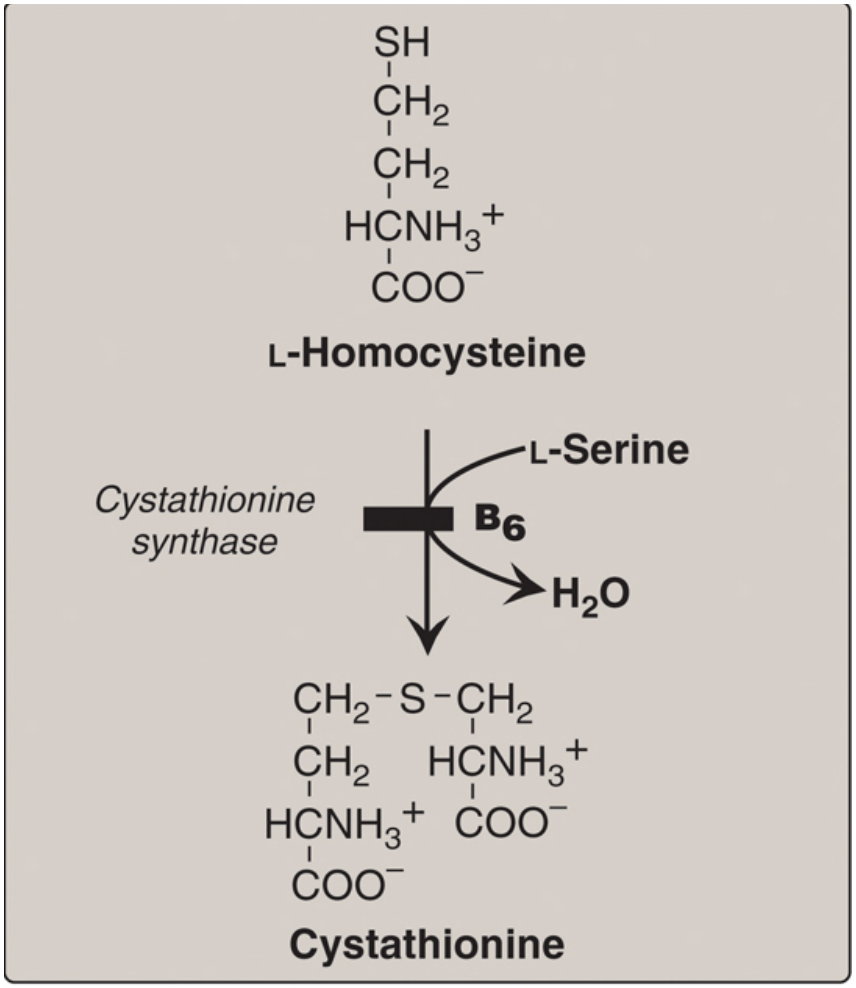
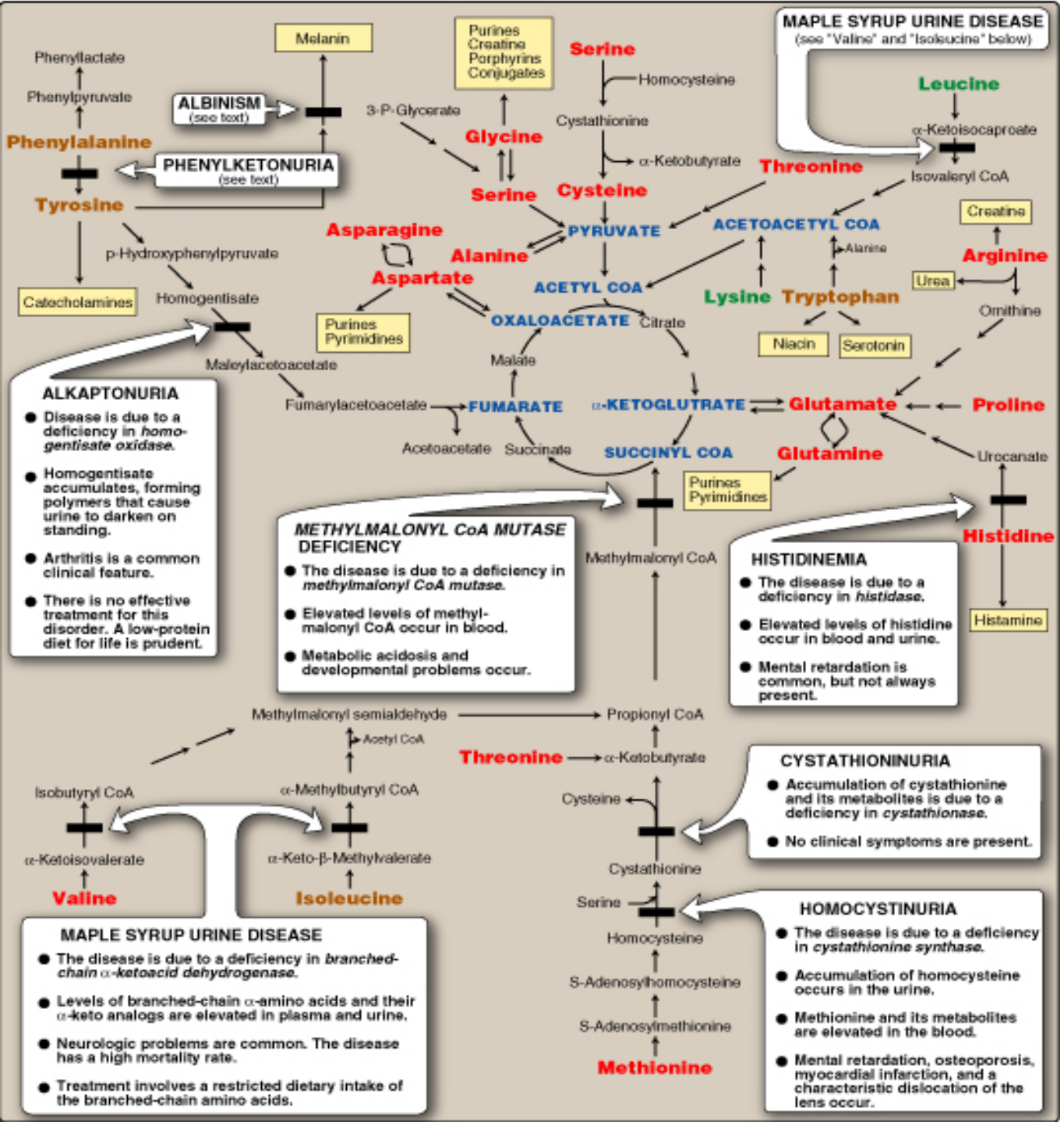


Figure 20.21
Enzyme deficiency in homocystinuria.

- Disorder involving defects in the metabolism of homocysteine (autosomal recessive) High plasma and urinary levels of this amino acid and methionine and low levels of cysteine. Common cause is the defect of cystathionine synthase which converts homocysteine to cystathionine. Homozygous show ectopia lentis (displacement of the lens) skeletal abnormaliities, premature arterial disease, osteoporosis and mental retardation. Patients could or not be responsive to vitamin B_6 (cofactor).

TREATMENT: restriction of methionine intake and supplement with vitamins B_6 and B_{12} and folate.



Good review slide for metabolism of amino acids and diseases caused by enzyme deficiency. Notice glucogenic and ketogenic amino acids and metabolites of each amino acid

Summary

Amino acids that yield Pyruvate or intermediates in the TCA cycle are called glycogenic. They can give rise to glycogen or glucose in the liver and glycogen in muscle. Amino acids that whose catabolism yield acetyl CoA, acetoacetyl Co A are termed ketogenic (Tyrosine, phenylalanine, tryptophan isoleucine are both ketogenic and glucogenic Leucine and lysine are ketogenic. Non-essential AA can be synthesized from metabolic intermediates or carbon skeletons of essential AA. Alanine, aspartate, glutamate, glutamine, asparagine, proline, cysteine, serine, glycine, and tyrosine.

Essential AA in diet methionine, phenylalanine.

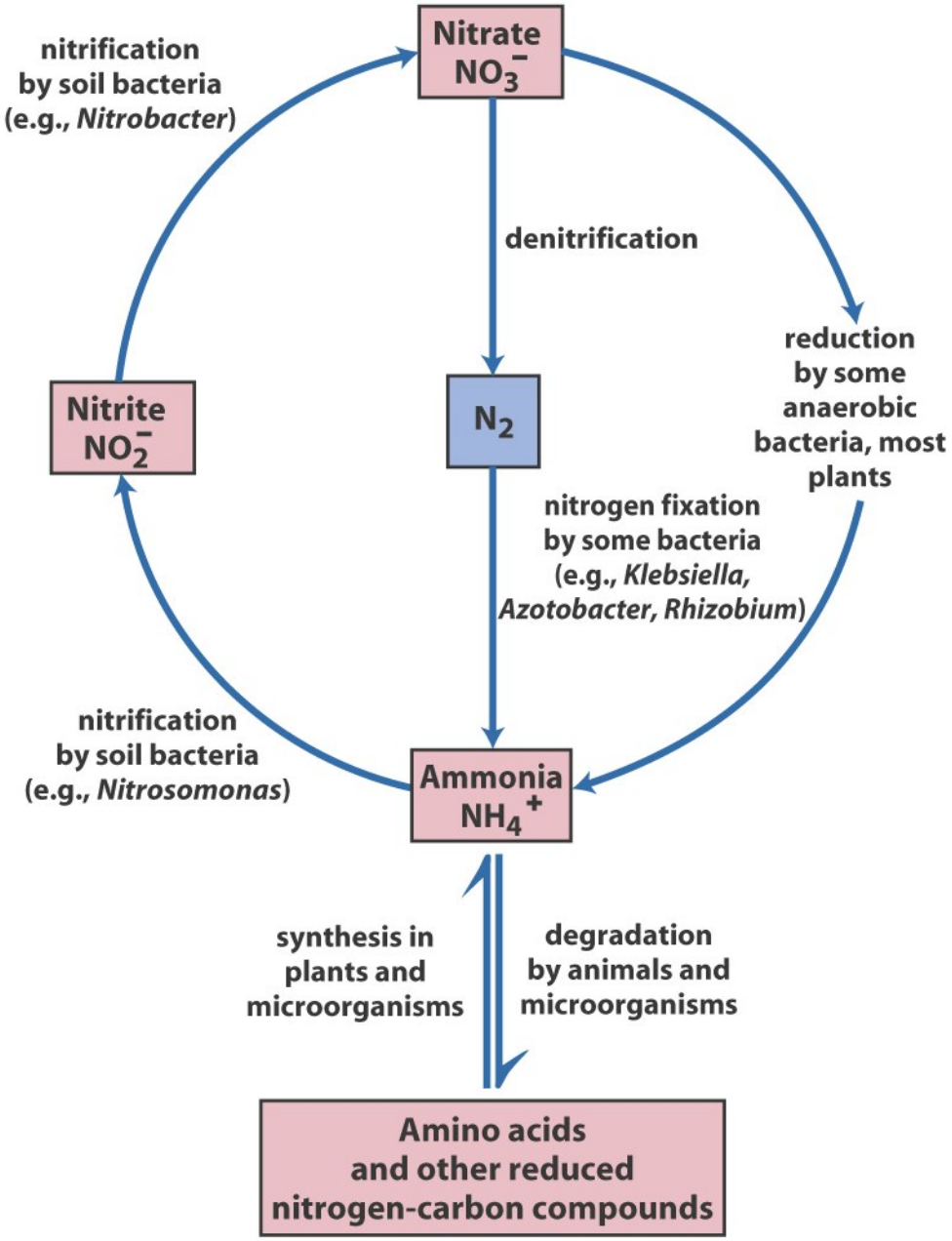
Metabolic diseases

PKU (-) phenylalanine hydroxylase,

Hyperphenylalanine (-) BH_4 Synthetase or reductase coenzyme of PH tetrahydrobiopterin. Untreated patients of PKU suffer mental retardation failure to walk or talk, seizure, hyperactivity, tremor etc. Tyrosine becomes essential under this condition.

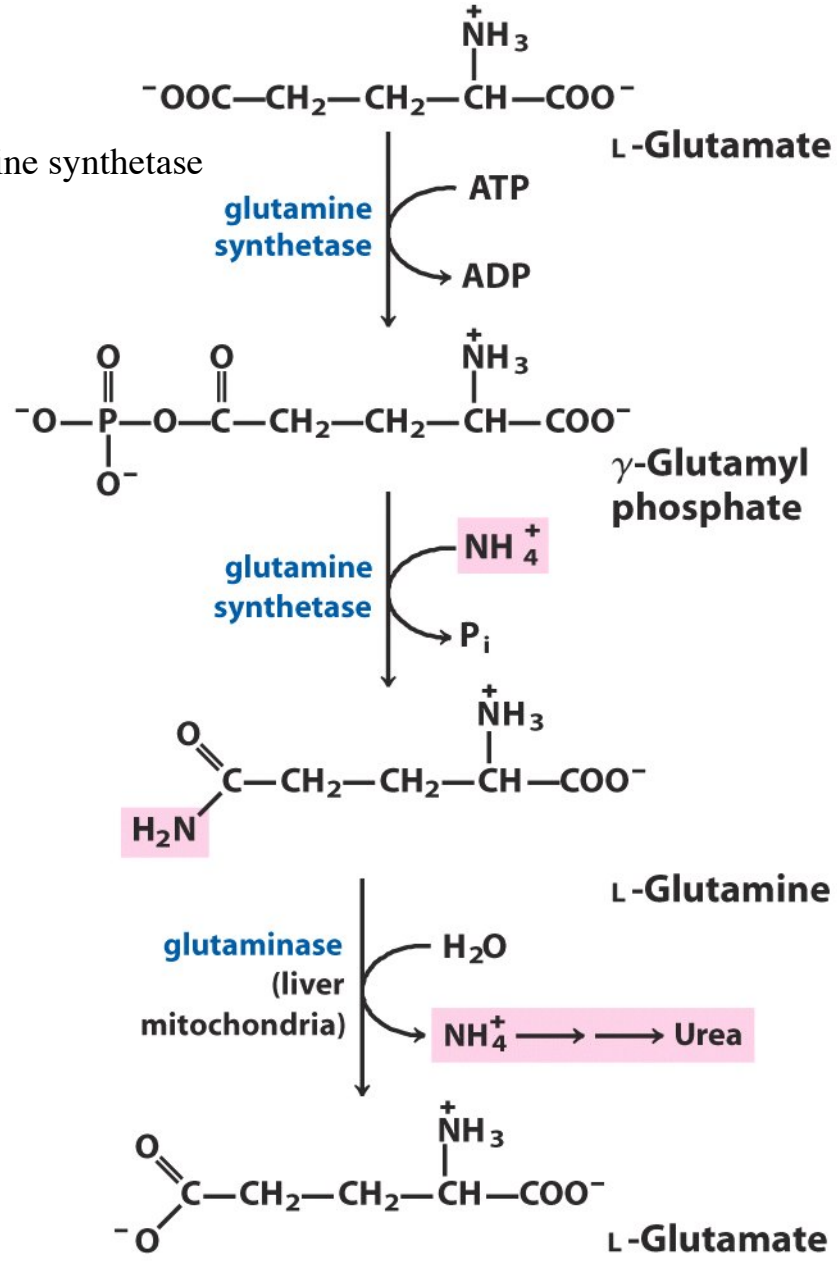
(MSUD) (-) branched chain α-ketoacid dehydrogenase

- Biosynthesis of amino acids (non-essential)
- most N2 is bound to amino acids and nucleotides
- pathways of amino acid synthesis and nucleotides are intertwined with common intermediates. Amino acids are incorporated into the structures of pyrimidines and purines and the purine ring is incorporated into an amino acid Histidine.

