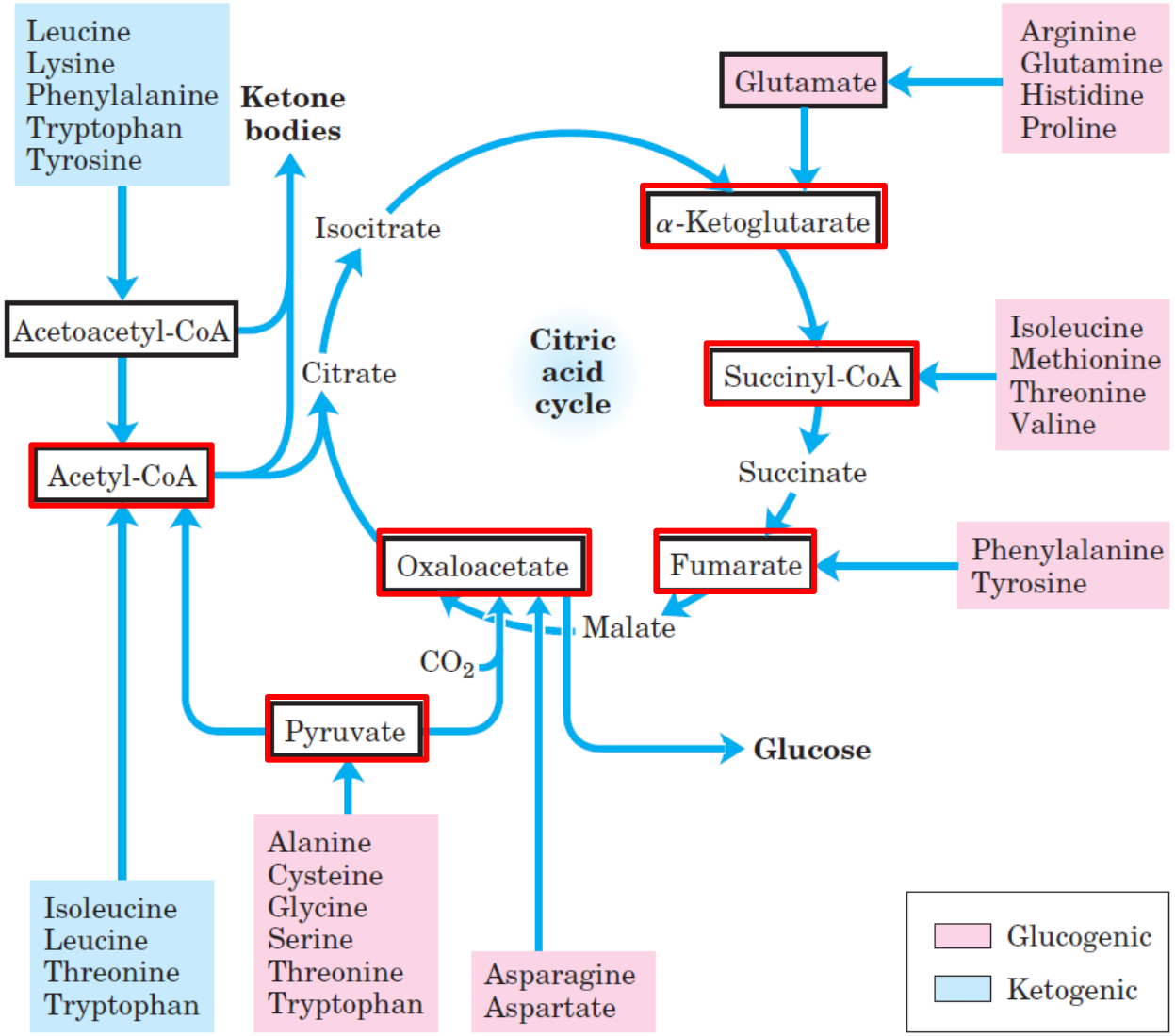
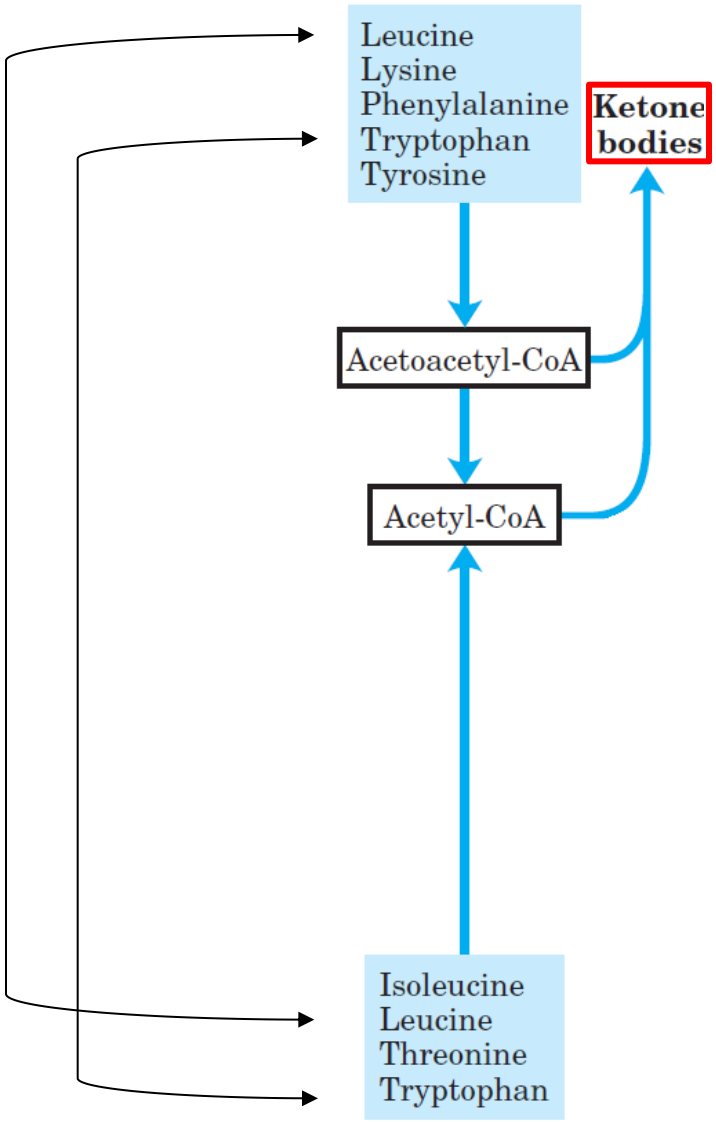
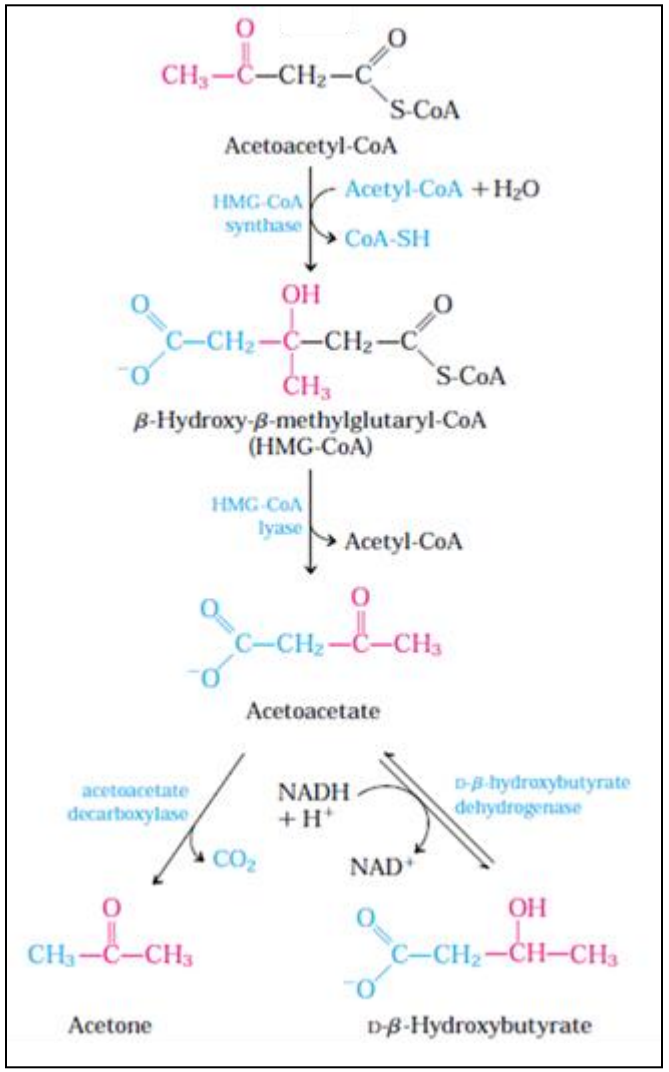
FATE OF THE CARBON SKELETON OF AMINO ACIDS

The pathways of amino acid catabolism, taken together, normally account for only 10% to 15% of the human body's energy production; these pathways are not nearly as active as glycolysis and fatty acid oxidation. Flux through these catabolic routes also varies greatly, depending on the balance between requirements for biosynthetic processes and the availability of a particular amino acid.

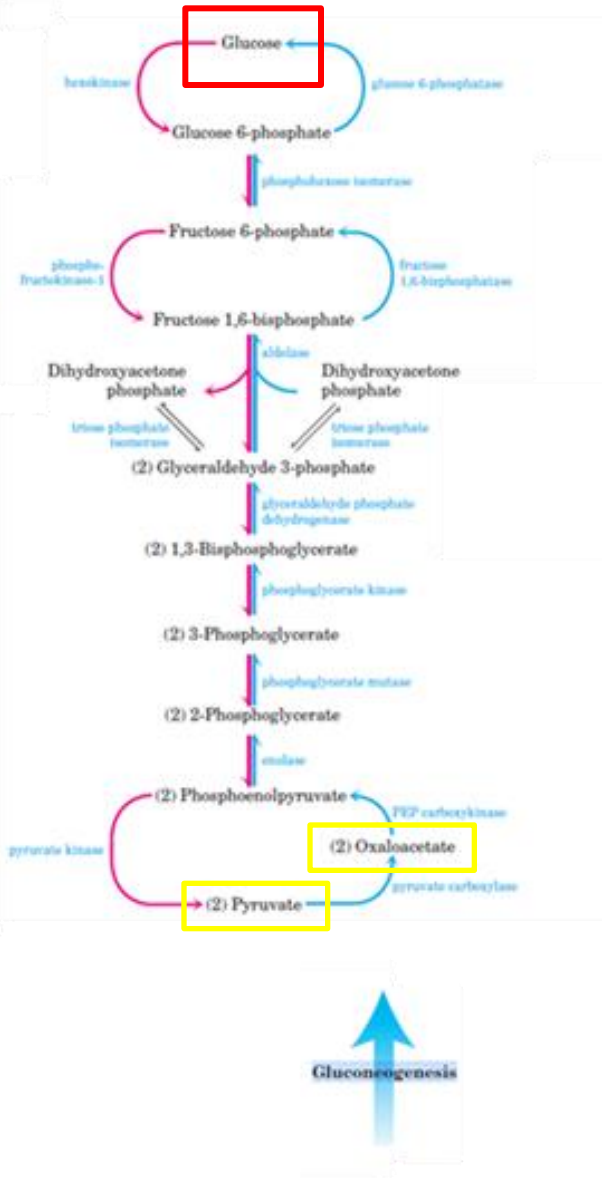


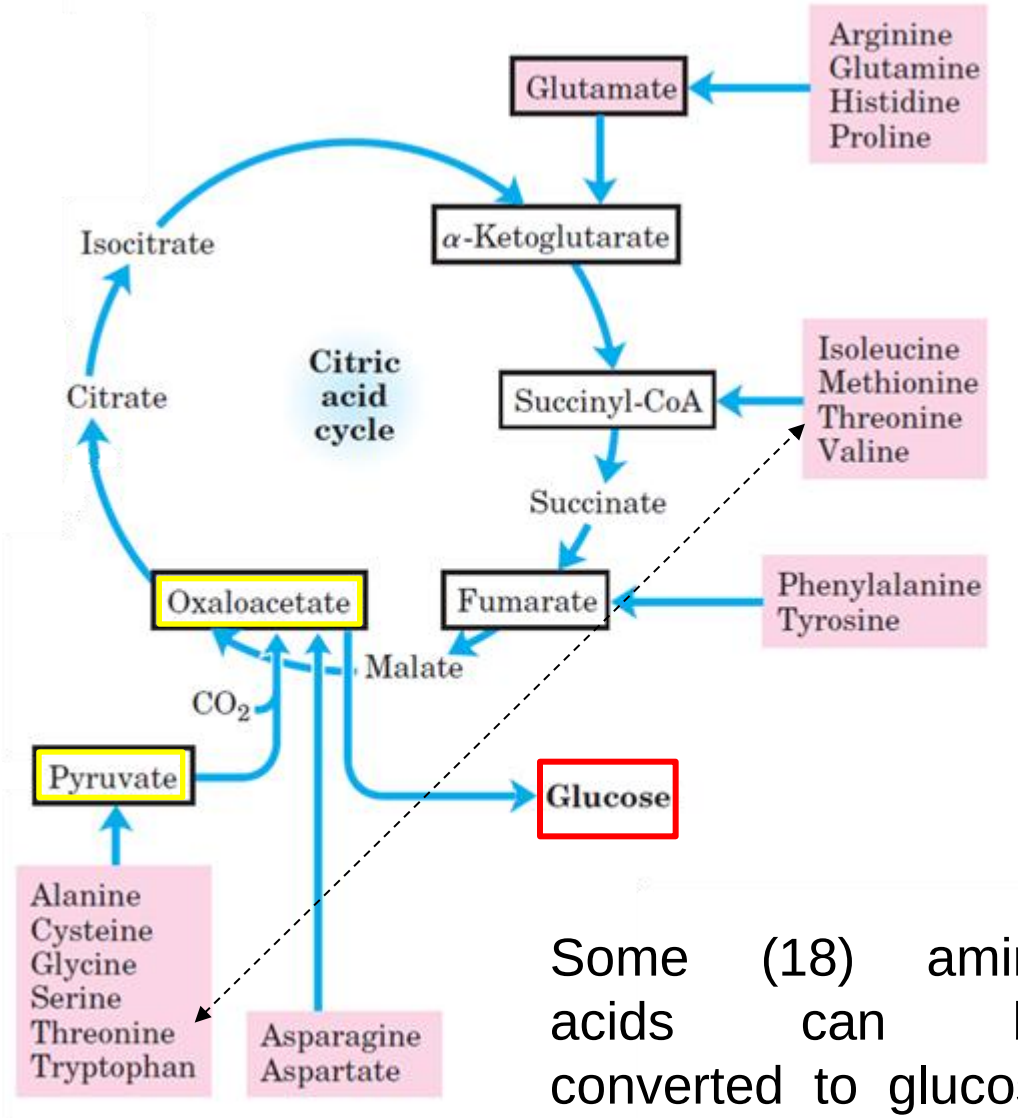
The metabolism of the 20 proteinogenic amino acids converges towards 6 main products that enter the citric acid cycle and can be oxidized to terminal form (CO_2 and H_2O)