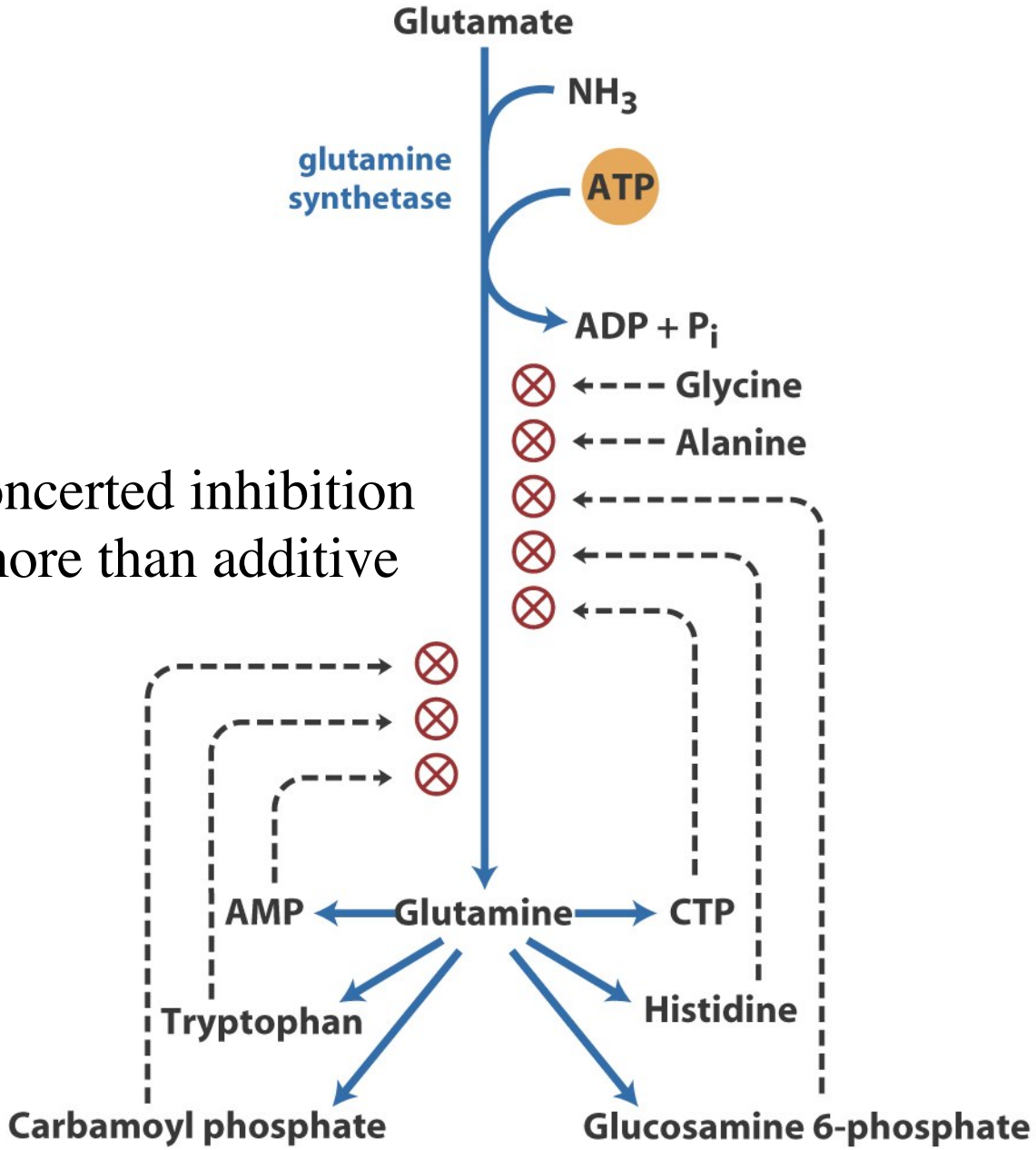

Nitrate
NO_3^-
nitrification
by soil bacteria
(e.g., *Nitrobacter*)
denitrification
reduction
by some
anaerobic
bacteria, most
plants
Nitrite
NO_2^-
N_2
nitrogen fixation
by some bacteria
(e.g., *Klebsiella*,
Azotobacter, *Rhizobium*)
nitrification
by soil bacteria
(e.g., *Nitrosomonas*)
Ammonia
NH_4^+
synthesis in
plants and
microorganisms
degradation
by animals and
microorganisms
Amino acids
and other reduced
nitrogen-carbon compounds

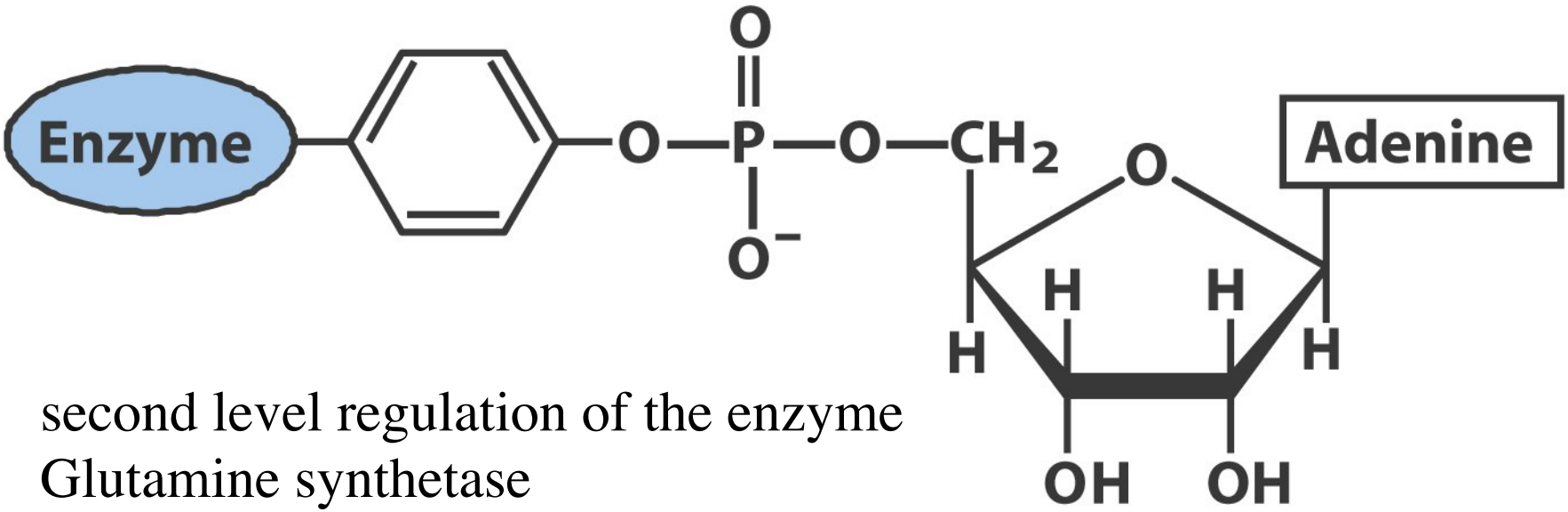
Ammonia is incorporated into biomolecules through Glutamate and Glutamine they provide the critical entry point. These same amino acids play a central role in catabolism. They are present at high conc. in extracellular fluid up to an order of magnitude higher

incorporation of NH4 into
glutamate requires glutamine synthetase

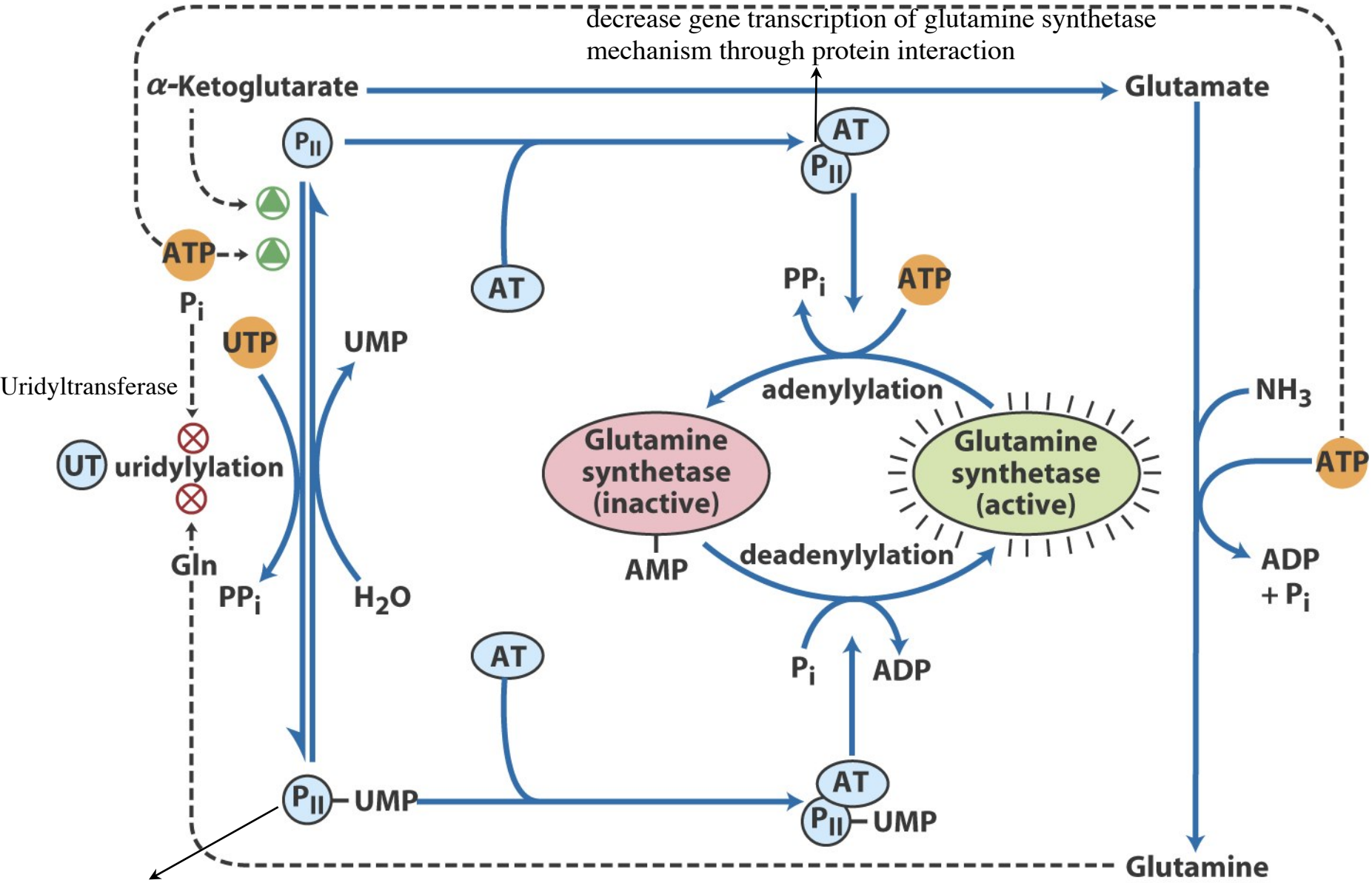


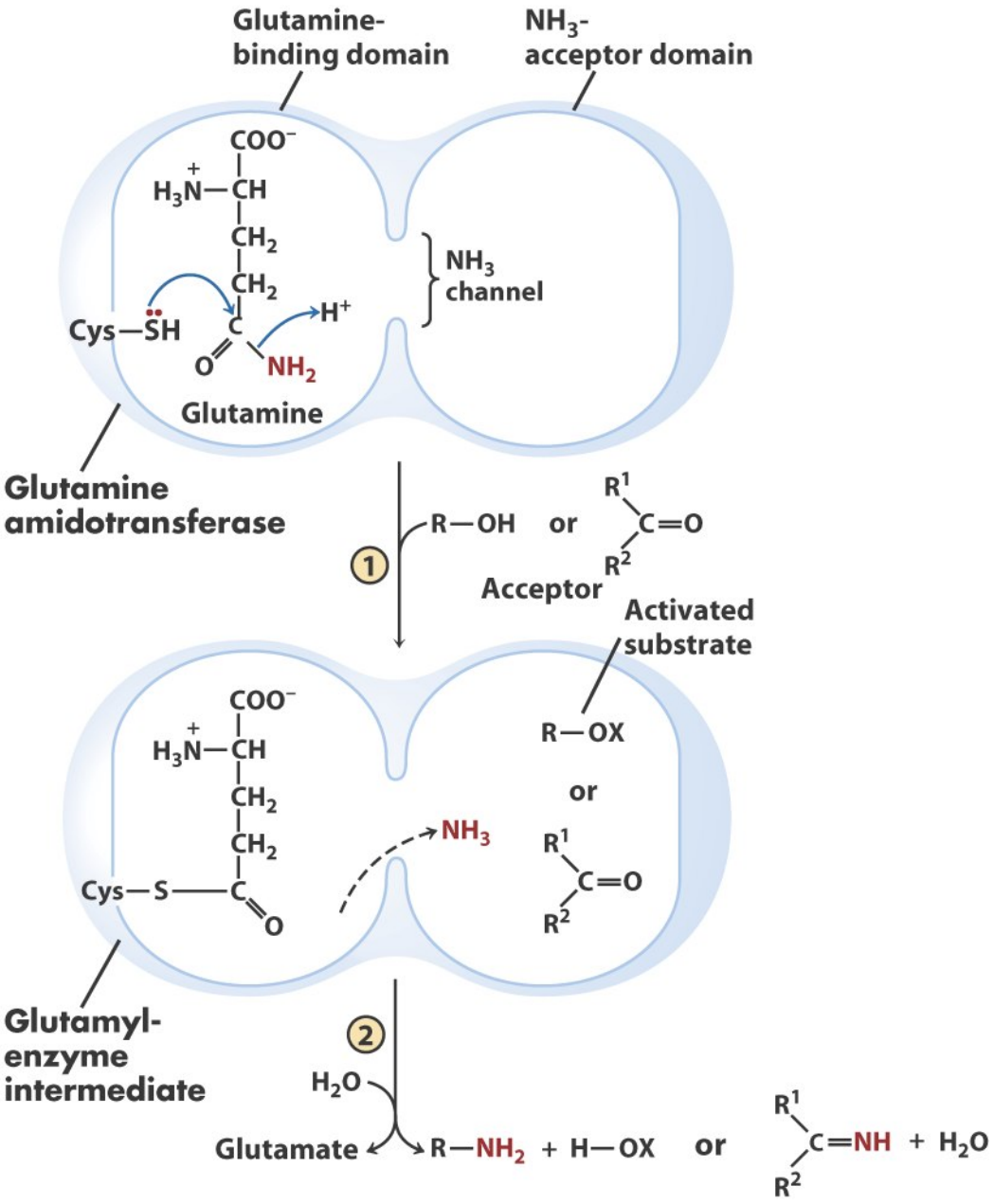
concerted inhibition
more than additive





second level regulation of the enzyme
Glutamine synthetase
adenylylation (AMP) of Tyr 397 covalent
binding increases sensitivity to inhibitors
adenylyltransferase (AT next figure)
this enzyme responds to levels of glutamine, alpha ketoglutarate, ATP and Pi


decrease gene transcription of glutamine synthetase
mechanism through protein interaction
α-Ketoglutarate
Glutamate
PII
AT
PII
ATP
Pi
AT
PPi
ATP
UTP
UMP
Uridyltransferase
adenylylation
NH3
Glutamine synthetase (inactive)
Glutamine synthetase (active)
ATP
UT
uridylylation
AMP
deadenylylation
ADP + Pi
Gln
PPi
H2O
AT
Pi
ADP
PII
UMP
AT
PII
UMP
Glutamine
induces gene transcription of glutamine synthetase


Glutamine-binding domain
NH3-acceptor domain
COO⁻
H3N—CH
CH2
CH2
Cys—SH
H+
NH2
O
Glutamine
NH3 channel
Glutamine amidotransferase
1
R—OH
or
R1
C=O
R2
Acceptor
Activated substrate
R—OX
or
NH3
Cys—S
Glutamyl-enzyme intermediate
2
H2O
Glutamate
R—NH2 + H—OX
or
C=NH + H2O

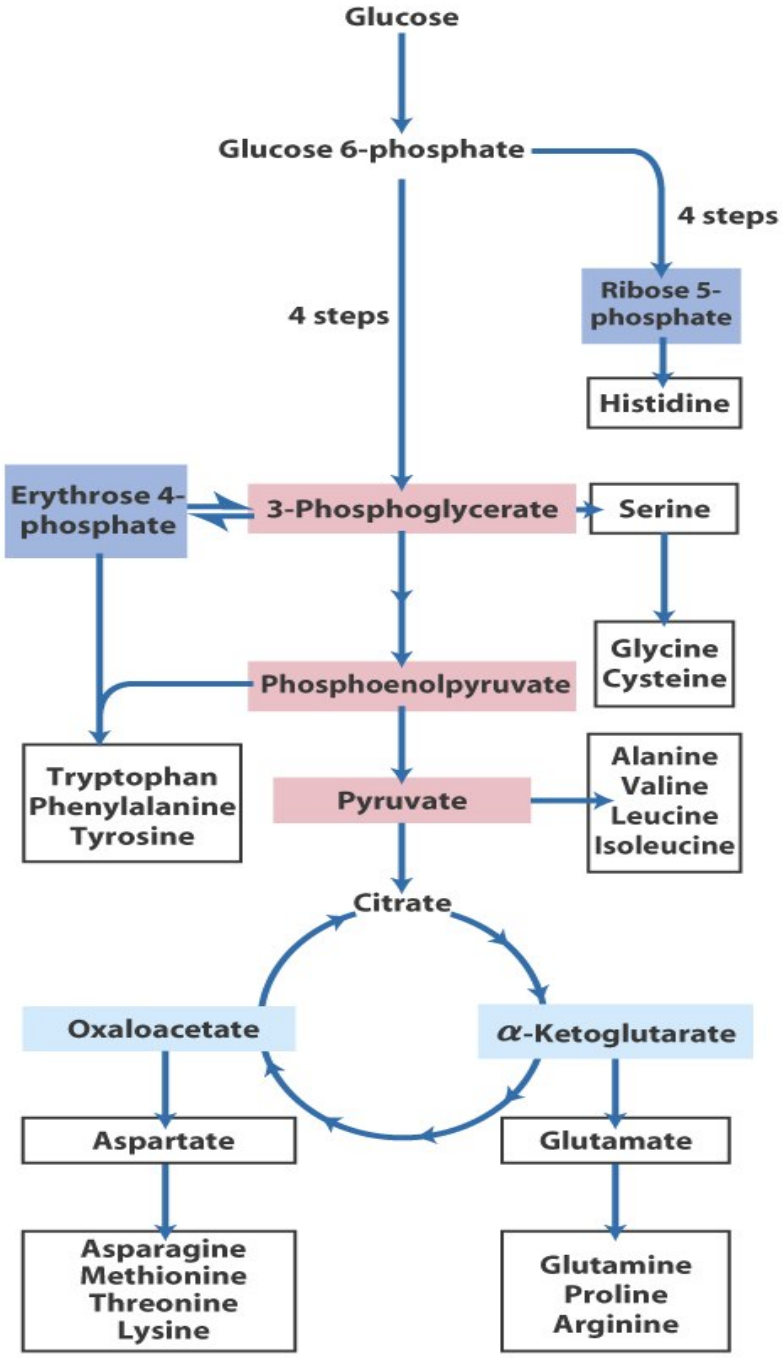

Glucose
Glucose 6-phosphate
4 steps
Ribose 5-phosphate
Histidine
4 steps
Erythrose 4-phosphate
3-Phosphoglycerate
Serine
Glycine
Cysteine
Phosphoenolpyruvate
Tryptophan
Phenylalanine
Tyrosine
Pyruvate
Alanine
Valine
Leucine
Isoleucine
Citrate
Oxaloacetate
α-Ketoglutarate
Aspartate
Glutamate
Asparagine
Methionine
Threonine
Lysine
Glutamine
Proline
Arginine

TABLE 22–1 Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate
- Glutamate
- Glutamine
- Proline
- Arginine

3-Phosphoglycerate
- Serine
- Glycine
- Cysteine

Oxaloacetate
- Aspartate
- Asparagine
- Methionine*
- Threonine*
- Lysine*

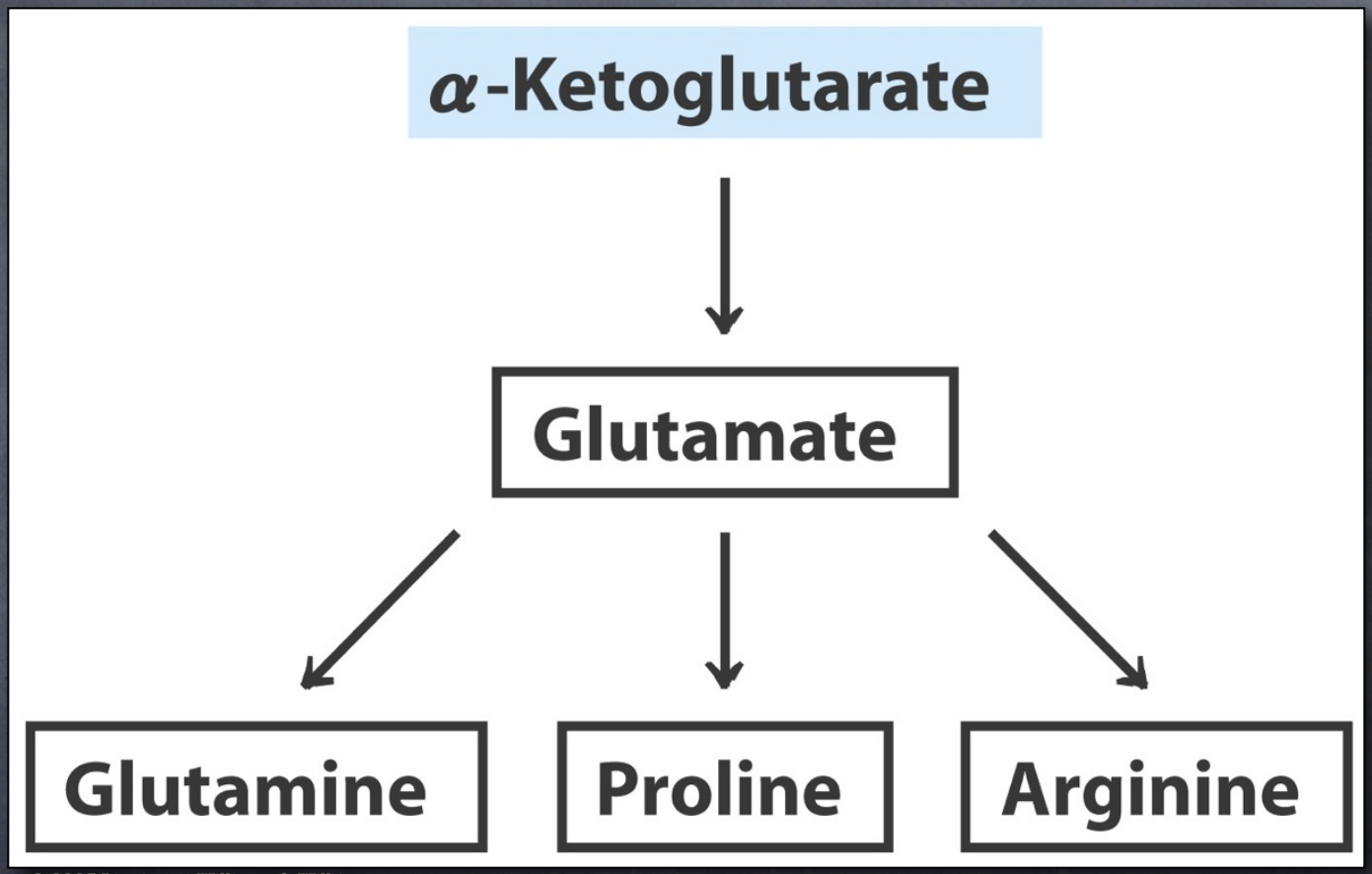
Pyruvate
- Alanine
- Valine*
- Leucine*
- Isoleucine*

Phosphoenolpyruvate and erythrose 4-phosphate
- Tryptophan*
- Phenylalanine*
- Tyrosine†