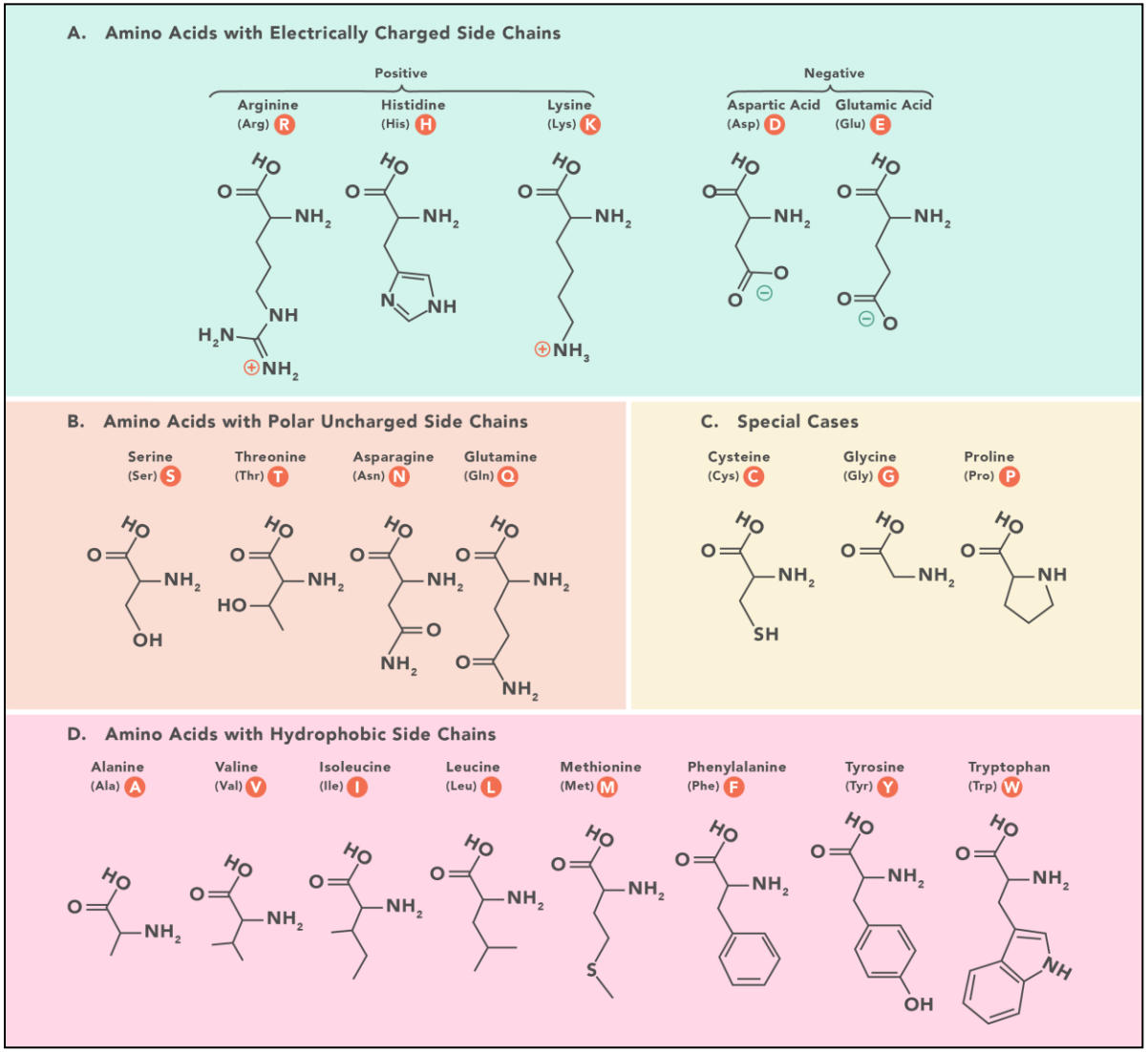


Some (7) amino acids can be converted into ketone bodies = ketogenic

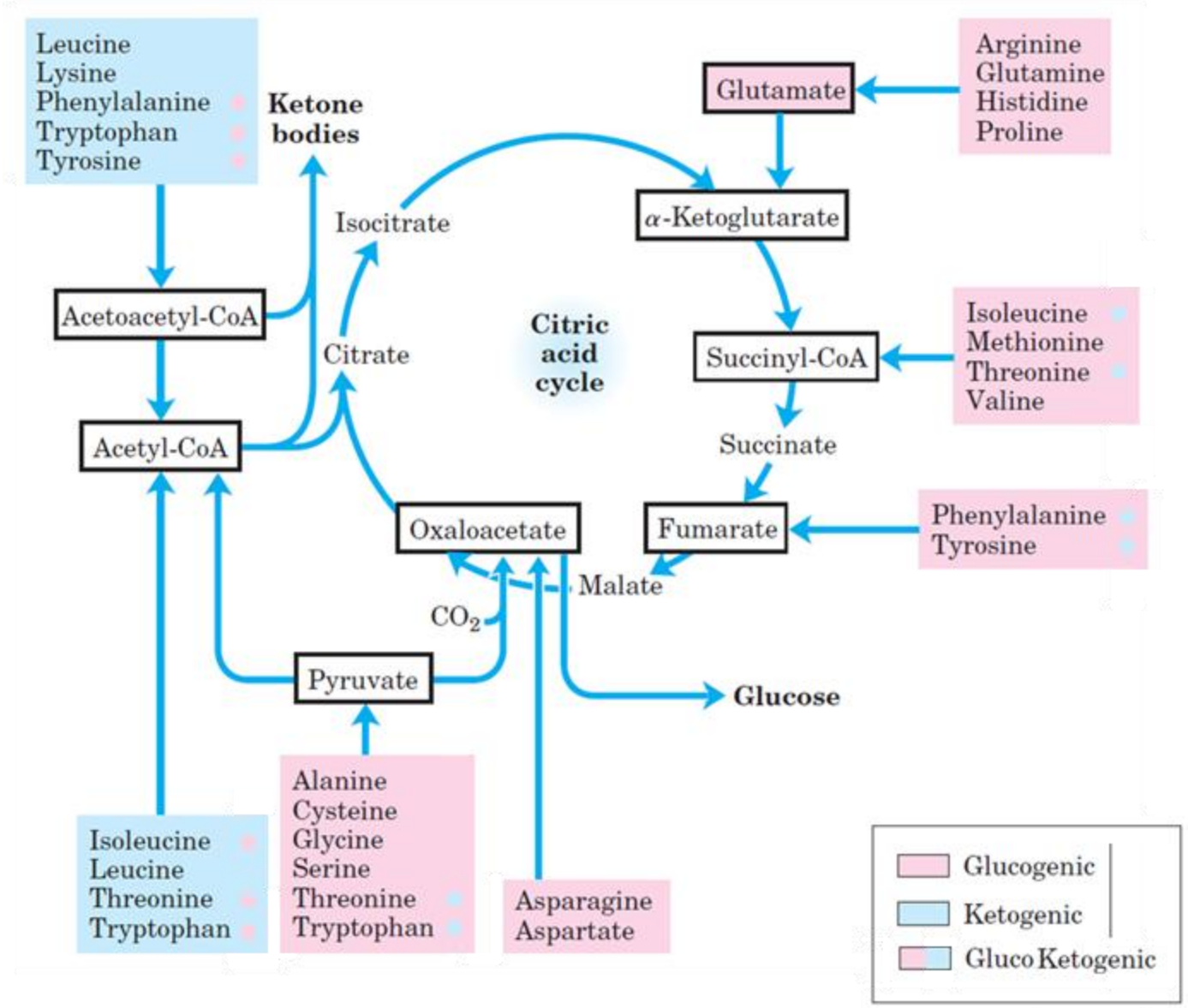




Some (18) amino acids can be converted to glucose = glucogenic

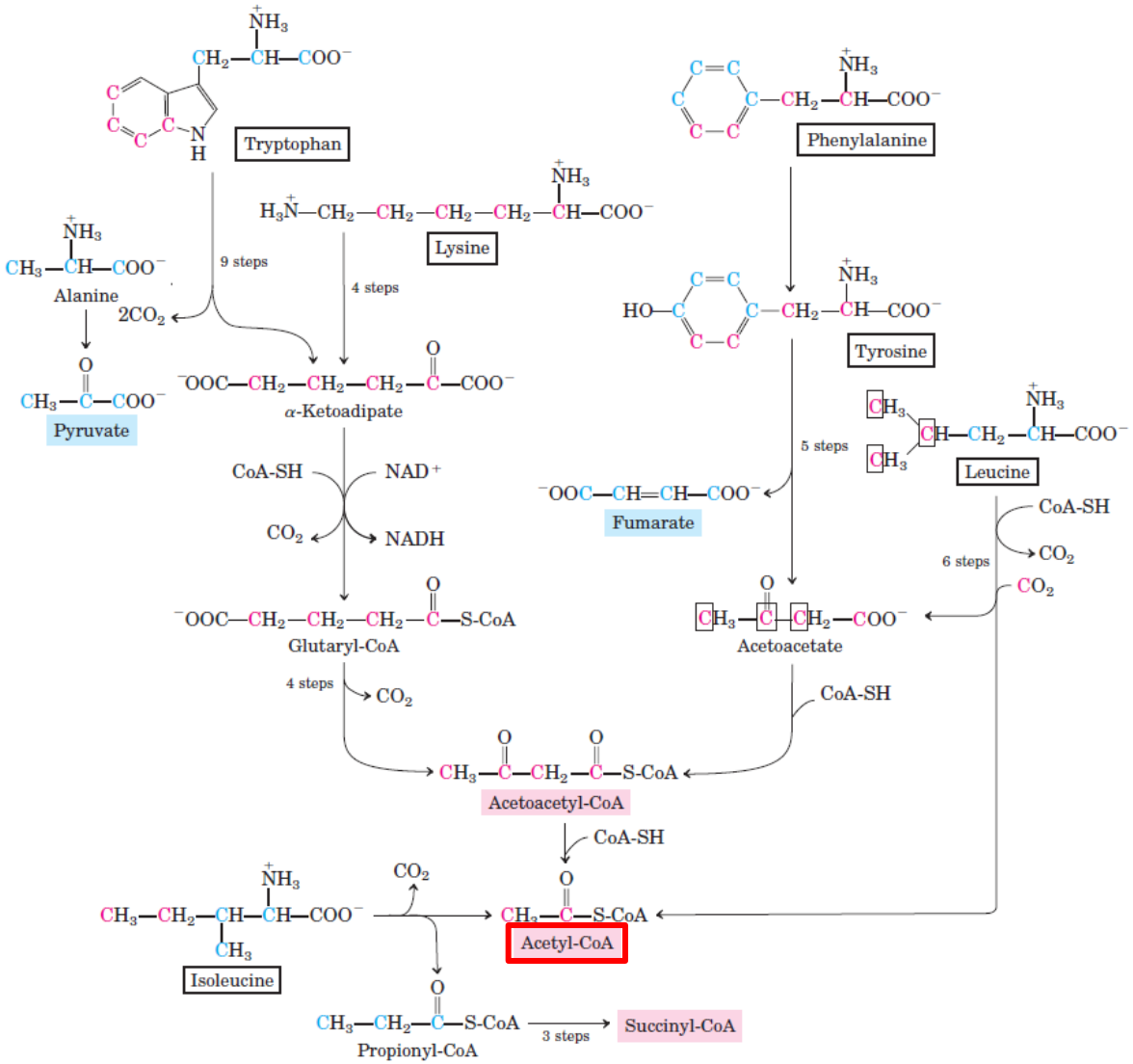


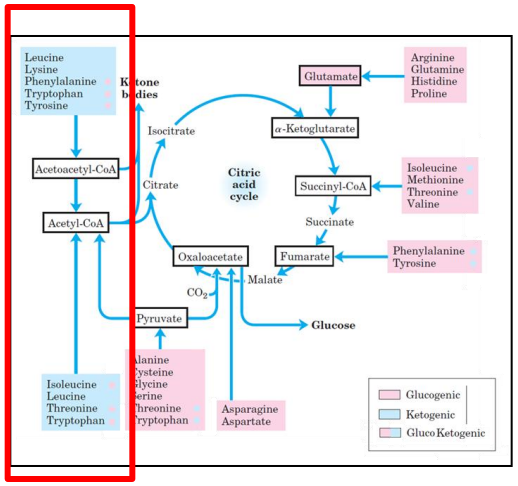
There are 20 proteinogenic amino acids, but 7 + 18 = 25…

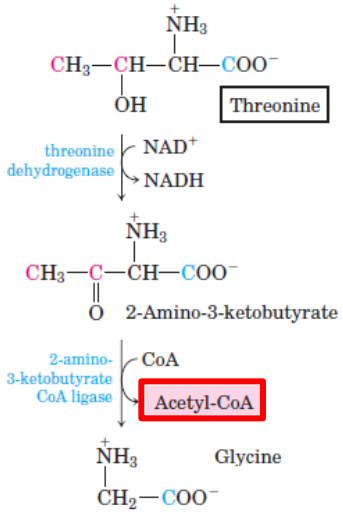


Note that some (5) amino acids can be, alternatively, both keto- and gluco-genic.

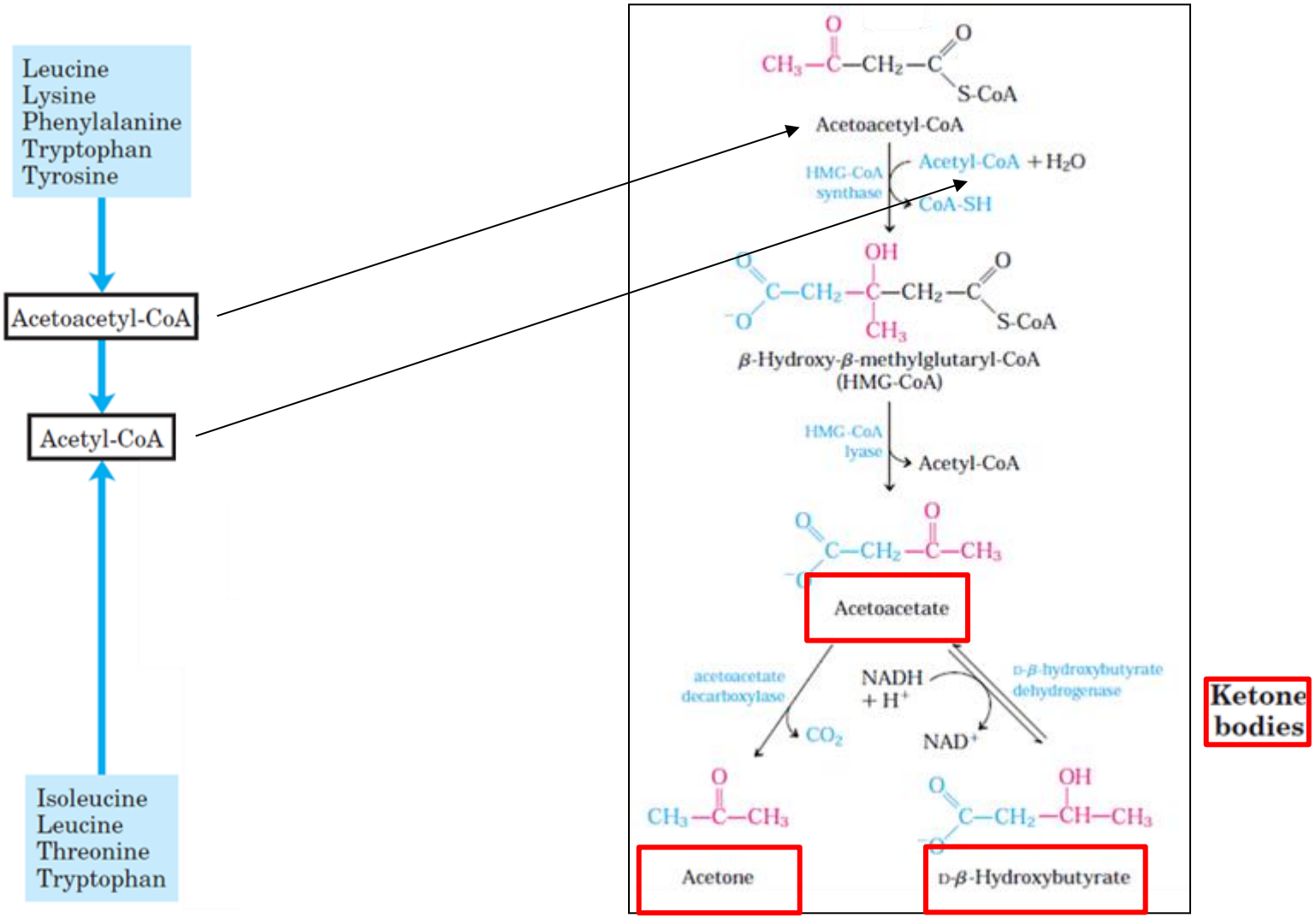
Amino acid	Three letter code	One letter code	
alanine	ala	A	Glucogenic
arginine	arg	R	Glucogenic
asparagine	asn	N	Glucogenic
aspartic acid	asp	D	Glucogenic
cysteine	cys	C	Glucogenic
glutamic acid	glu	E	Glucogenic
glutamine	gln	Q	Glucogenic
glycine	gly	G	Glucogenic
histidine	his	H	Glucogenic
isoleucine	ile	I	Gluco Ketogenic
leucine	leu	L	Ketogenic
lysine	lys	K	Ketogenic
methionine	met	M	Glucogenic
phenylalanine	phe	F	Gluco Ketogenic
proline	pro	P	Glucogenic
serine	ser	S	Glucogenic
threonine	thr	T	Gluco Ketogenic
tryptophan	trp	W	Gluco Ketogenic
tyrosine	tyr	Y	Gluco Ketogenic
valine	val	V	Glucogenic







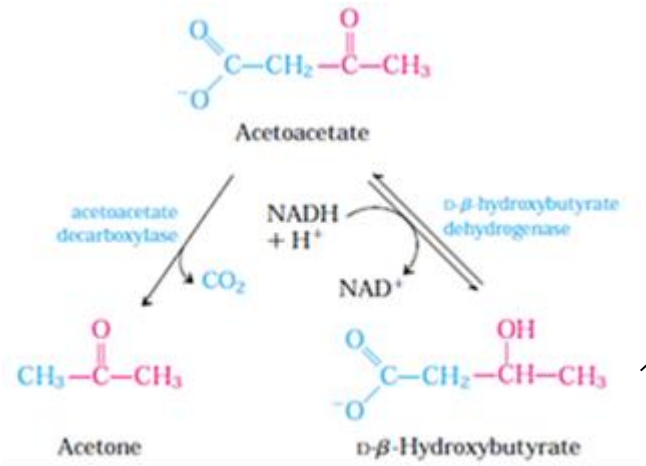
Portions of the carbon skeletons of 7 amino acids — **tryptophan**, **lysine**, **phenylalanine**, **tyrosine**, **leucine**, **isoleucine**, and **threonine** —yield acetyl-CoA and/or acetoacetyl-CoA, the latter being converted to acetyl-CoA.

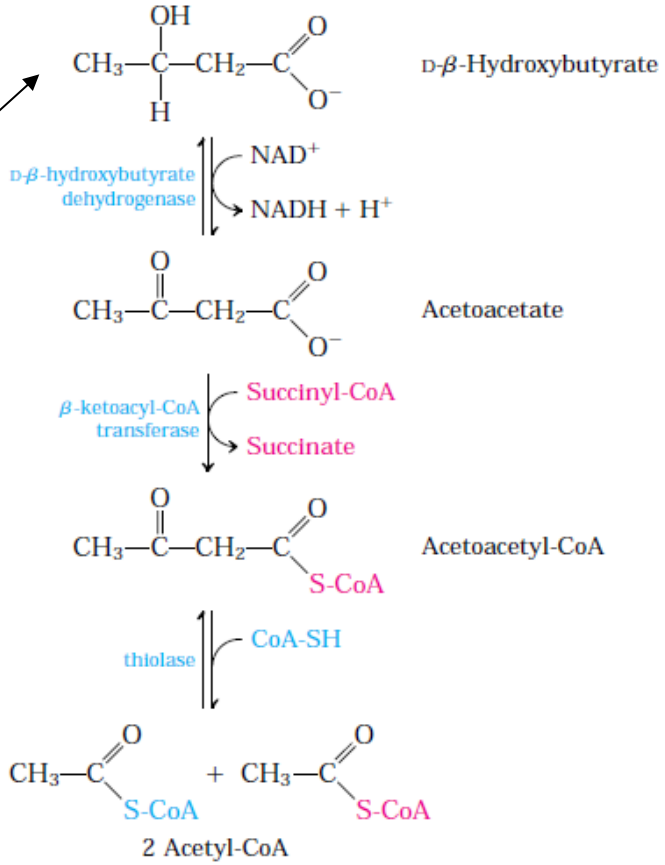


Acetoacetyl-CoA (and acetyl-CoA) can yield ketone bodies in the liver, where it is converted to acetoacetate and then to acetone and D-β-hydroxybutyrate.

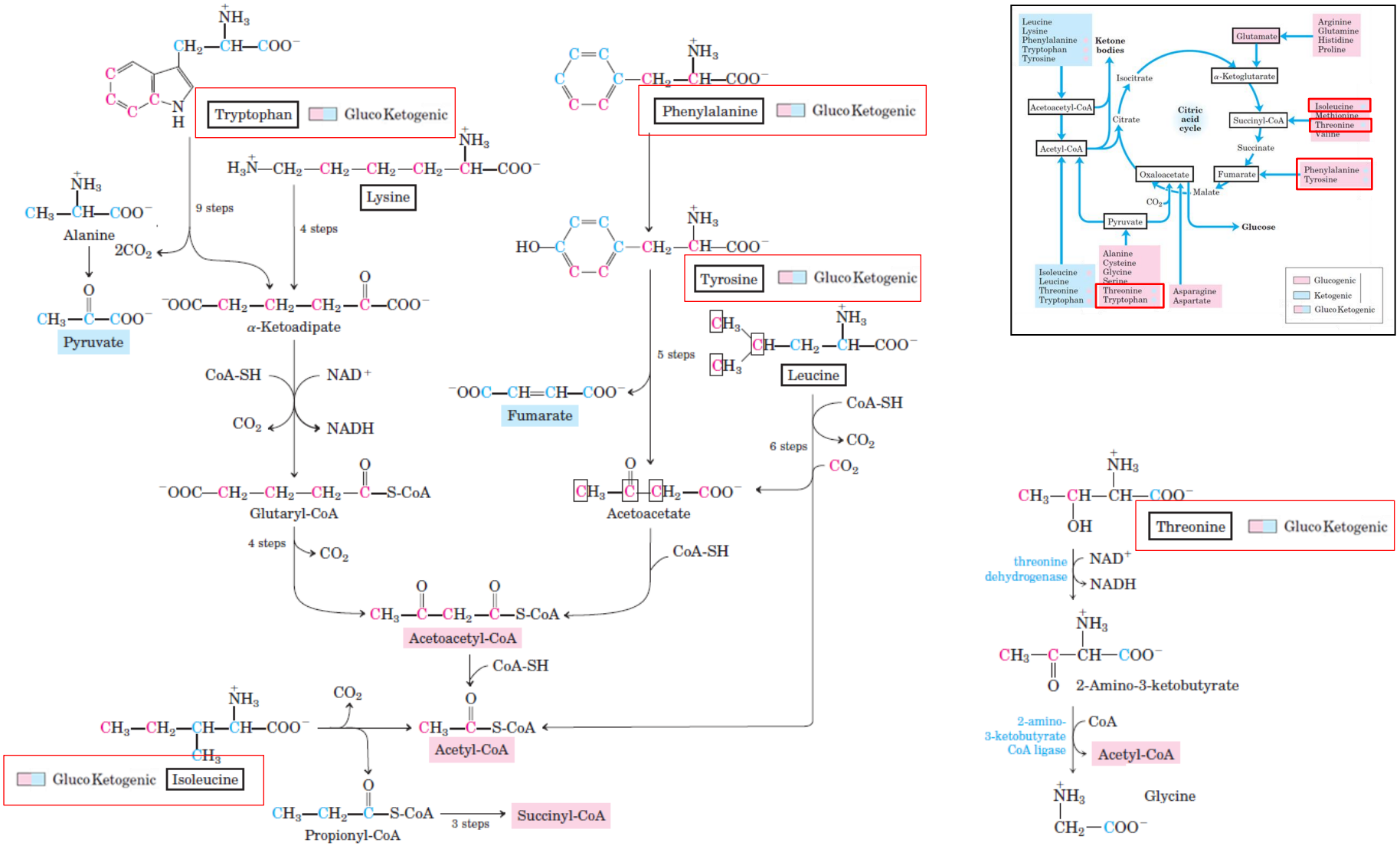
Ketone bodies

D-β-Hydroxybutyrate, synthesized in the liver, passes into the blood and thus to other tissues, where it is converted in three steps to acetyl-CoA. It is first oxidized to acetoacetate, which is activated with coenzyme A donated from succinyl-CoA, then split by thiolase. The acetyl-CoA thus formed is used for energy production.