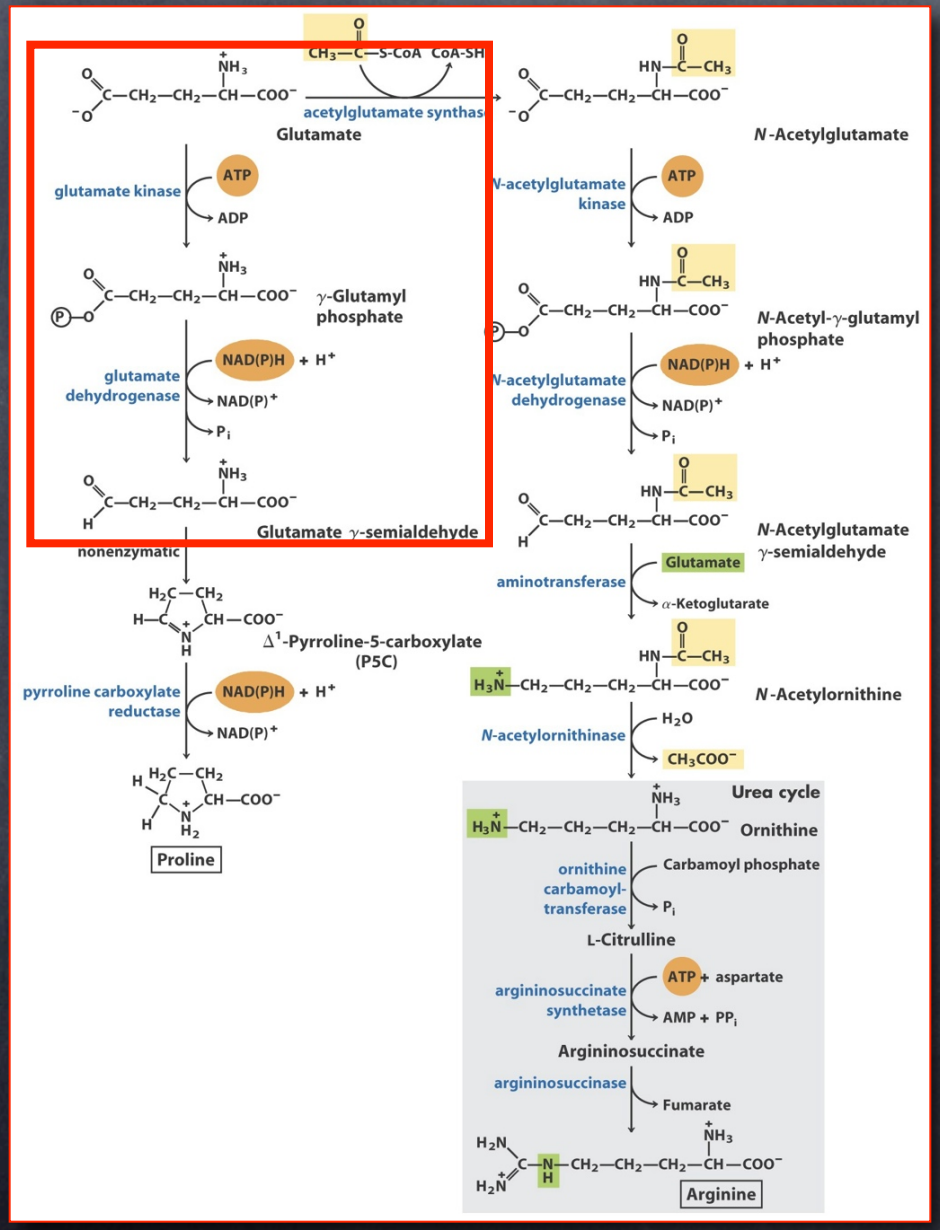
Ribose 5-phosphate
- Histidine*

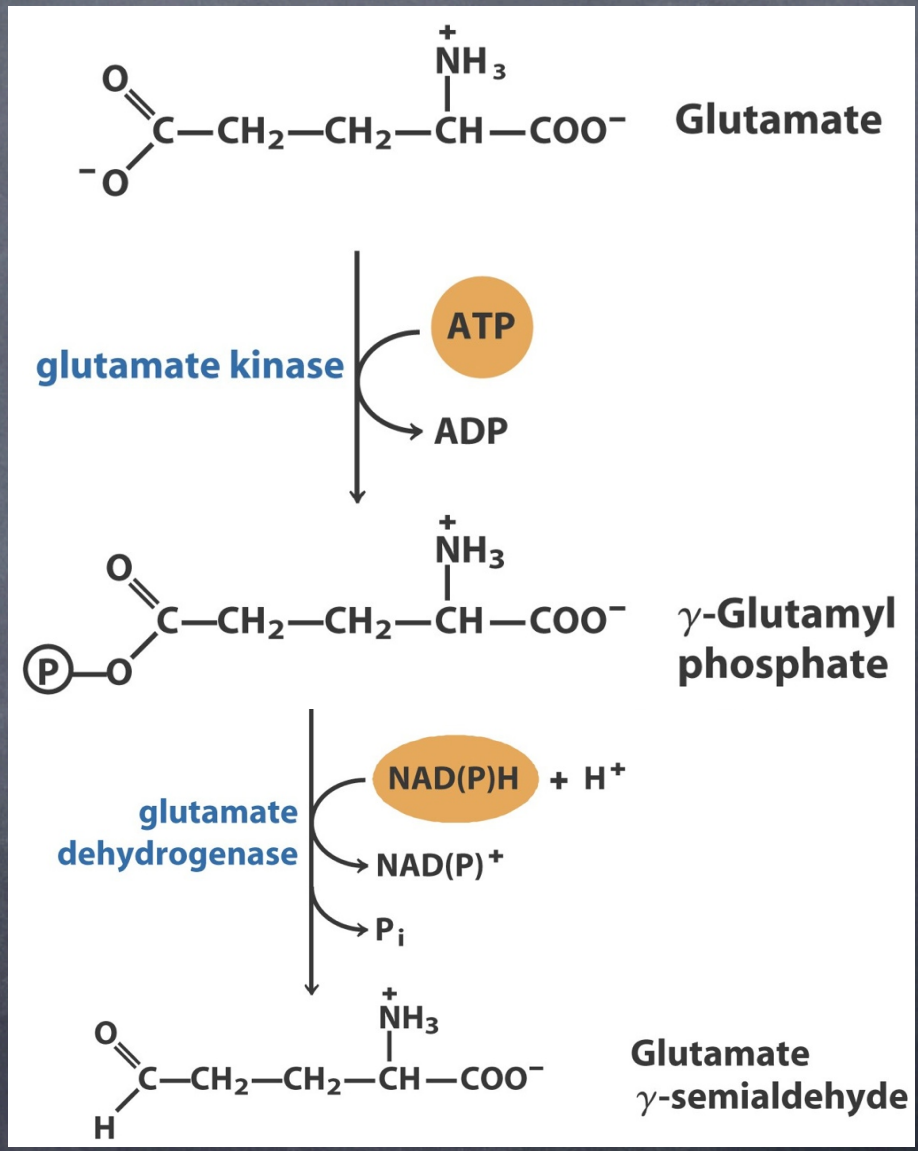
*Essential amino acids.
†Derived from phenylalanine in mammals.