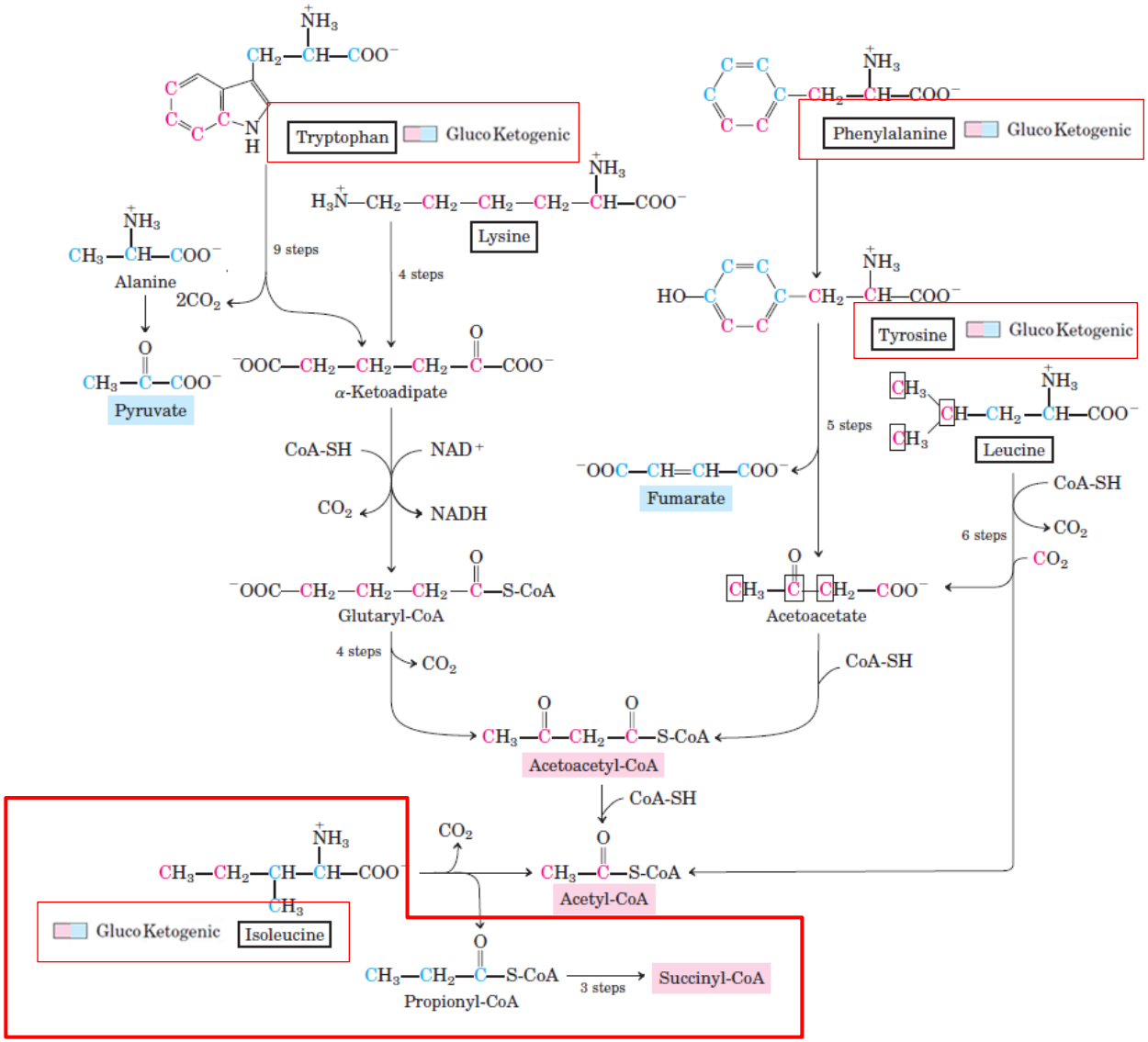


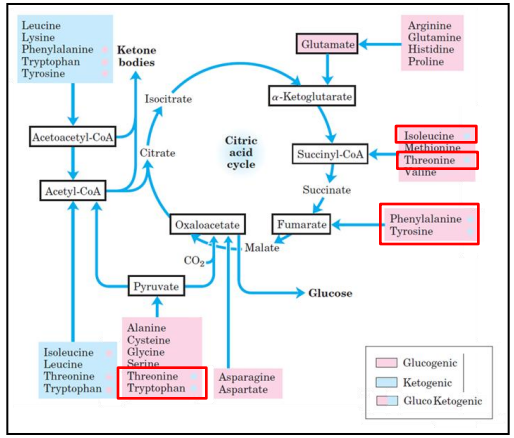


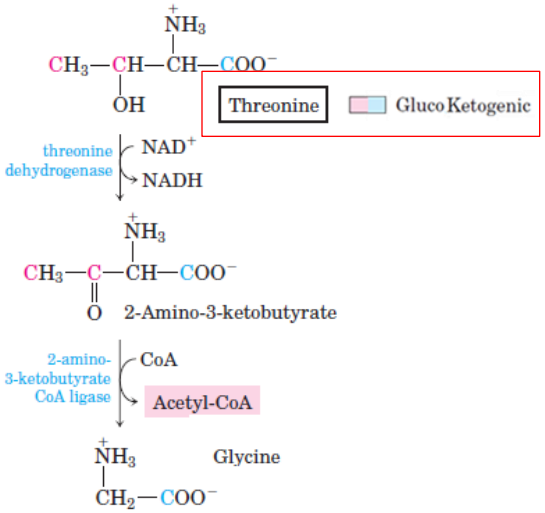
Amino acids ability to form ketone bodies is particularly evident in uncontrolled diabetes mellitus, in which the liver produces large amounts of ketone bodies from both fatty acids and the ketogenic amino acids.



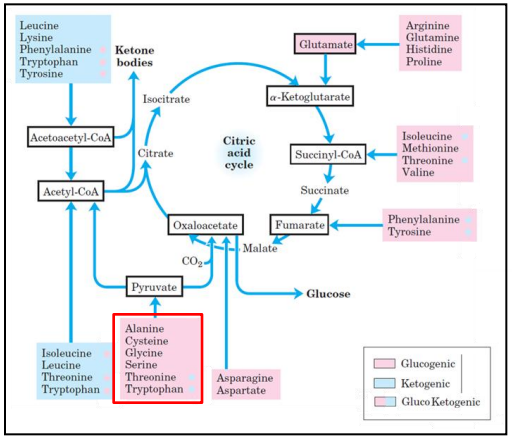
Portions of the carbon skeletons of 5 of the ketogenic amino acids — **tryptophan**, **phenylalanine**, **isoleucine**, **threonine** and **tyrosine** — can also be glucogenic.