Synthesis of Glutamate, Glutamine, Proline and Arginine

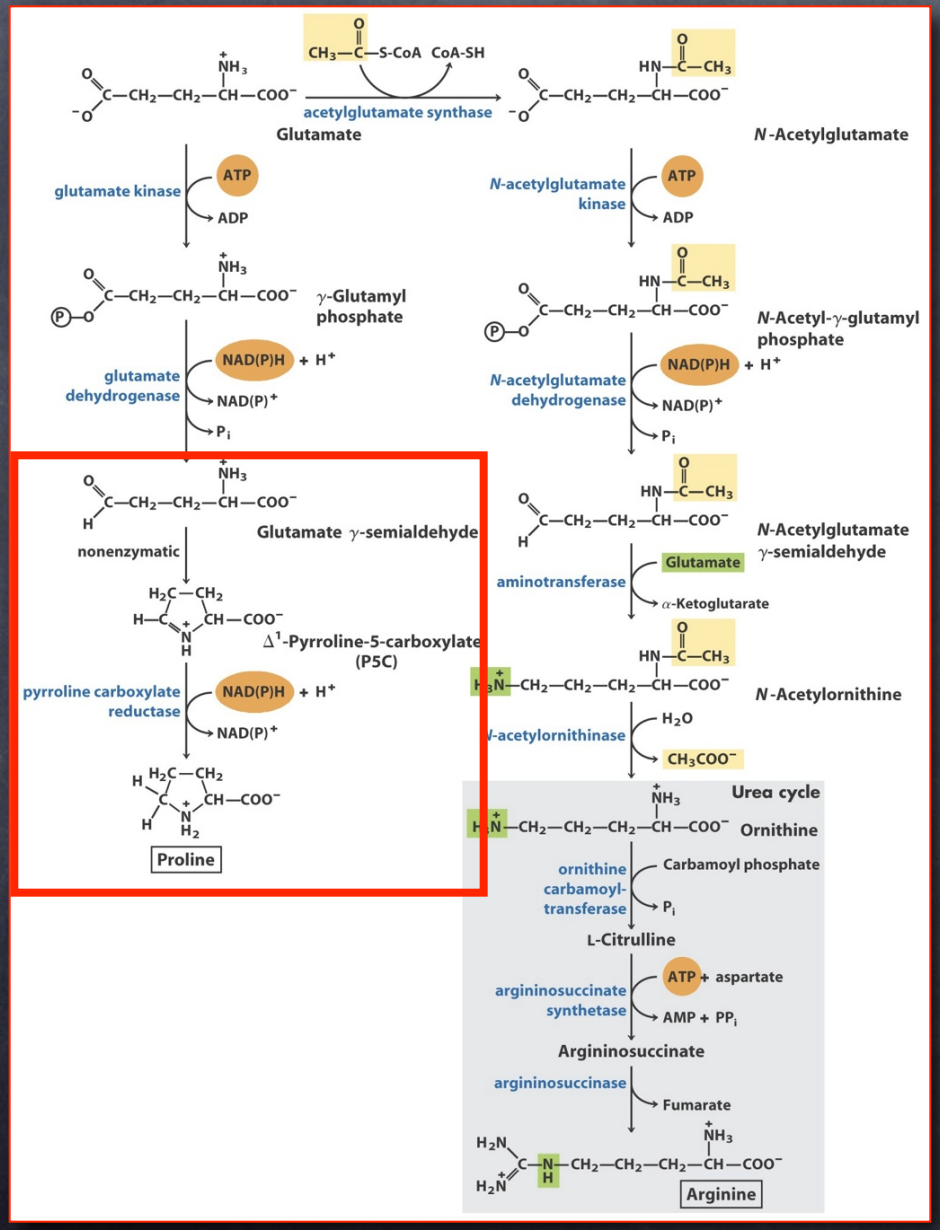


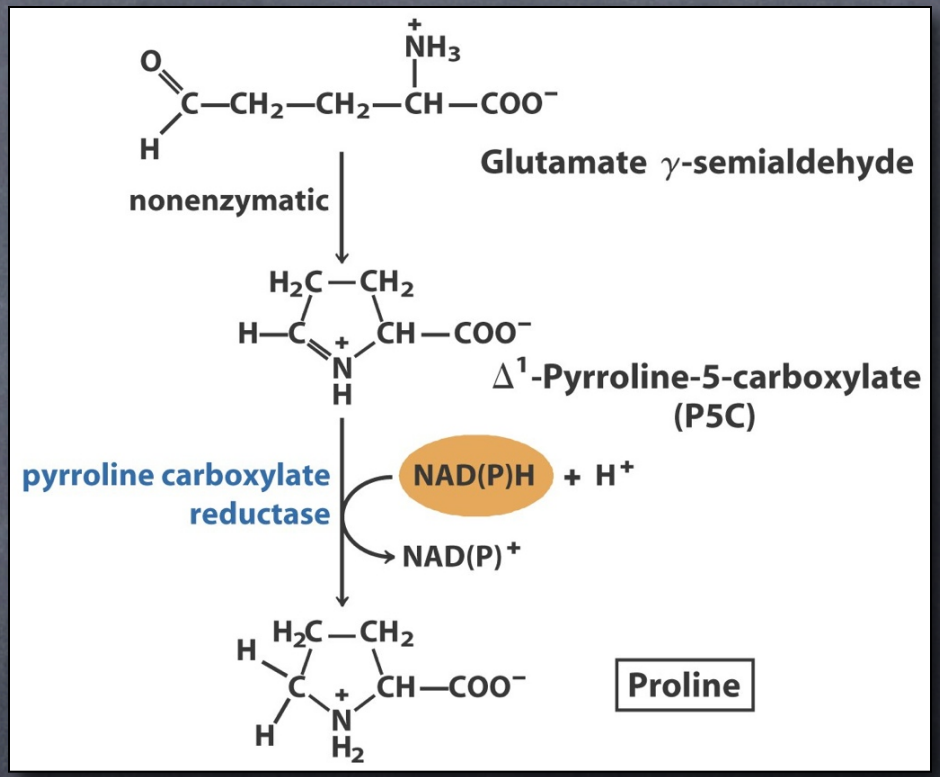
Biosynthesis of Proline



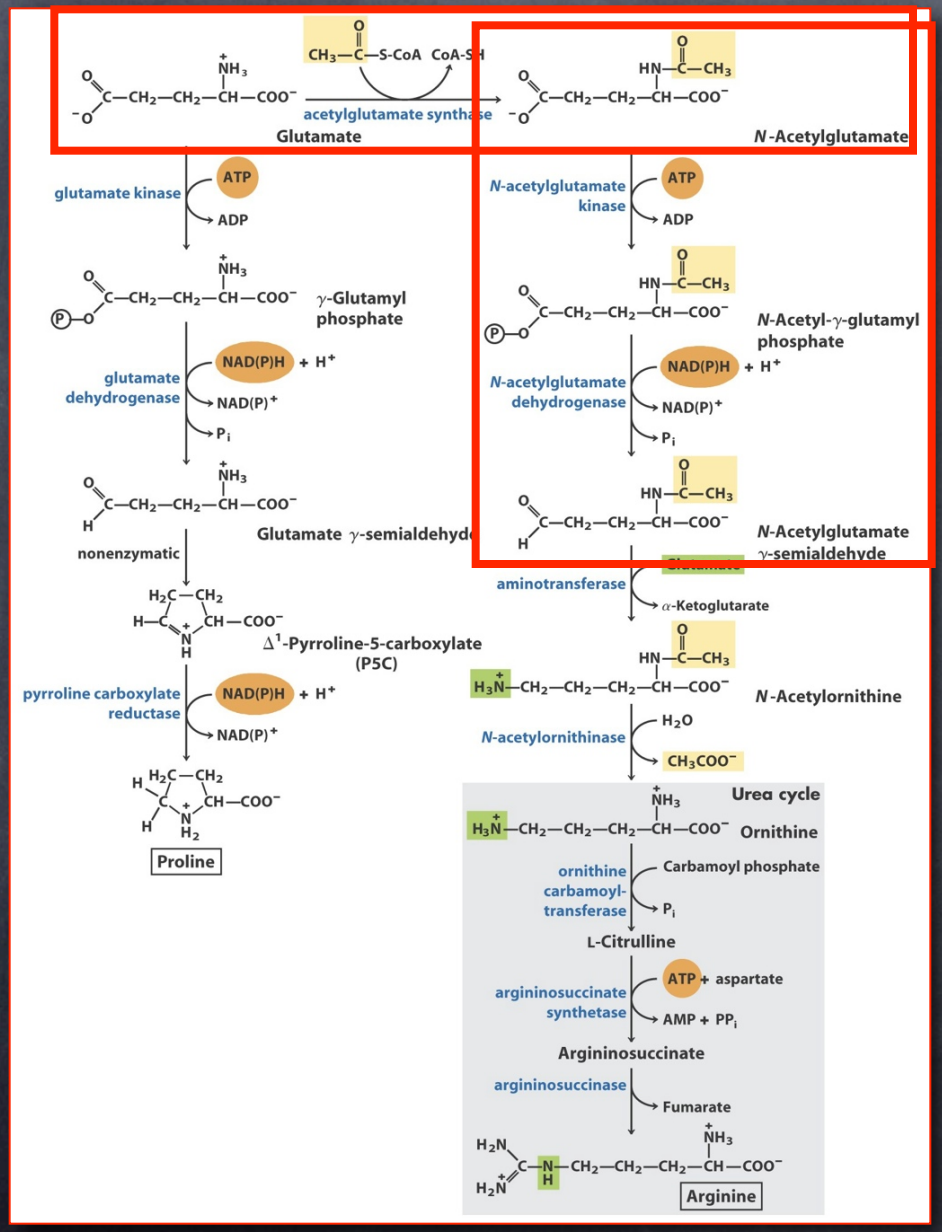


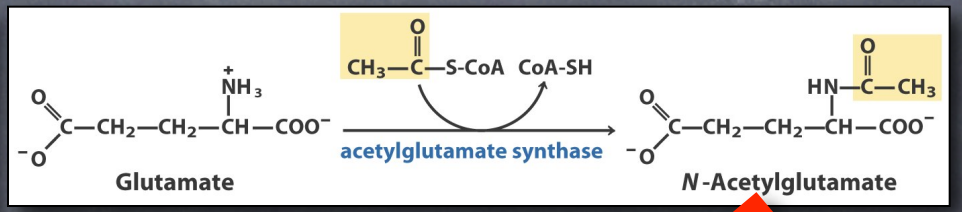
Biosynthesis of Proline

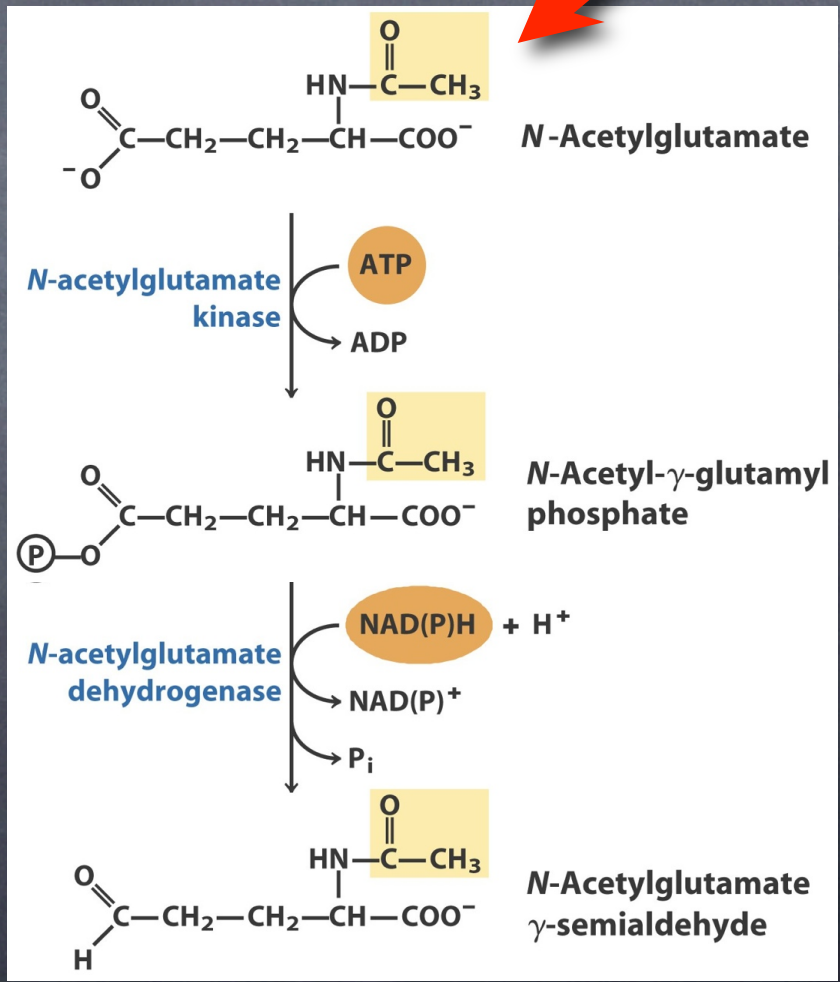




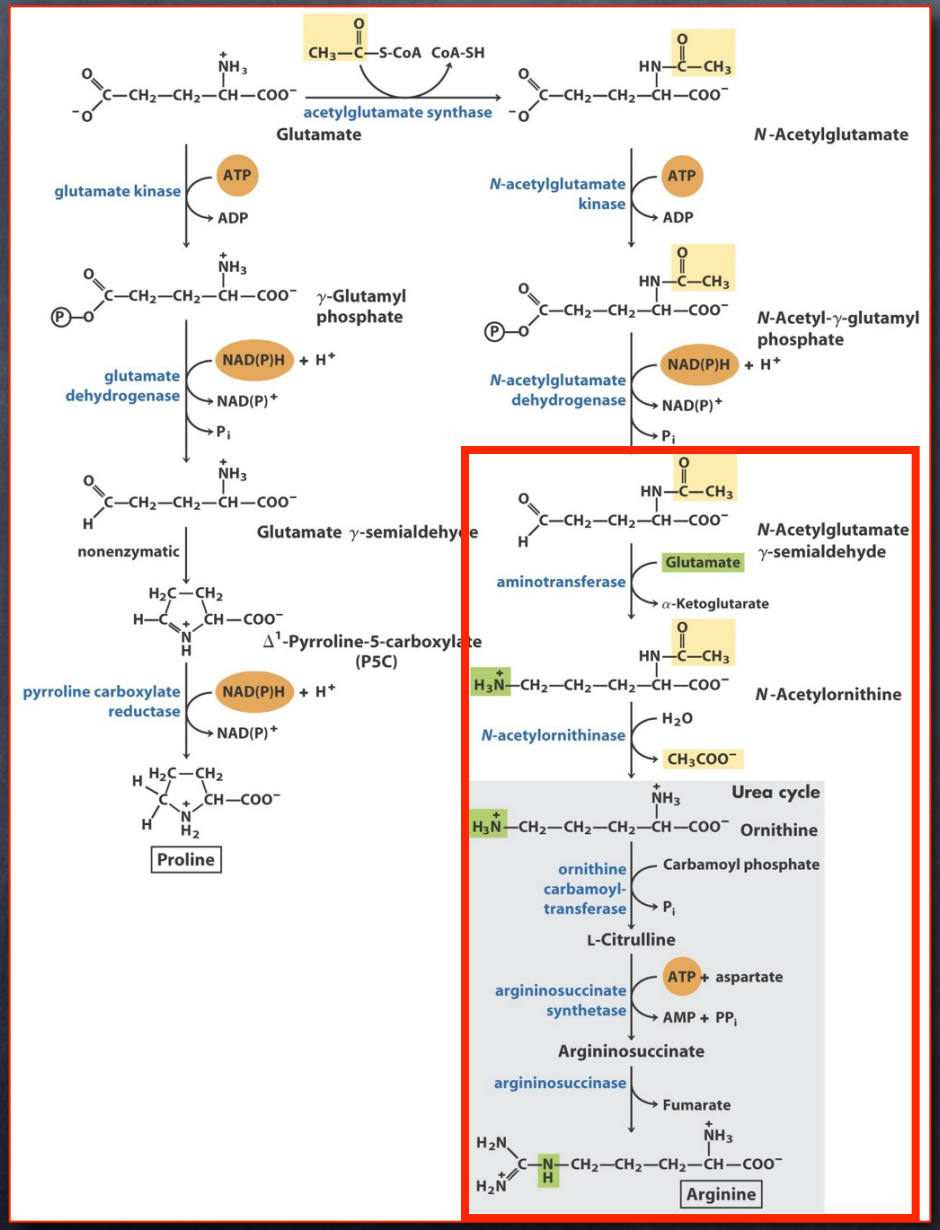
Biosynthesis of Arginine

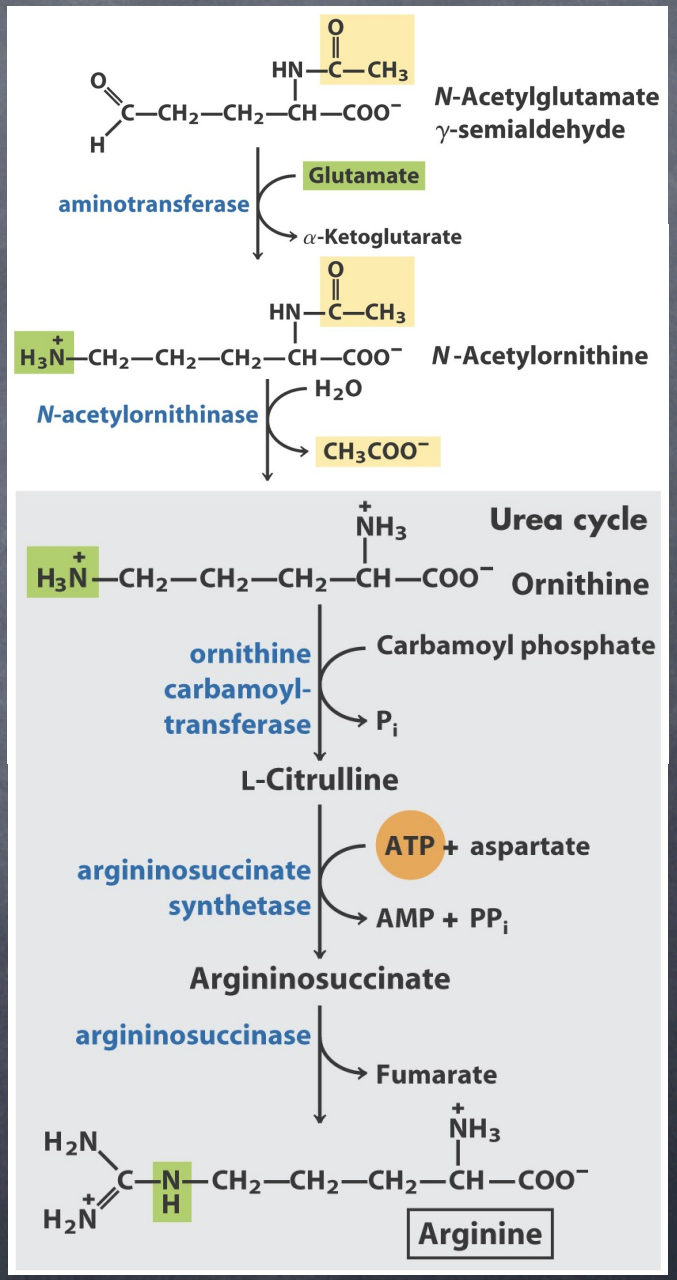


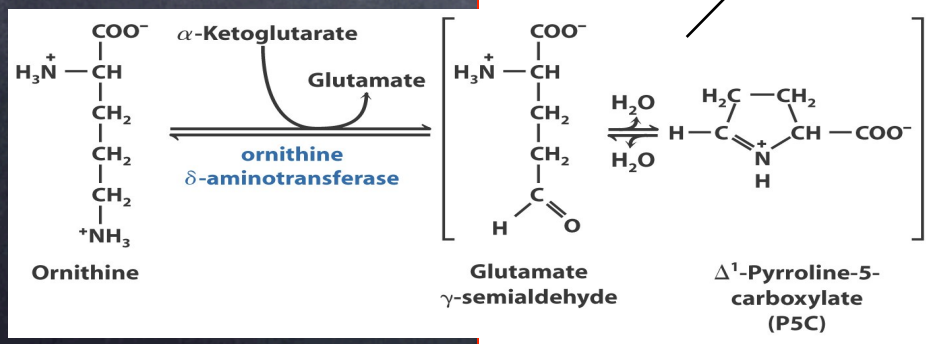


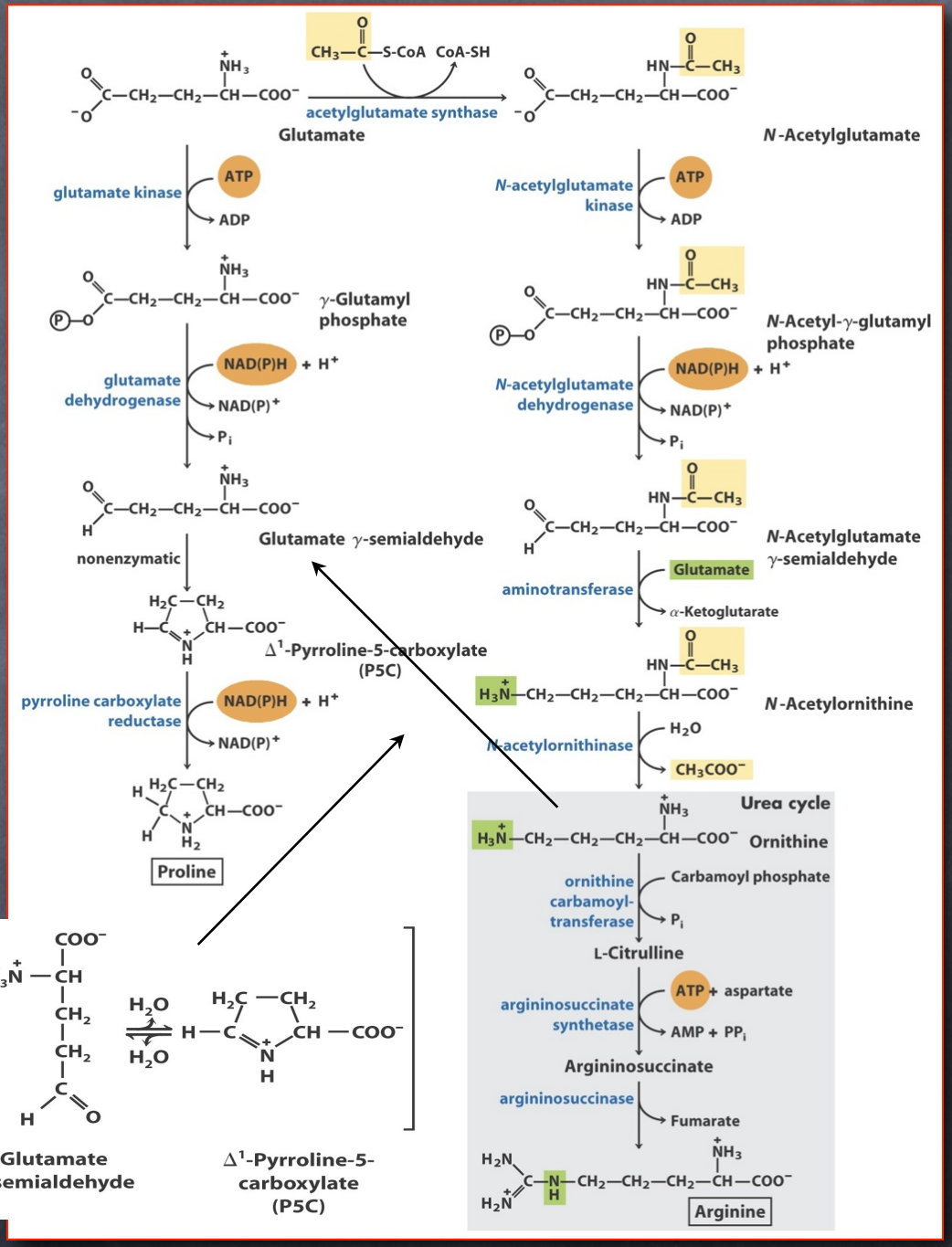


Biosynthesis of Arginine

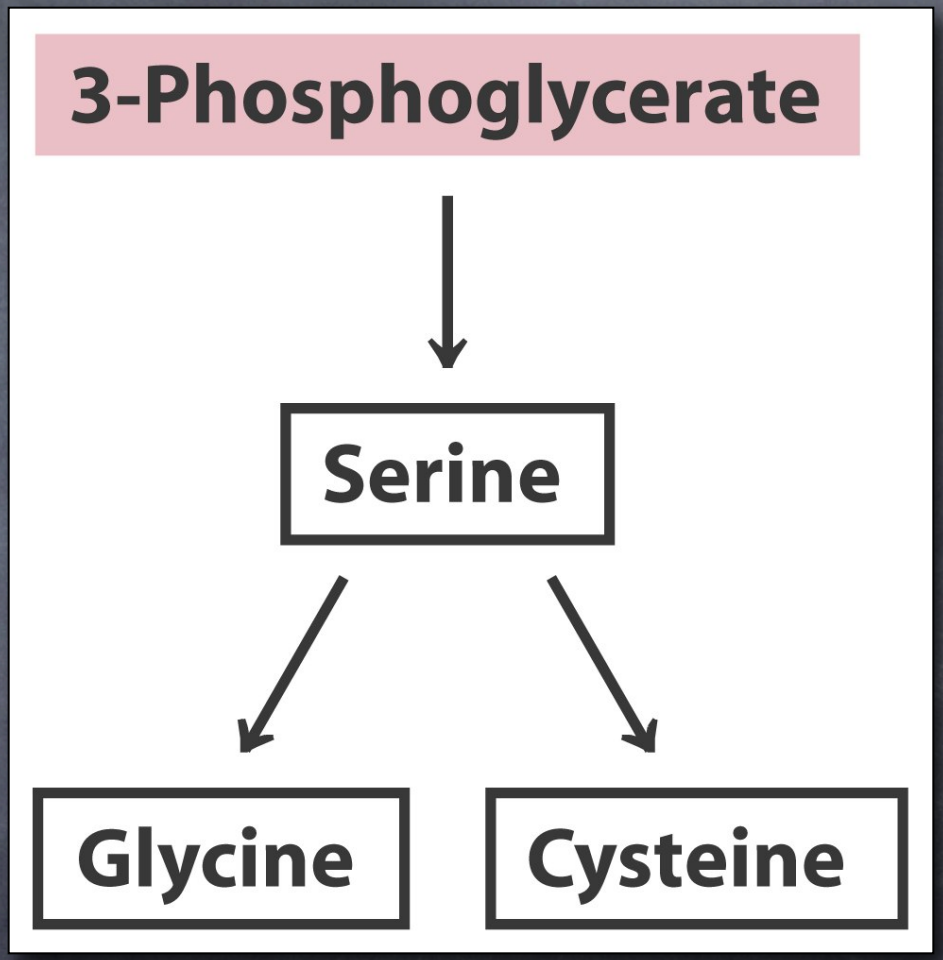





Ornithine
α-Ketoglutarate
Glutamate
ornithine
δ-aminotransferase
Glutamate
γ-semialdehyde
Δ¹-Pyrroline-5-
carboxylate
(P5C)


CoA-SH
acetylglutamate synthase