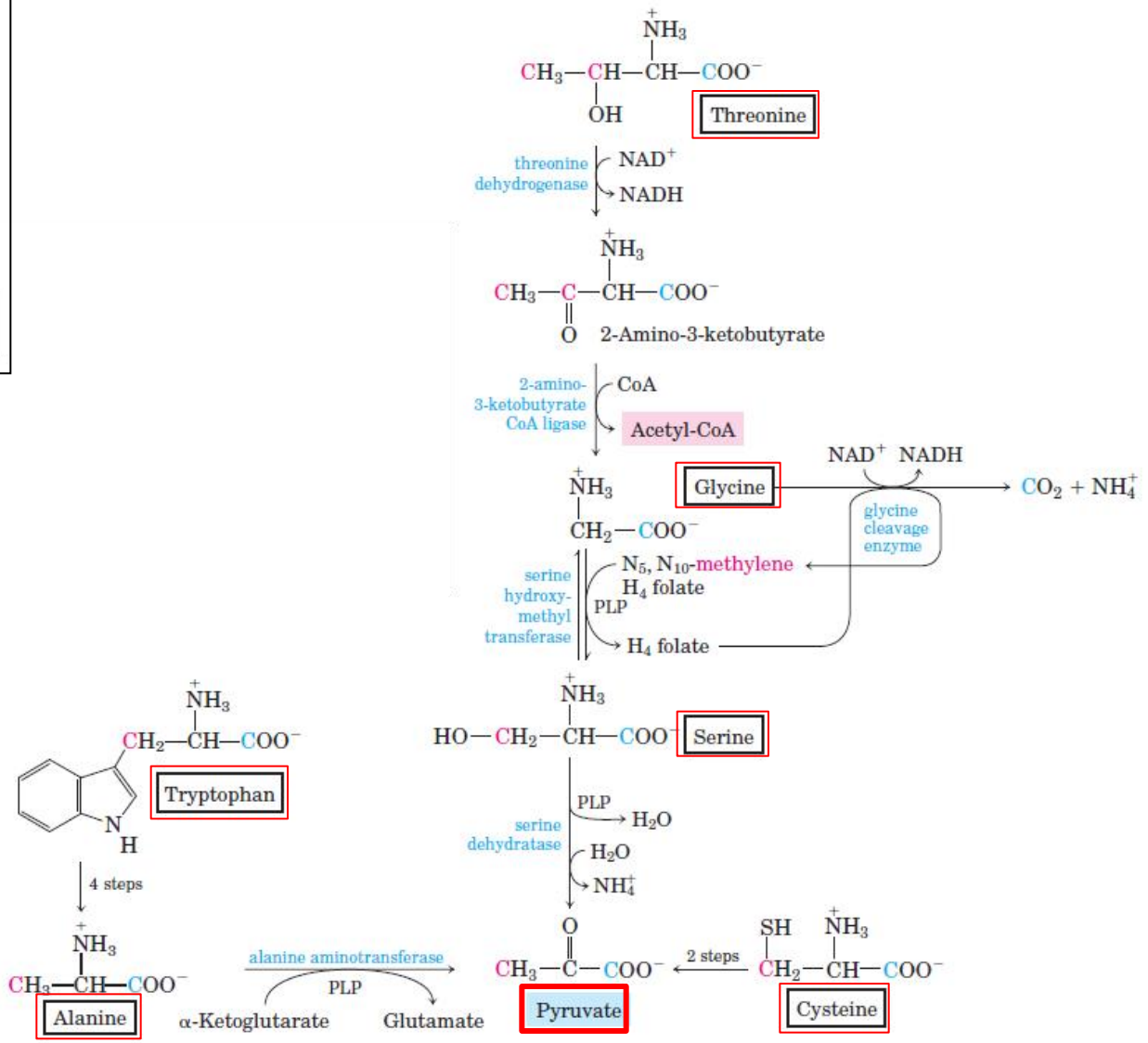




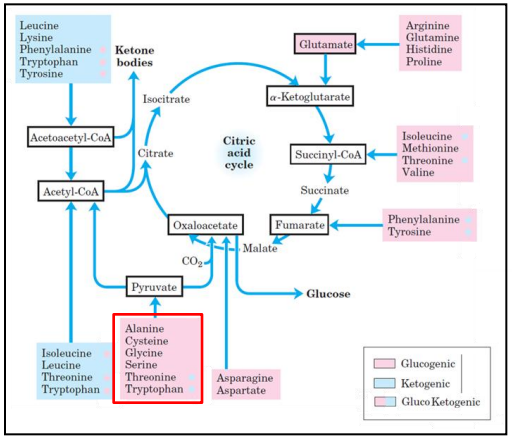


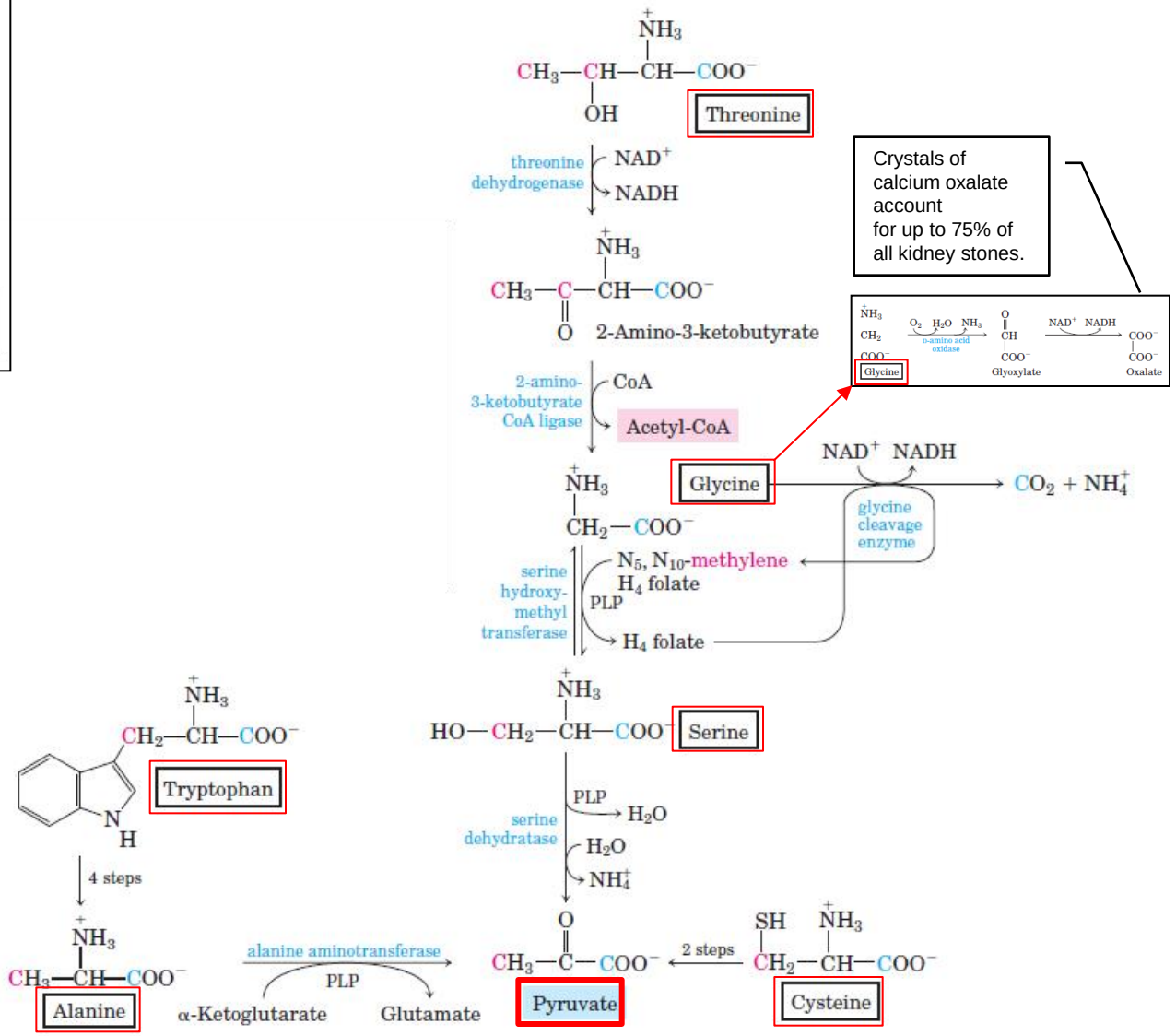
Some of the carbon atoms (C) of **isoleucine** are converted to succinyl-CoA.



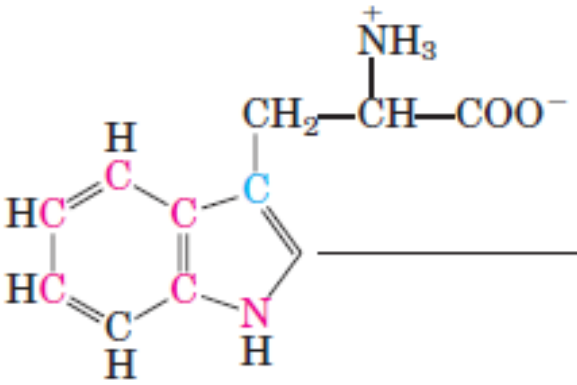


6 amino acids (**alanine**, **glycine**, **serine**, **cysteine**, **tryptophan** and **threonine**) are degraded to pyruvate.

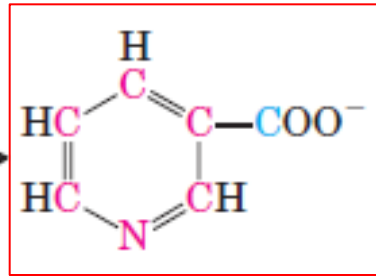




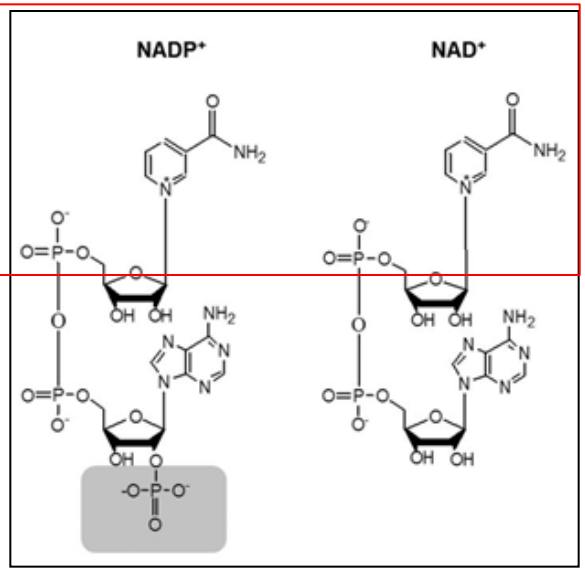
6 amino acids (**alanine**, **glycine**, **serine**, **cysteine**, **tryptophan** and **threonine**) are degraded to pyruvate.

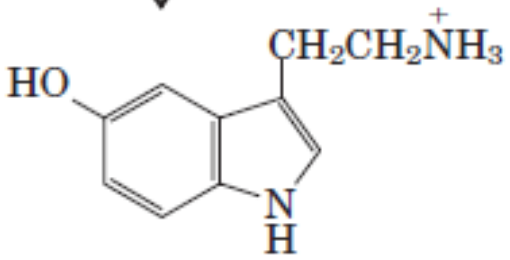


Tryptophan



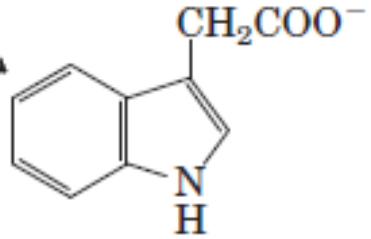
Nicotinate (niacin), a precursor of NAD and NADP





Serotonin, a neurotransmitter

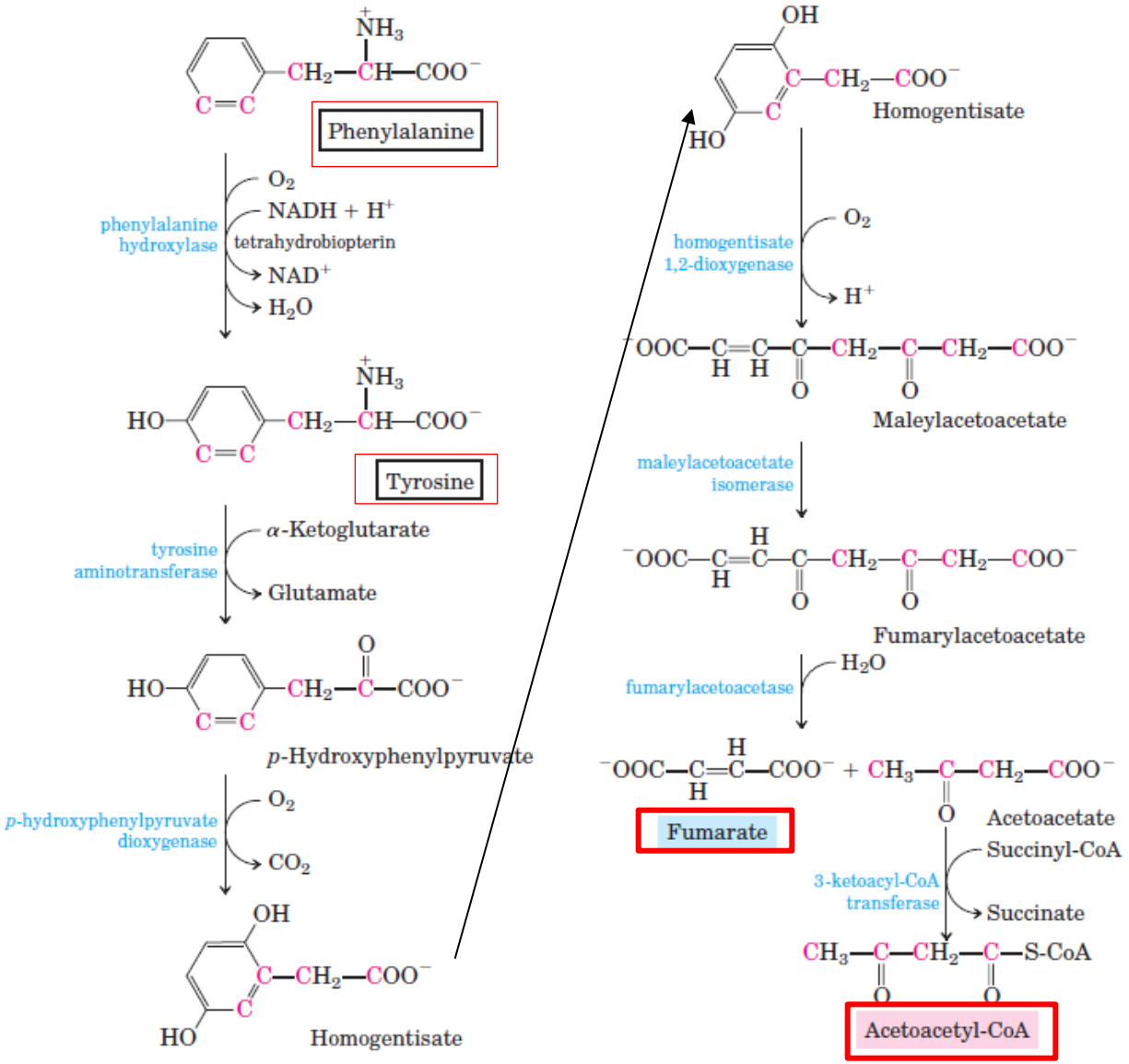
Gastrointestinal mucosa,
Platelets,
CNS neurons.



Indoleacetate, a plant growth factor

Tryptophan as precursor

The aromatic rings of tryptophan give rise to nicotinate, indoleacetate, and serotonin. Colored atoms trace the source of the ring atoms in nicotinate.



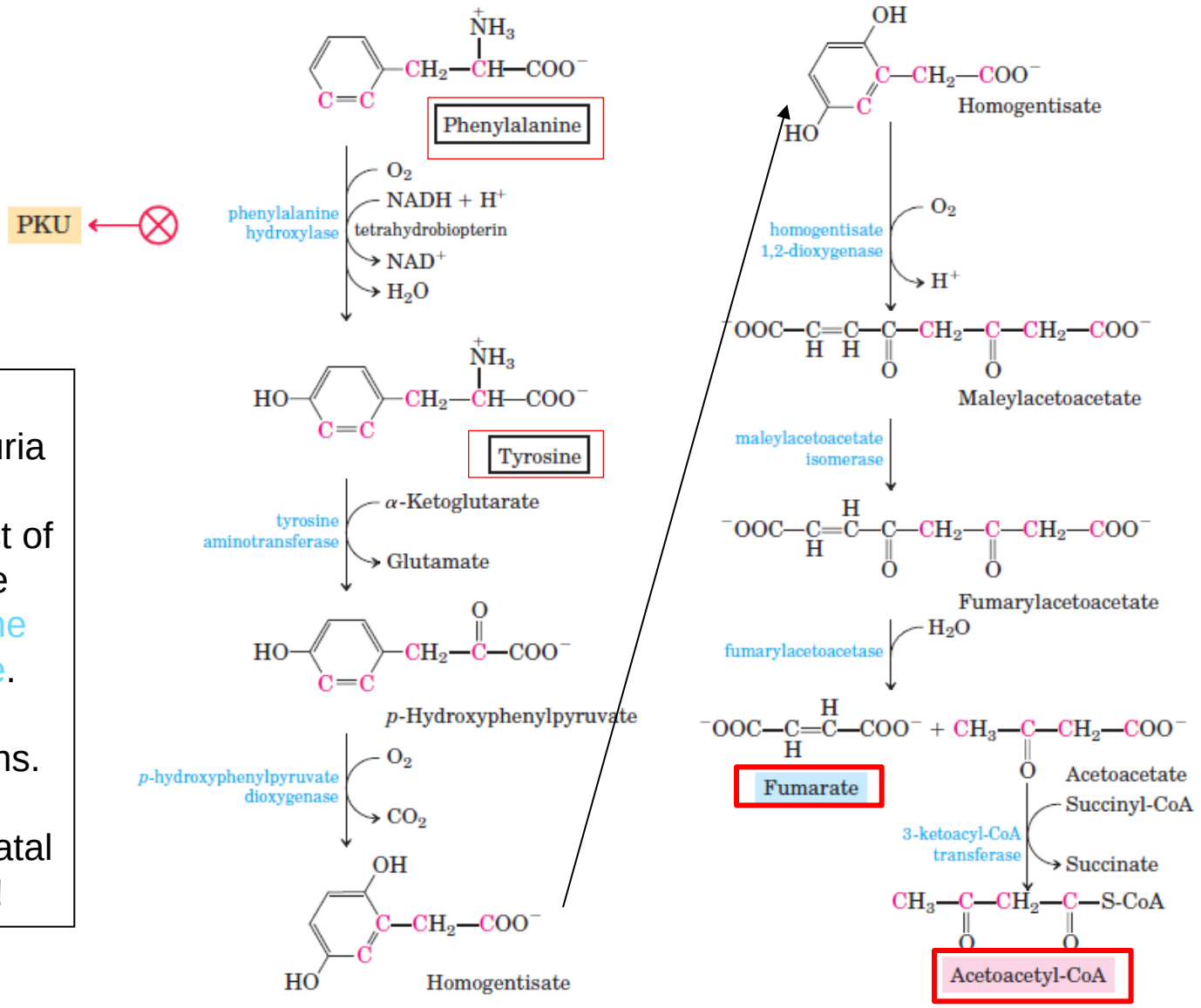
Catabolic pathways for phenylalanine and tyrosine

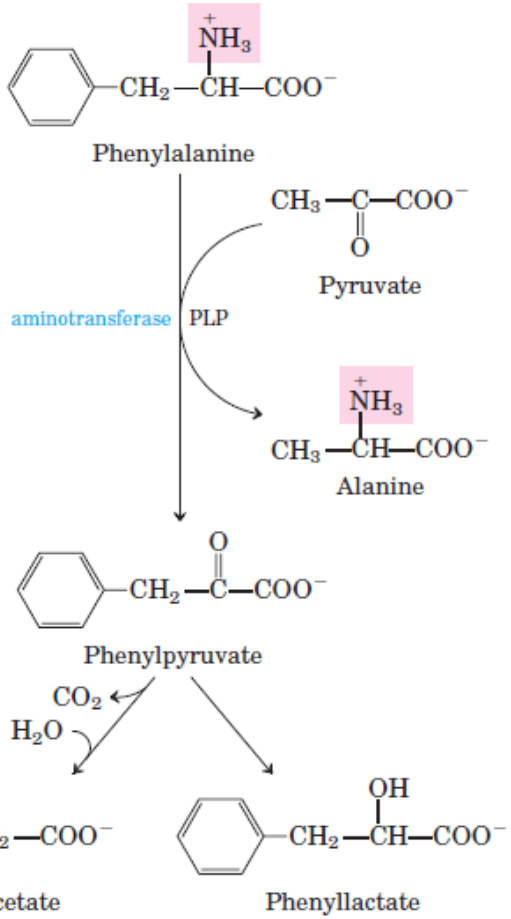
In humans these amino acids are normally converted to acetoacetyl-CoA and fumarate.

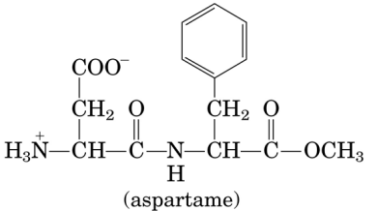
PKU* = Phenylketonuria

Genetic defect of the enzyme phenylalanine hydroxylase. Incidence 1:10,000 births.

Routine neonatal screening !

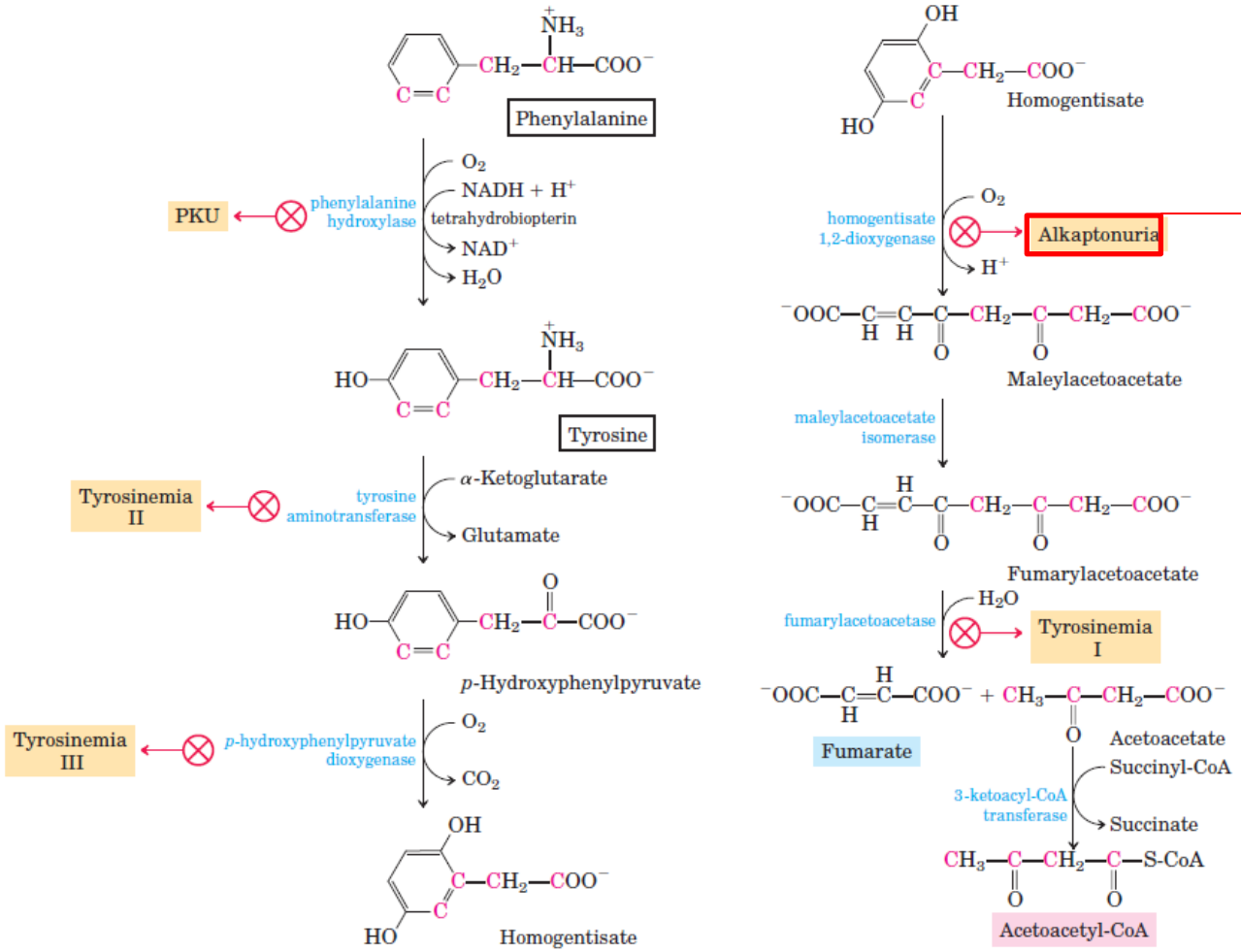






Alternative pathways for catabolism of phenylalanine in phenylketonuria

In PKU, phenylpyruvate accumulates in the tissues, blood, and urine. The urine may also contain phenylacetate and phenyllactate.

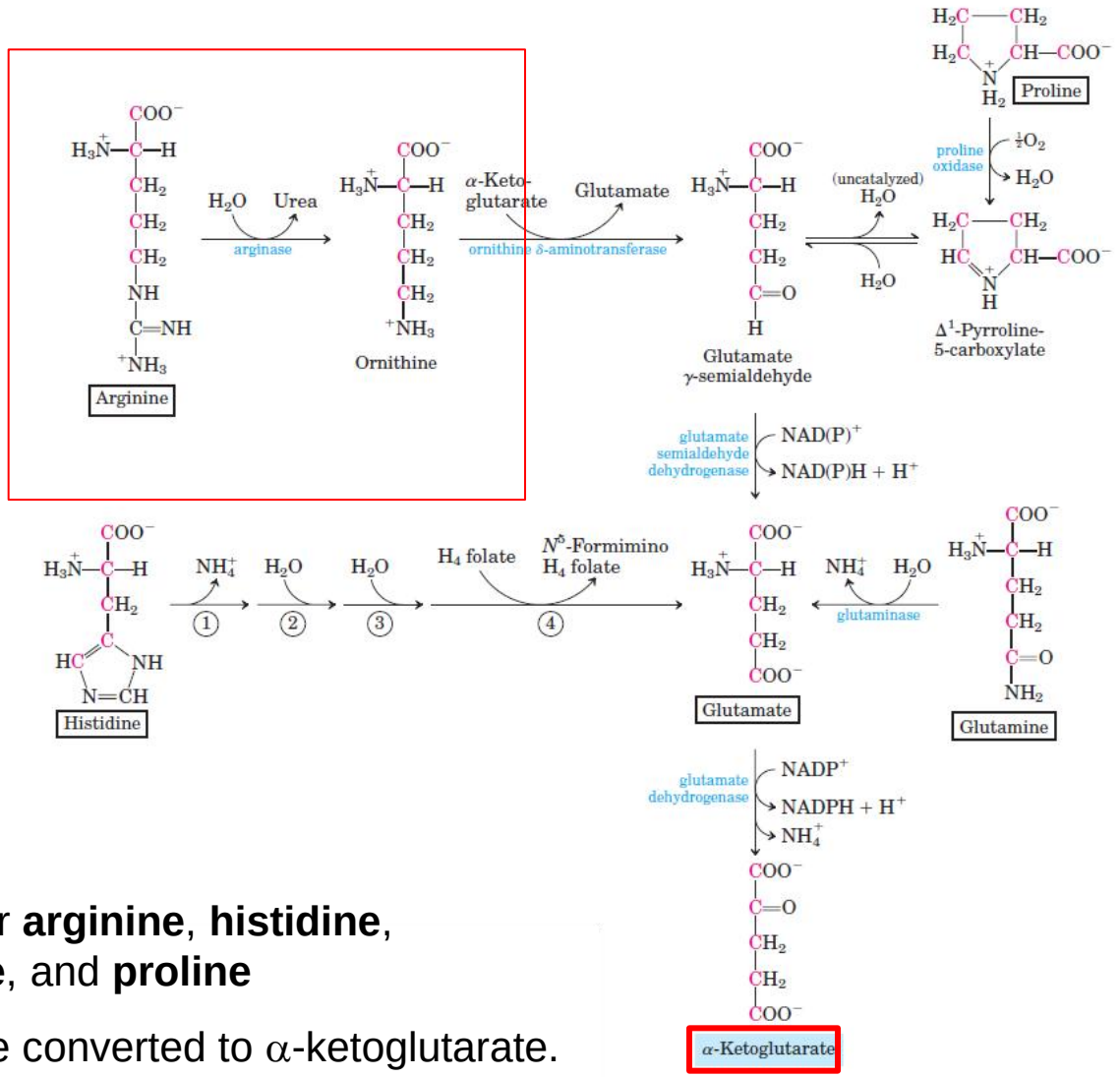


Genetic defect of the enzyme homogentisate dioxygenase,

the first enzyme whose absence has been linked to a hereditary disease.

Catabolic pathways for phenylalanine and tyrosine

Genetic defects in many of these enzymes cause inheritable human diseases (shaded yellow).

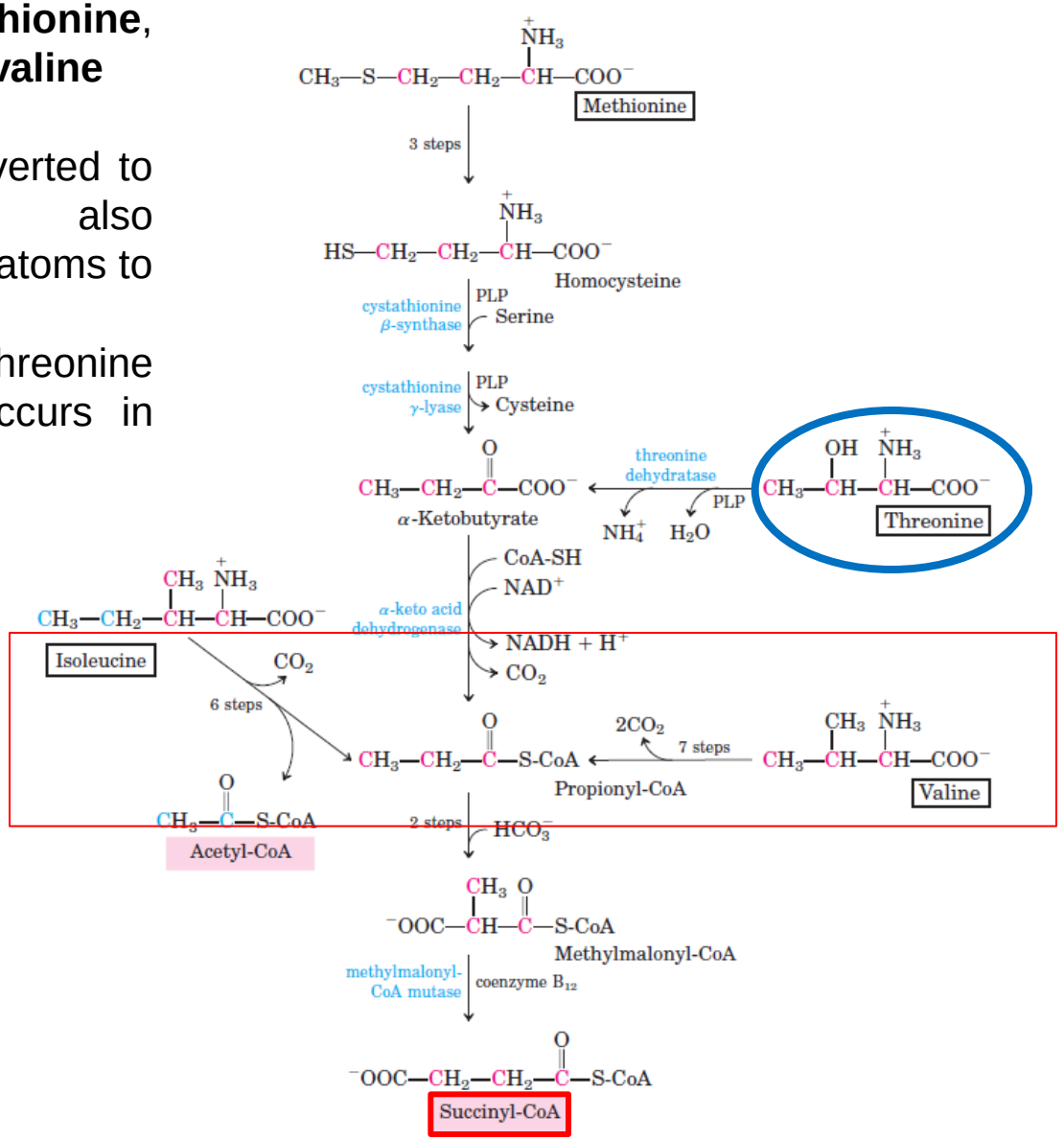


Catabolic pathways for **arginine**, **histidine**, **glutamate**, **glutamine**, and **proline**