Glutamate
N-Acetylglutamate
glutamate kinase
ATP
ADP
N-acetylglutamate kinase
γ-Glutamyl phosphate
N-Acetyl-γ-glutamyl phosphate
glutamate dehydrogenase
NAD(P)H + H⁺
NAD(P)⁺
Pi
N-acetylglutamate dehydrogenase
Glutamate γ-semialdehyde
N-Acetylglutamate γ-semialdehyde
nonenzymatic
aminotransferase
Glutamate
α-Ketoglutarate
Δ¹-Pyrroline-5-carboxylate (P5C)
N-Acetylornithine
pyrroline carboxylate reductase
N-acetylornithinase
H2O
CH3COO⁻
Proline
Urea cycle
Ornithine
ornithine carbamoyl-transferase
Carbamoyl phosphate
L-Citrulline
argininosuccinate synthetase
ATP + aspartate
AMP + PPi
Argininosuccinate
argininosuccinase
Fumarate
Arginine

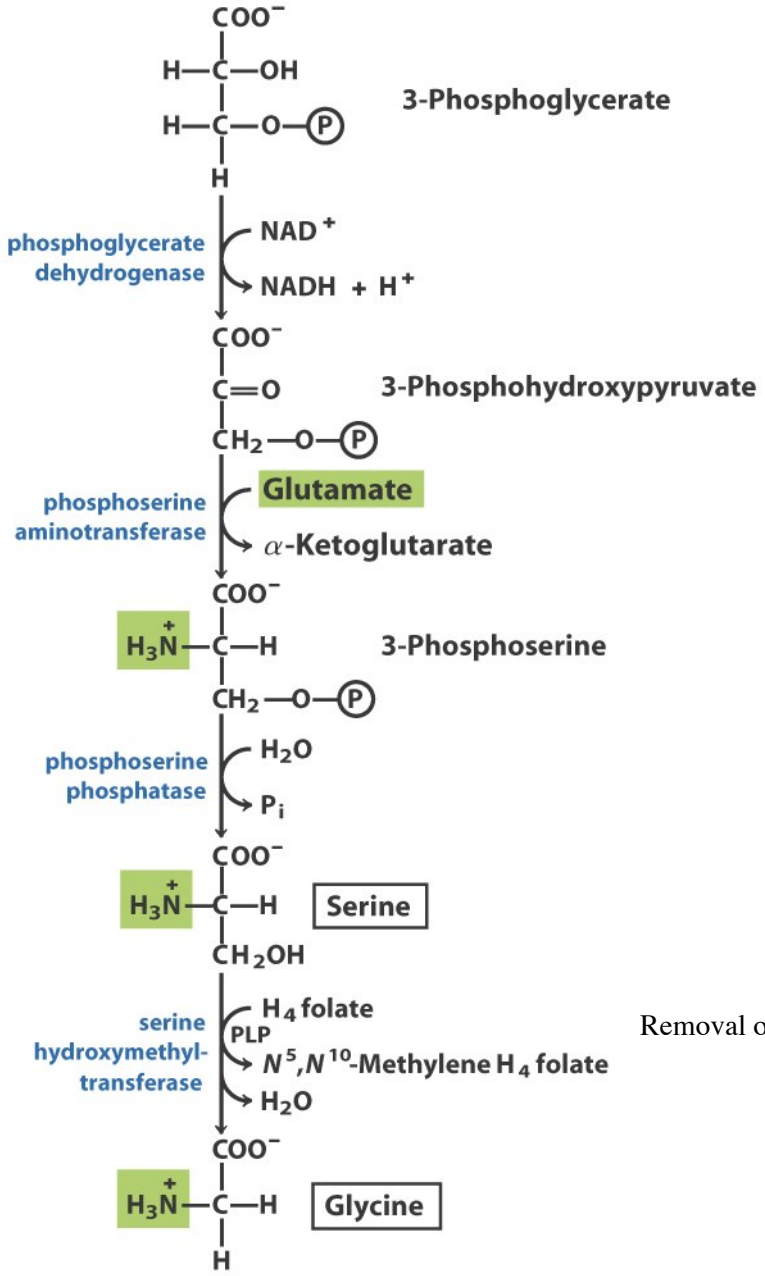
Biosynthesis of Serine, Glycine and Cysteine