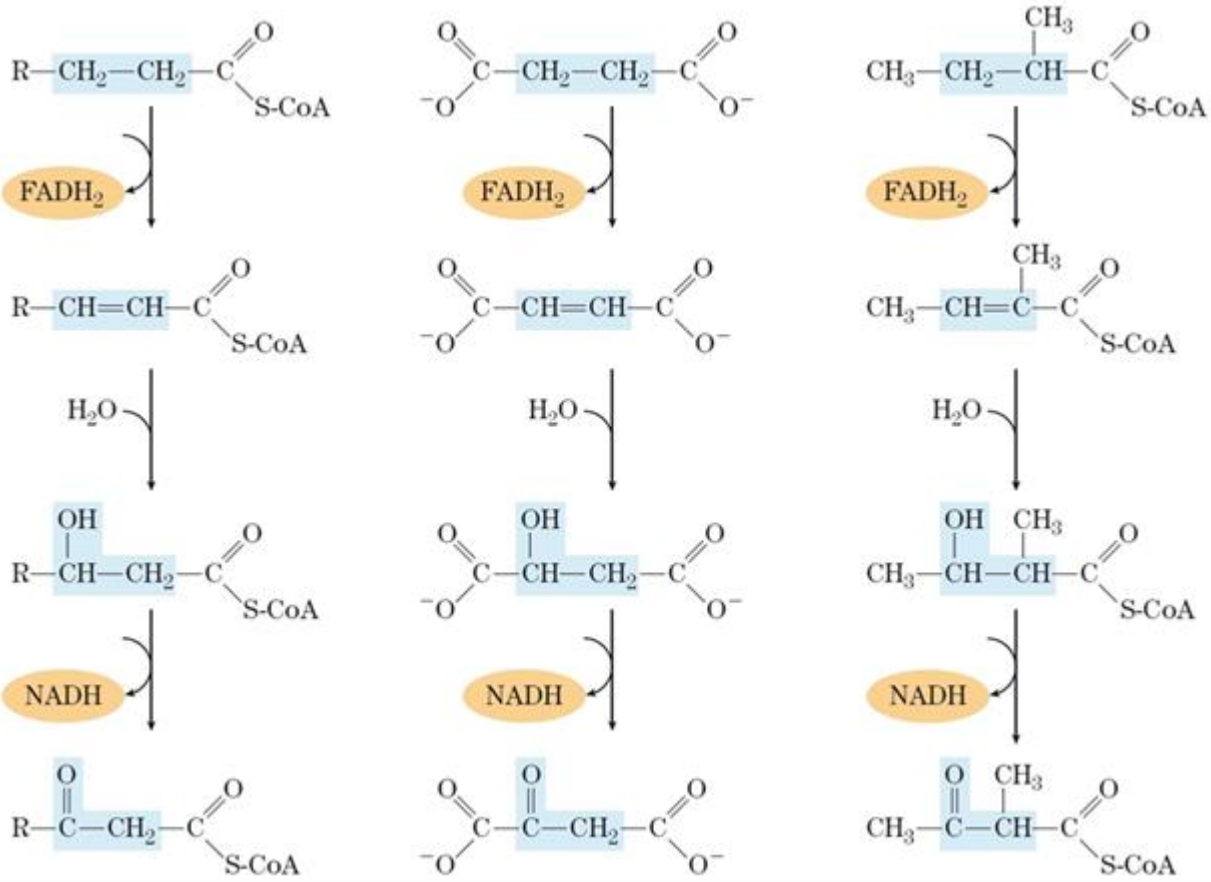
These amino acids are converted to α-ketoglutarate.

Catabolic pathways for **methionine**, **isoleucine**, **threonine**, **and valine**

These amino acids are converted to succinyl-CoA; isoleucine also contributes two of its carbon atoms to acetyl-CoA.
The pathway of threonine degradation shown here occurs in humans.

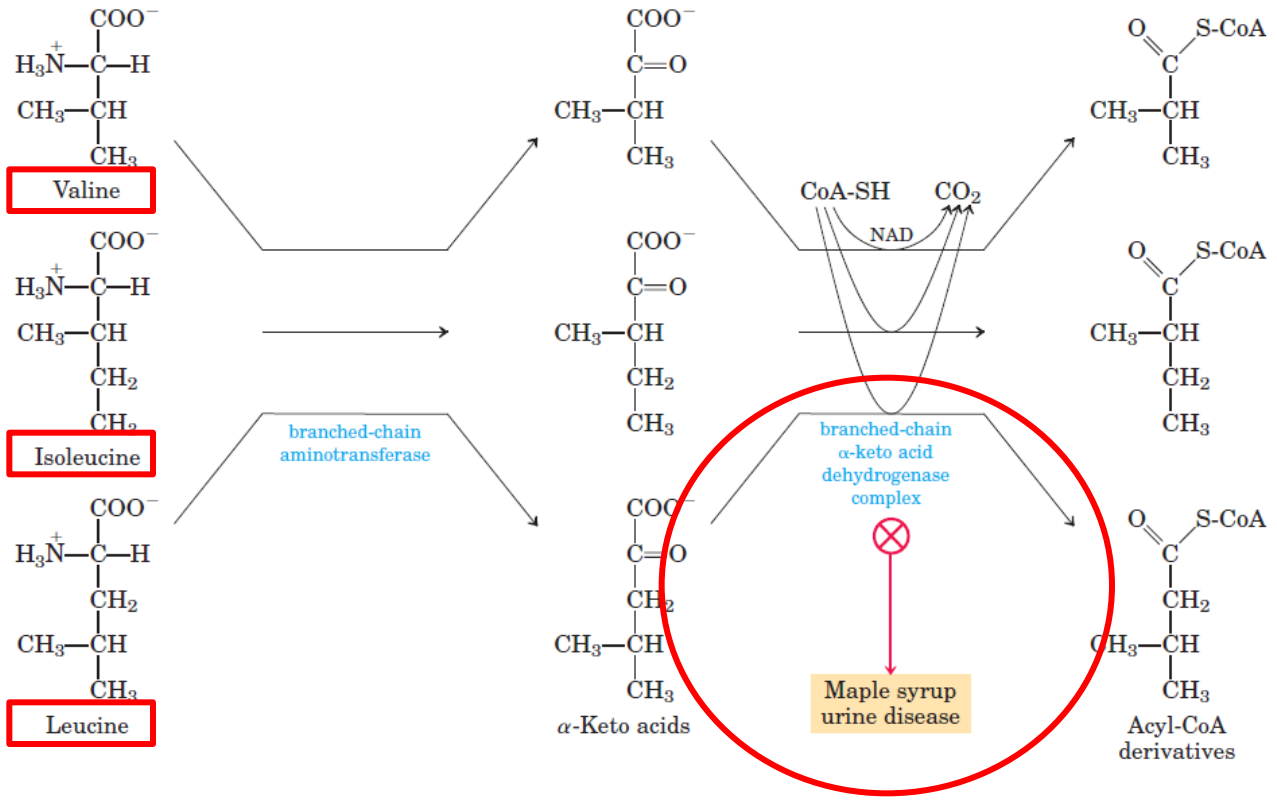


β-oxidation | citric acid cycle | isoleucin oxidation (leucin, valin)



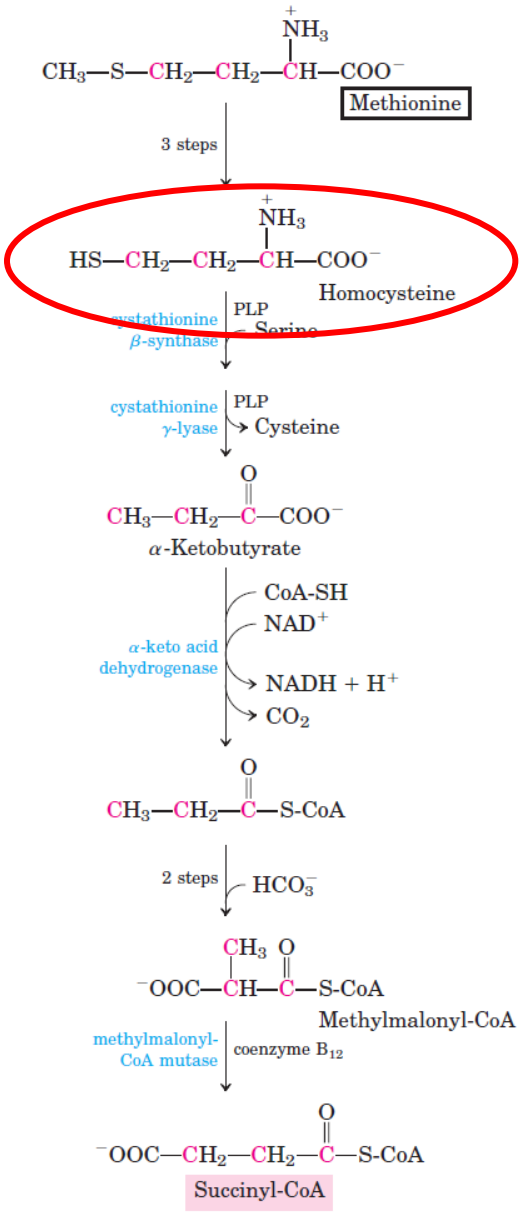
A conserved reaction sequence for the attachment o f a carbonyl functional group on the β-carbon (vs. a carboxyl group)

The: a) β-oxidation of fatty acid acyl-CoA, b) conversion of succinate to oxaloacetate in the citric acid cycle, and c) oxidation of the deaminated carbon skeletons of isoleucine, leucine, and valine to produce energy use the same reaction sequence.

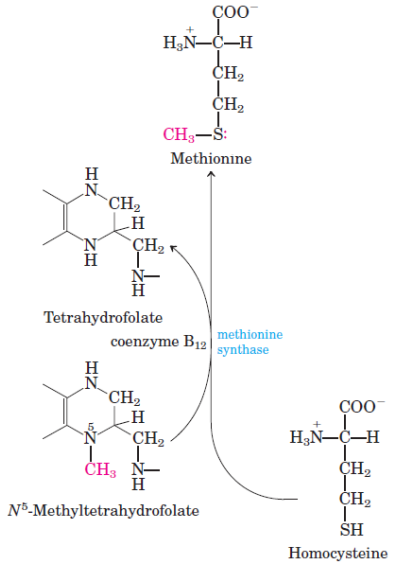


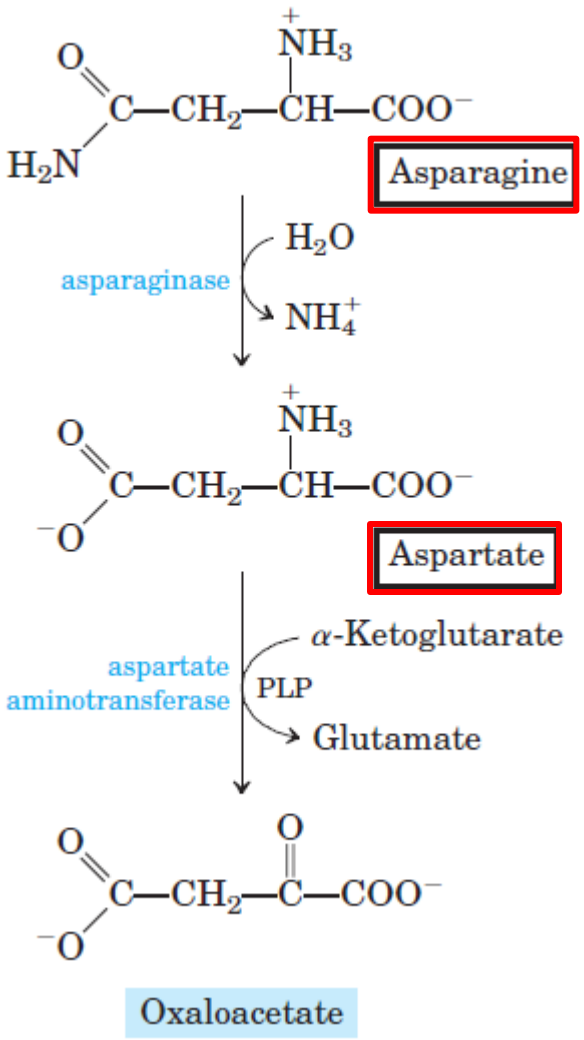
Catabolic pathways for the three branched-chain amino acids: **valine**, **isoleucine**, and **leucine**

The three pathways, which occur in extrahepatic tissues, share the first two enzymes, as shown here. The branched-chain -keto acid dehydrogenase complex is analogous to the pyruvate and -ketoglutarate dehydrogenase complexes and requires the same five cofactors (some not shown here).
This enzyme is defective in people with maple syrup urine disease.