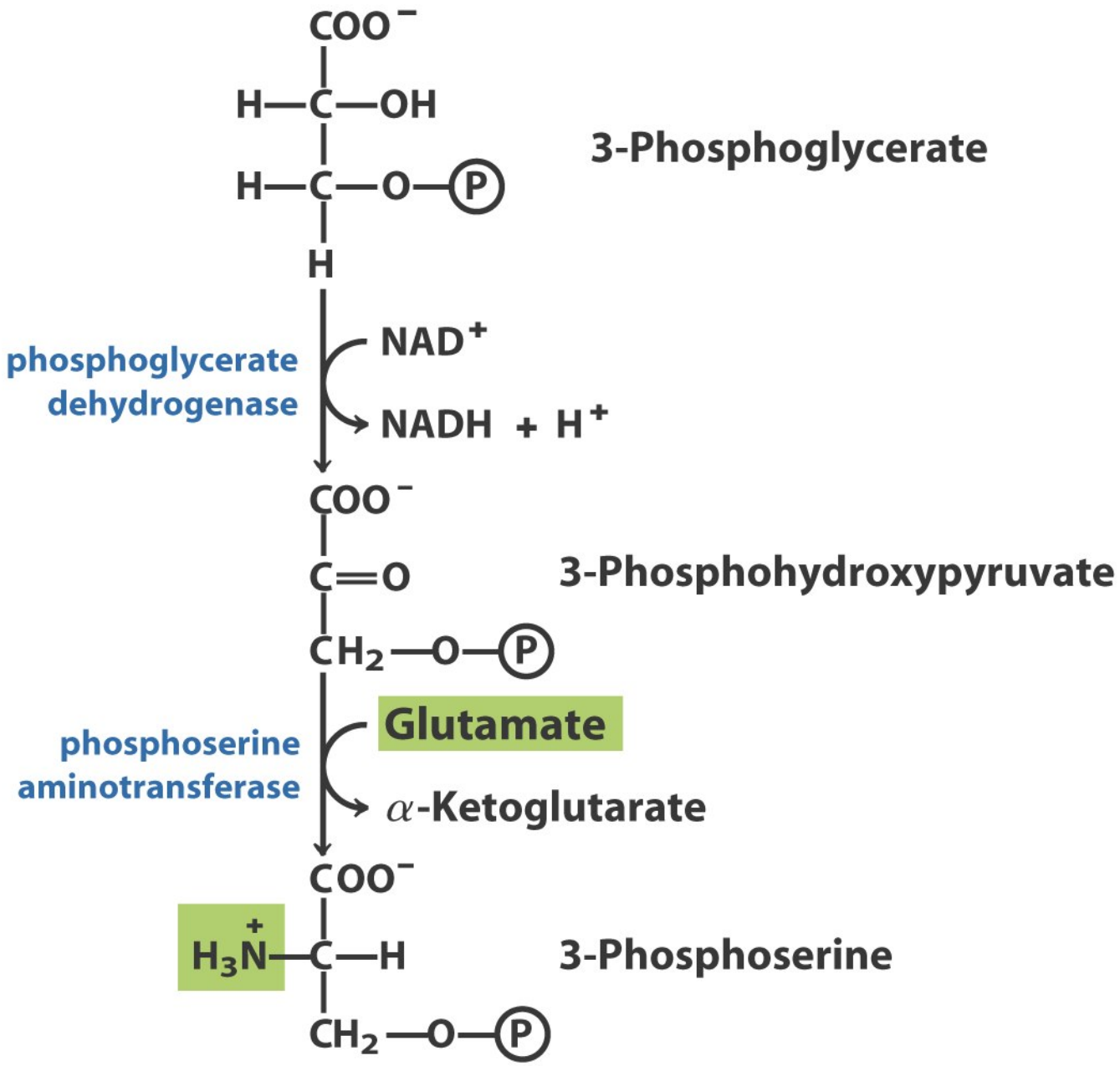
oxidation of the OH group

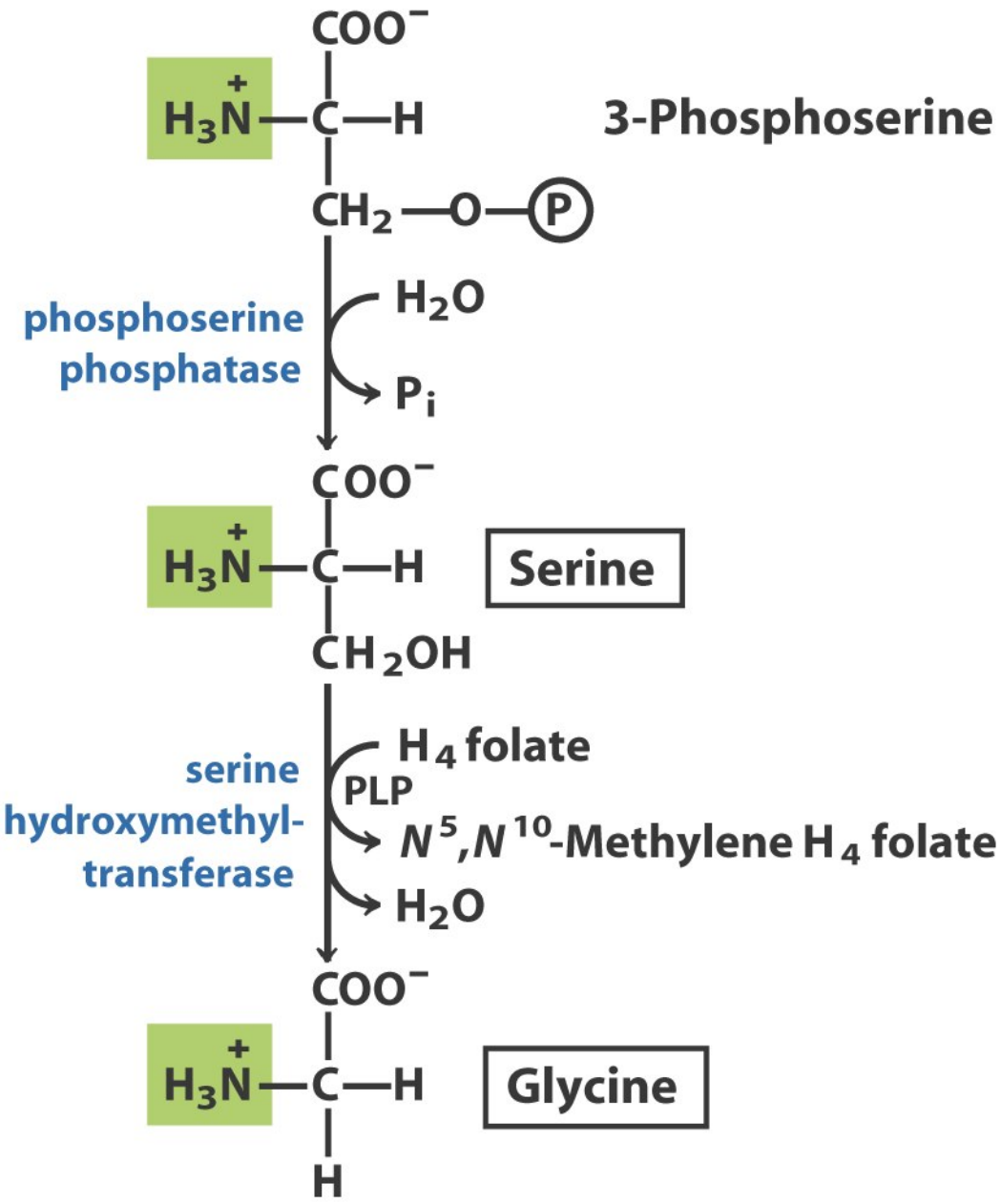
transamination

hydrolysis



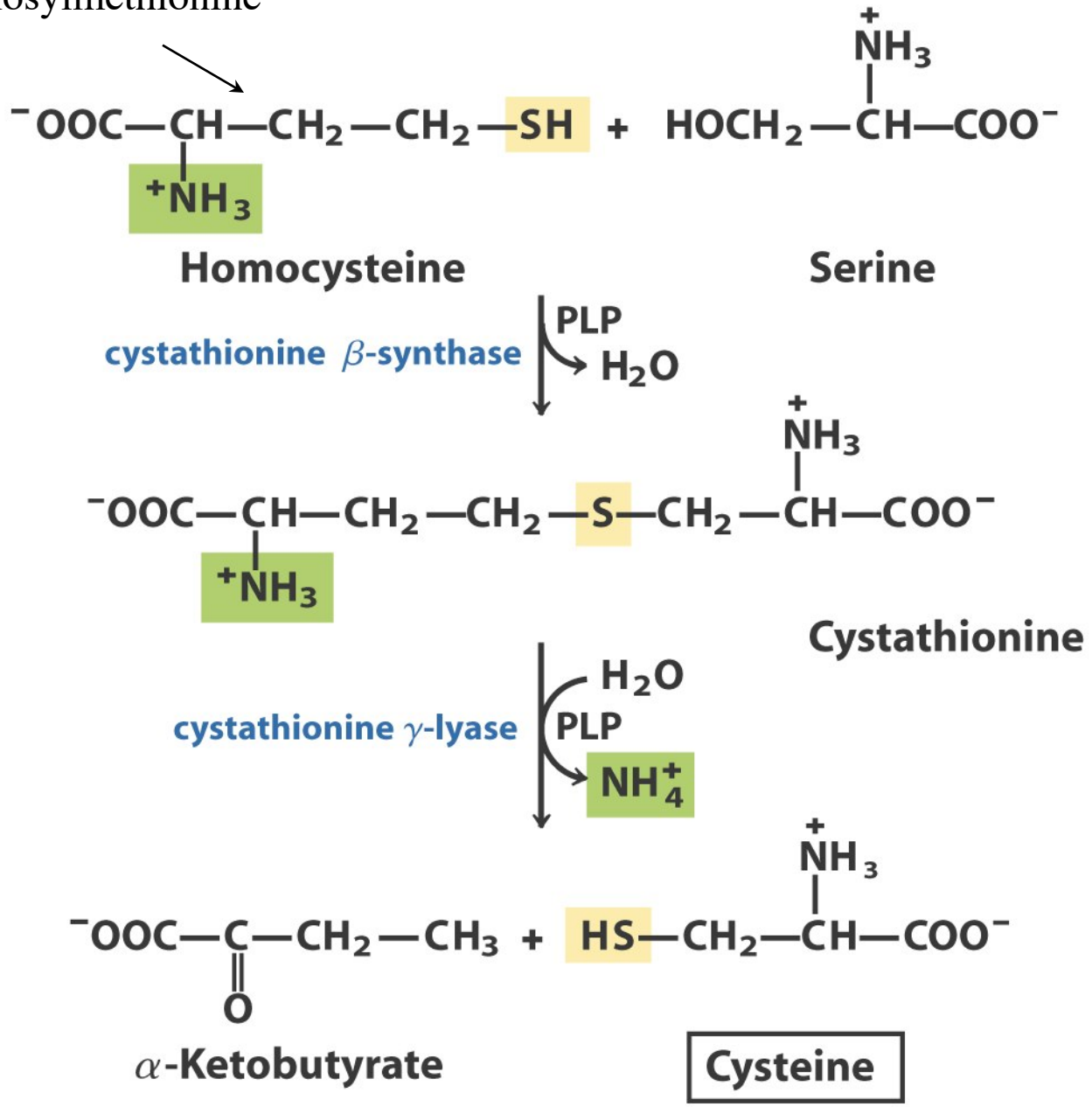
Removal of the B-C (C-3) accepted by H4 folate


COO⁻
H—C—OH
H—C—O—P
H
3-Phosphoglycerate
phosphoglycerate dehydrogenase
NAD⁺
NADH + H⁺
COO⁻
C=O
CH₂—O—P
3-Phosphohydroxypyruvate
phosphoserine aminotransferase
Glutamate
α-Ketoglutarate
COO⁻
H₃N⁺—C—H
CH₂—O—P
3-Phosphoserine

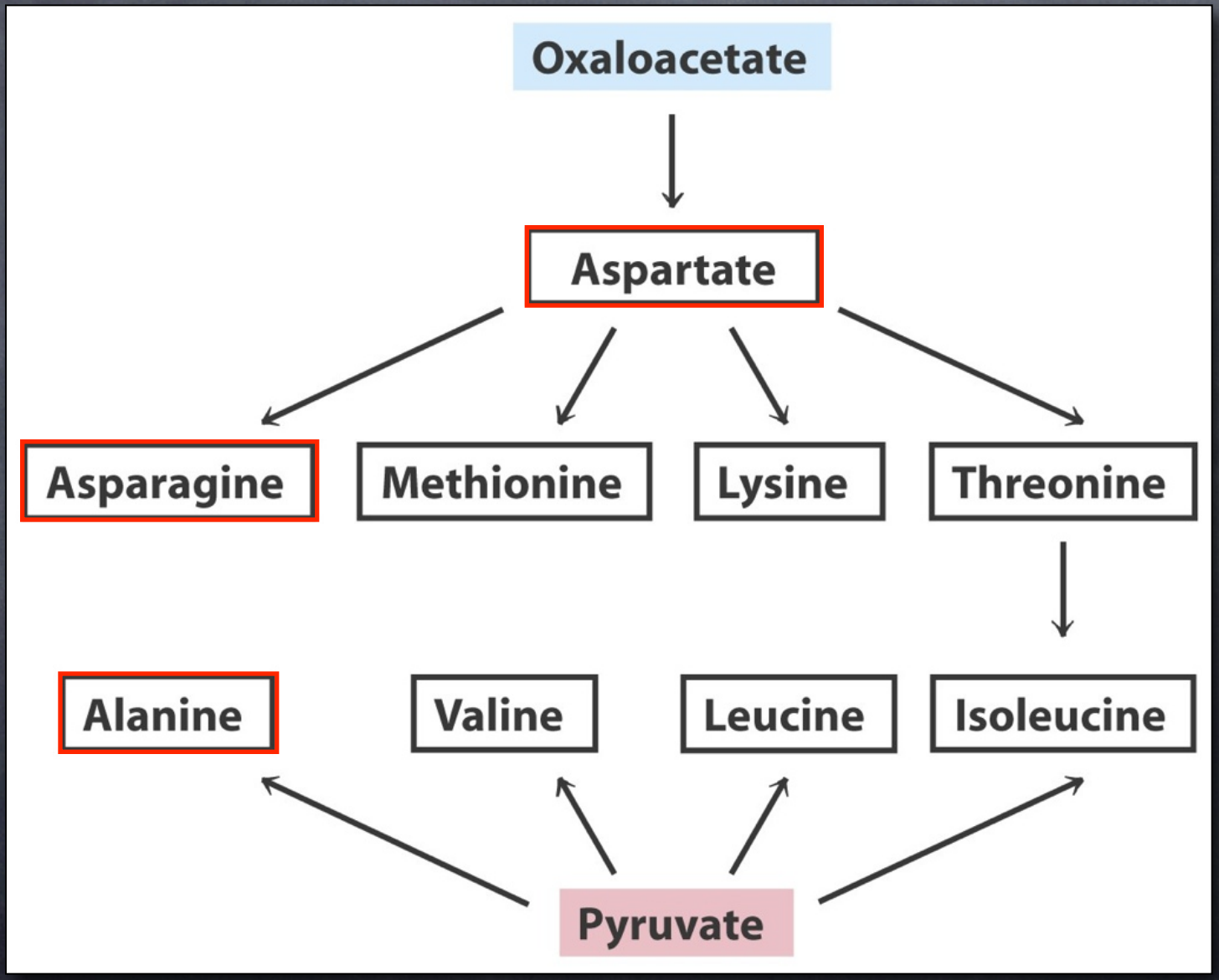

COO⁻
H₃N⁺—C—H
3-Phosphoserine
CH₂—O—P
phosphoserine phosphatase
H₂O
Pi
COO⁻
H₃N⁺—C—H
Serine
CH₂OH
H4 folate
serine hydroxymethyl-transferase
PLP
N5,N10-Methylene H4 folate
H₂O
COO⁻
H₃N⁺—C—H
Glycine
H

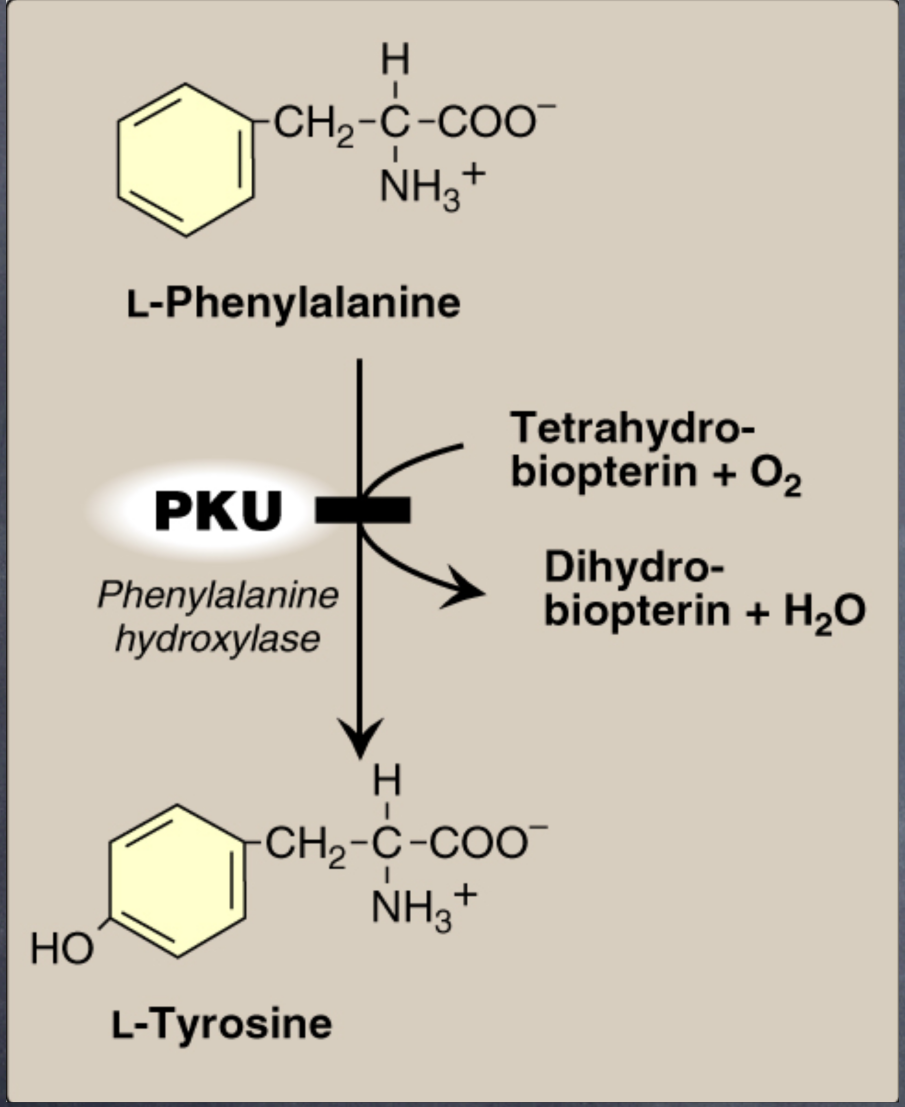
Methionine

S-adenosylmethionine

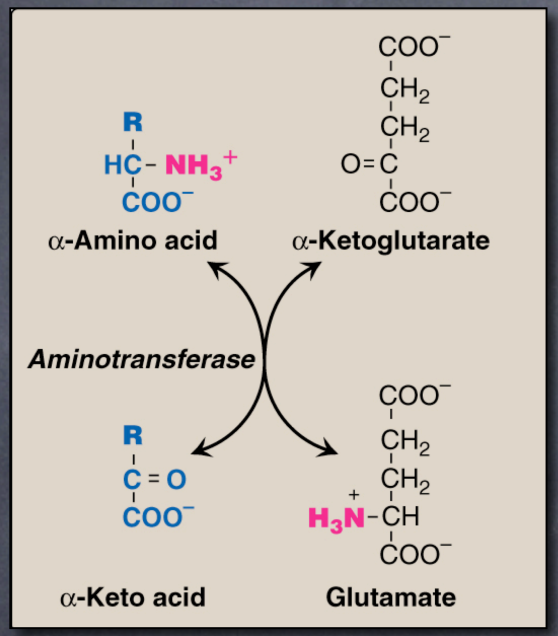


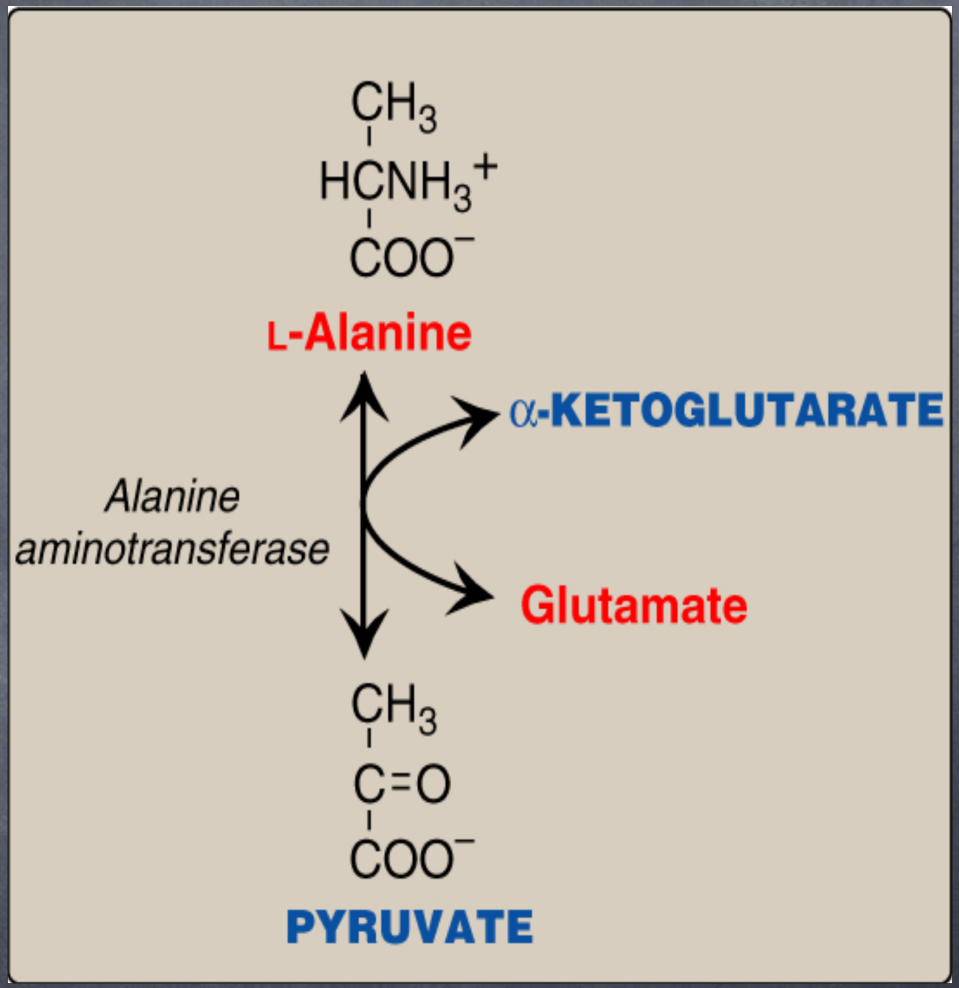
Biosynthesis of Three Nonessential and Six Essential From Oxaloacetate and Pyruvate



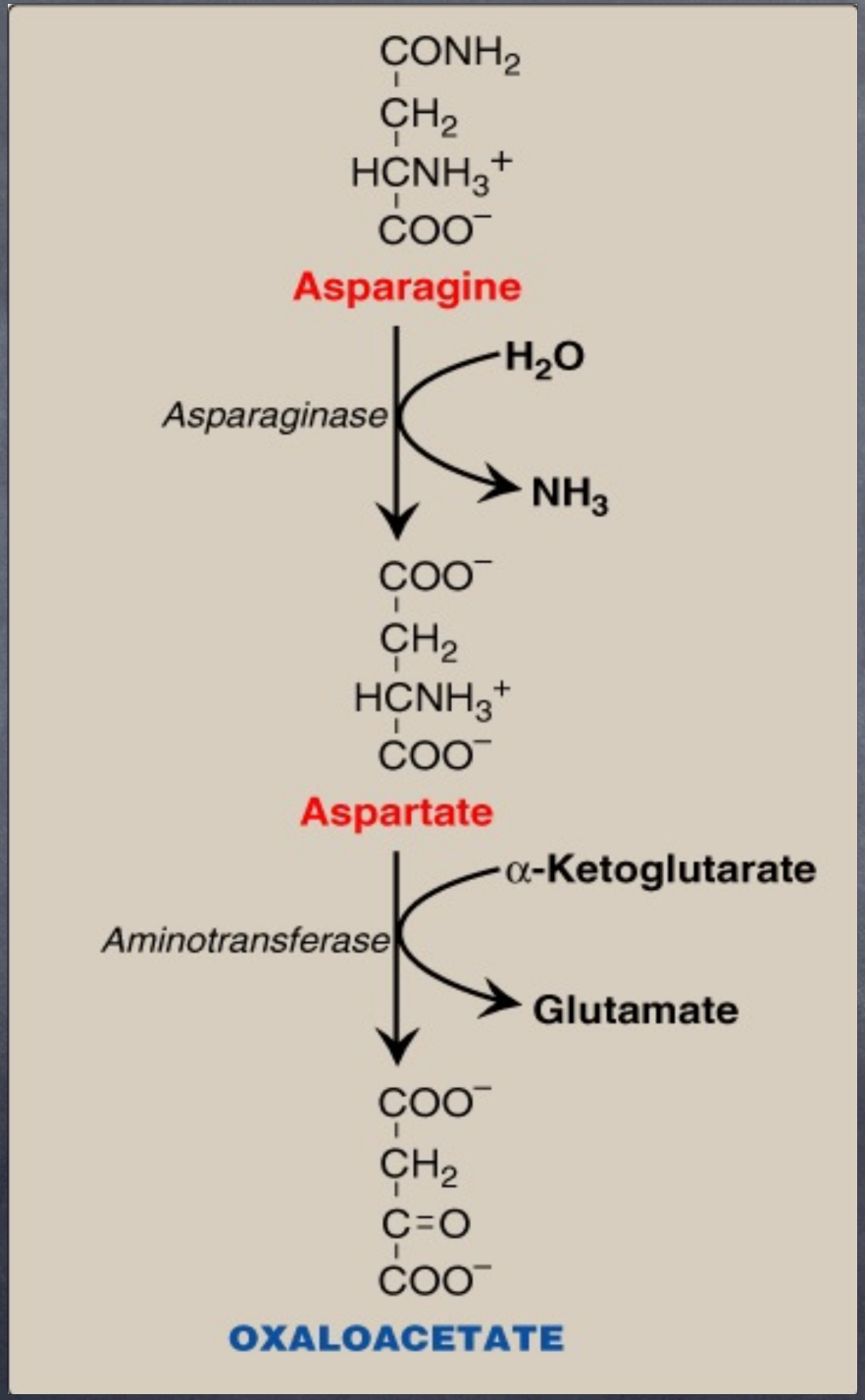

L-Phenylalanine
PKU
Phenylalanine hydroxylase
Tetrahydro-biopterin + O_2
Dihydro-biopterin + H_2O
L-Tyrosine

Biosynthesis of Alanine

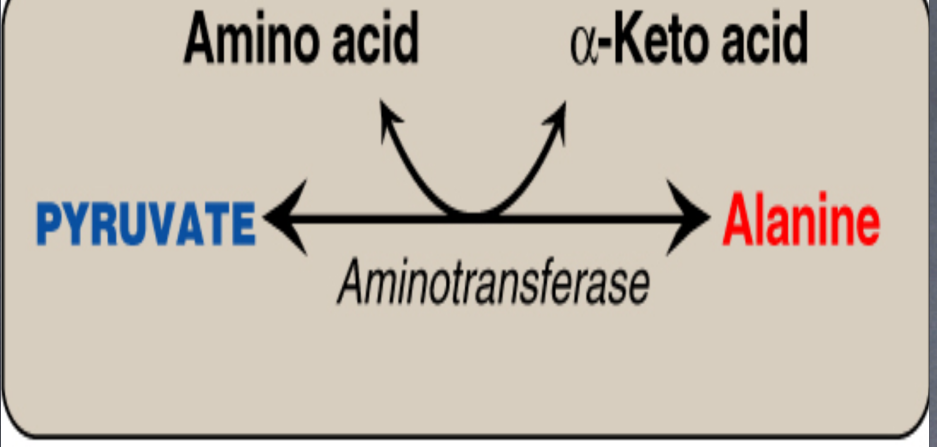


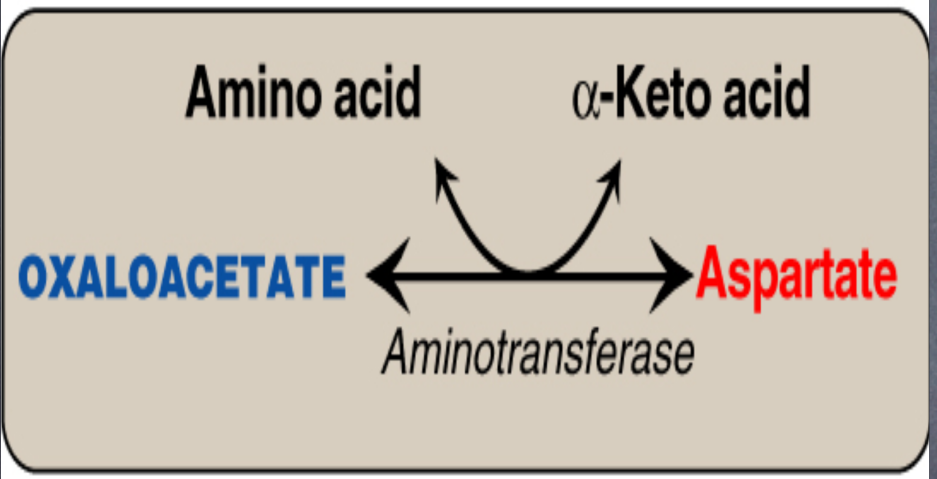


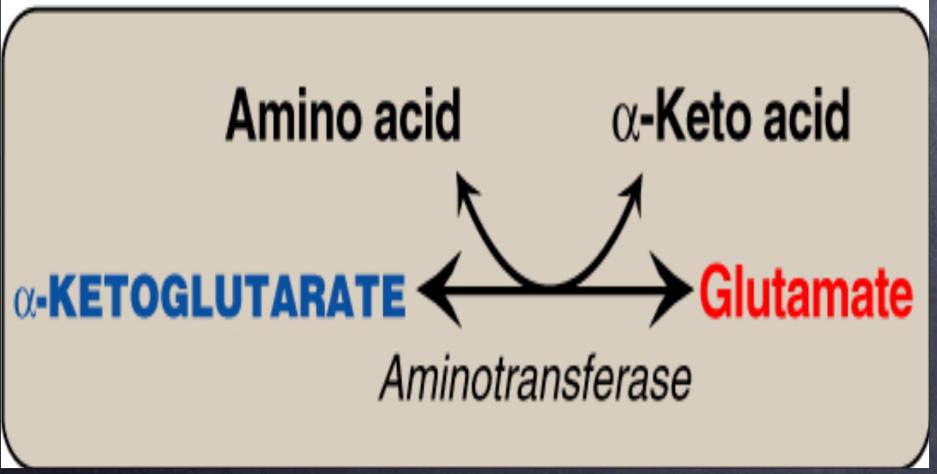
amidation



Glutamine donates NH4







Biosynthesis on non-essential amino acids

They are synthesized from intermediates of metabolism or from essential amino acids like the case of tyrosine and cysteine. Histidine and arginine are generally classified as non-essential depending on conc.

From -keto acids

From amidation (glutamine) formed from glutamate important in synthesis and degradation providing detoxification of ammonia in liver and brain as previously discussed in Urea cycle. Asparagine formed from aspartate

Proline formed from glutamate

Serine (from 3 phosphoglycerate-3 phosphopyruvate-3 phosphoserine-serine and glycine), glycine(serine) and cysteine (homocysteine- cystathionine-cysteine depends on methionine (essential)

Tyrosine (20.7) phenylalanine (essential) requires BH4 tetrahydrobiopterin

Allosteric regulation of amino acid biosynthesis