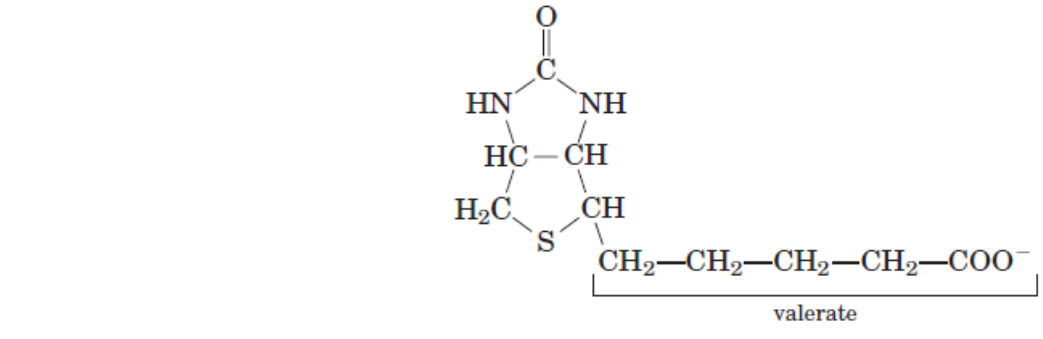
Accumulation of homocysteine in the blood causes damage to the endothelium, an increased risk of thrombosis, and therefore coronary heart disease and stroke, at a young age.



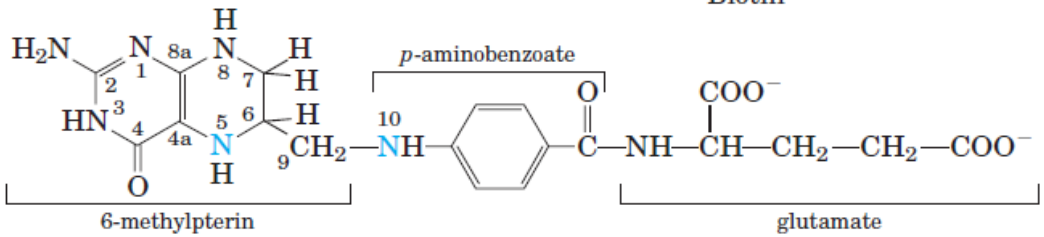


Catabolic pathway for asparagine and aspartate

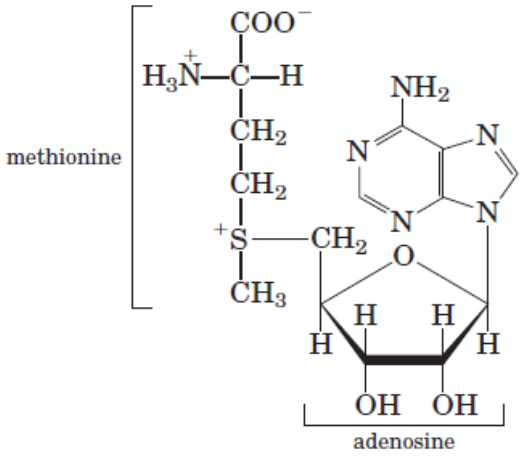
Both amino acids are converted to oxaloacetate.



Biotin



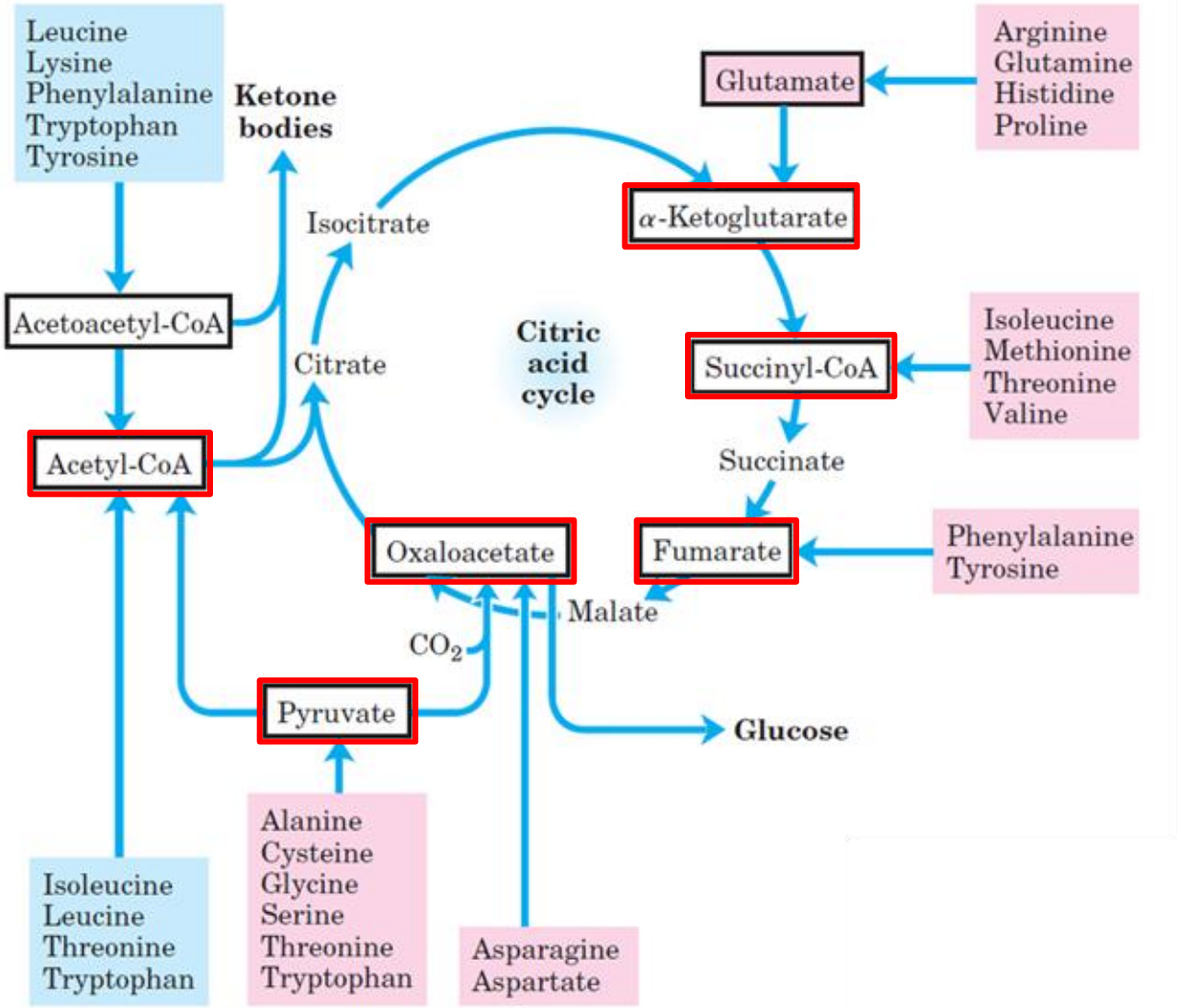
Tetrahydrofolate (H_4 folate)



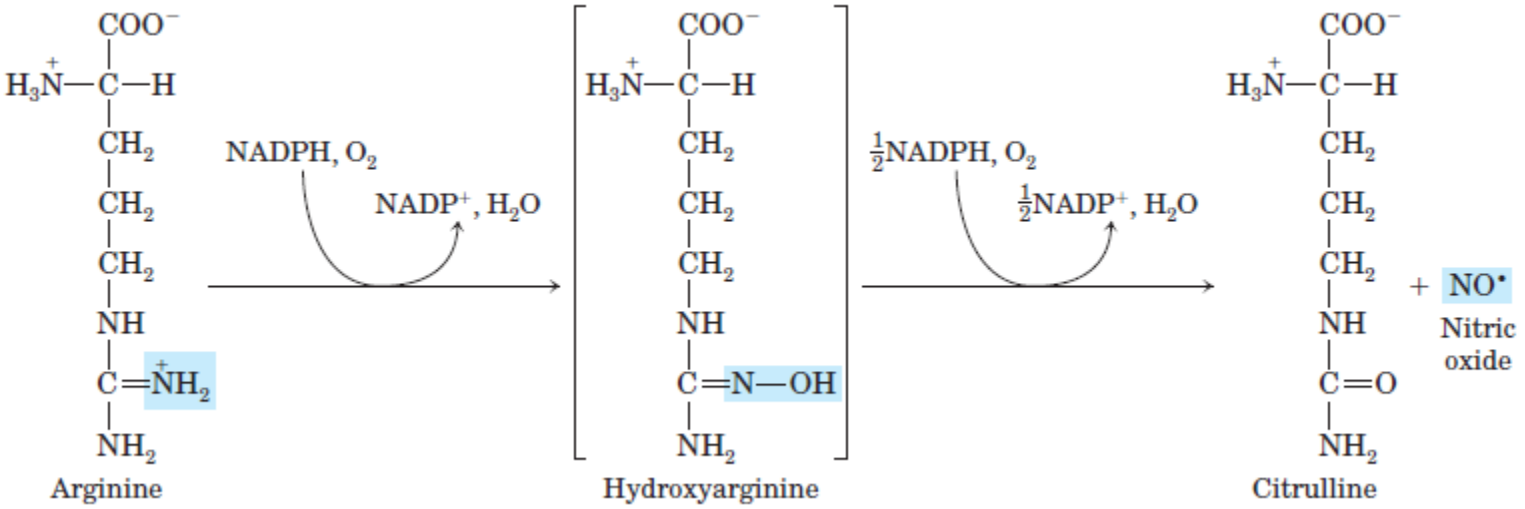
S-Adenosylmethionine (adoMet)

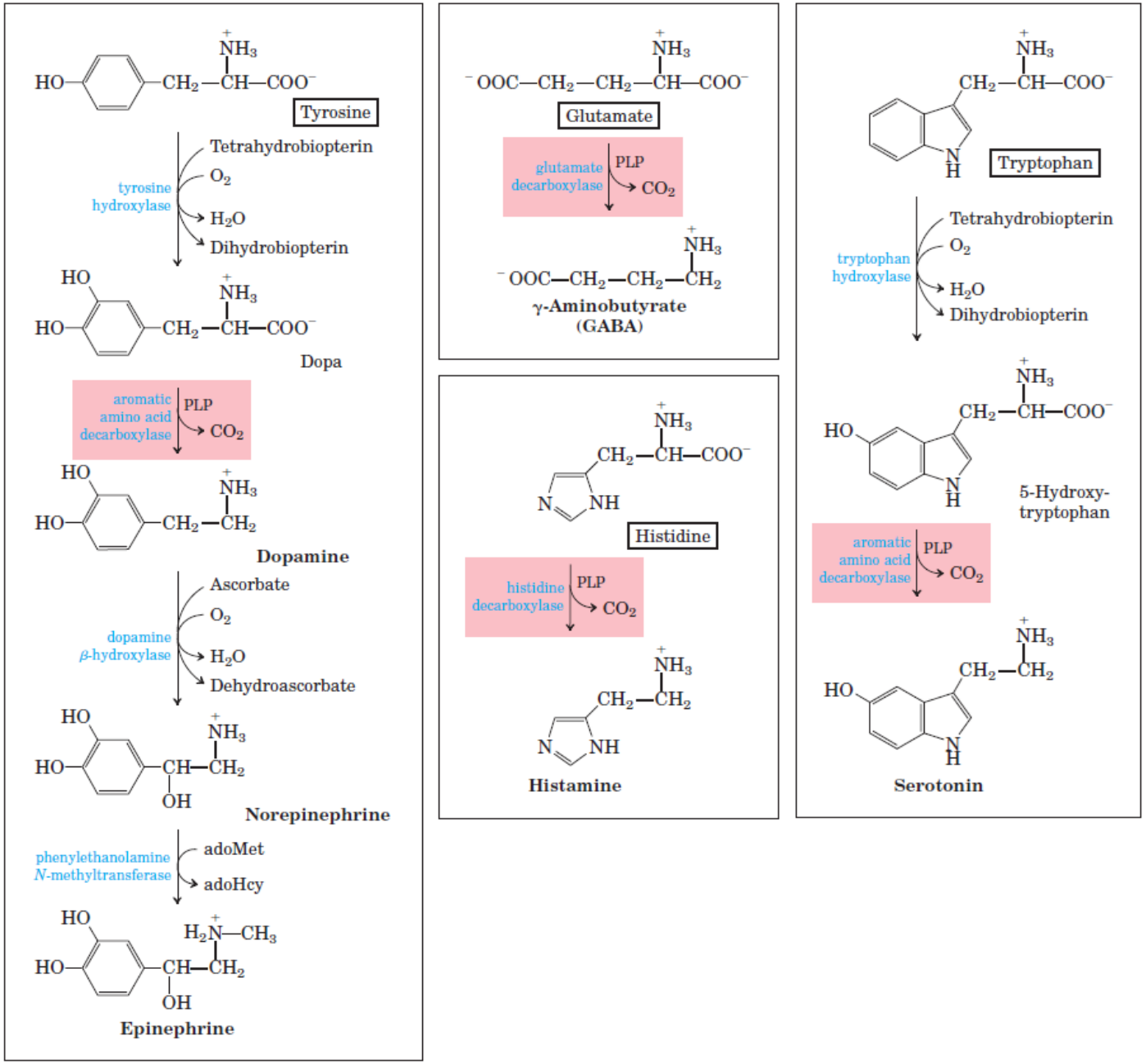
Carbon transfers generally involve one of three cofactors illustrated

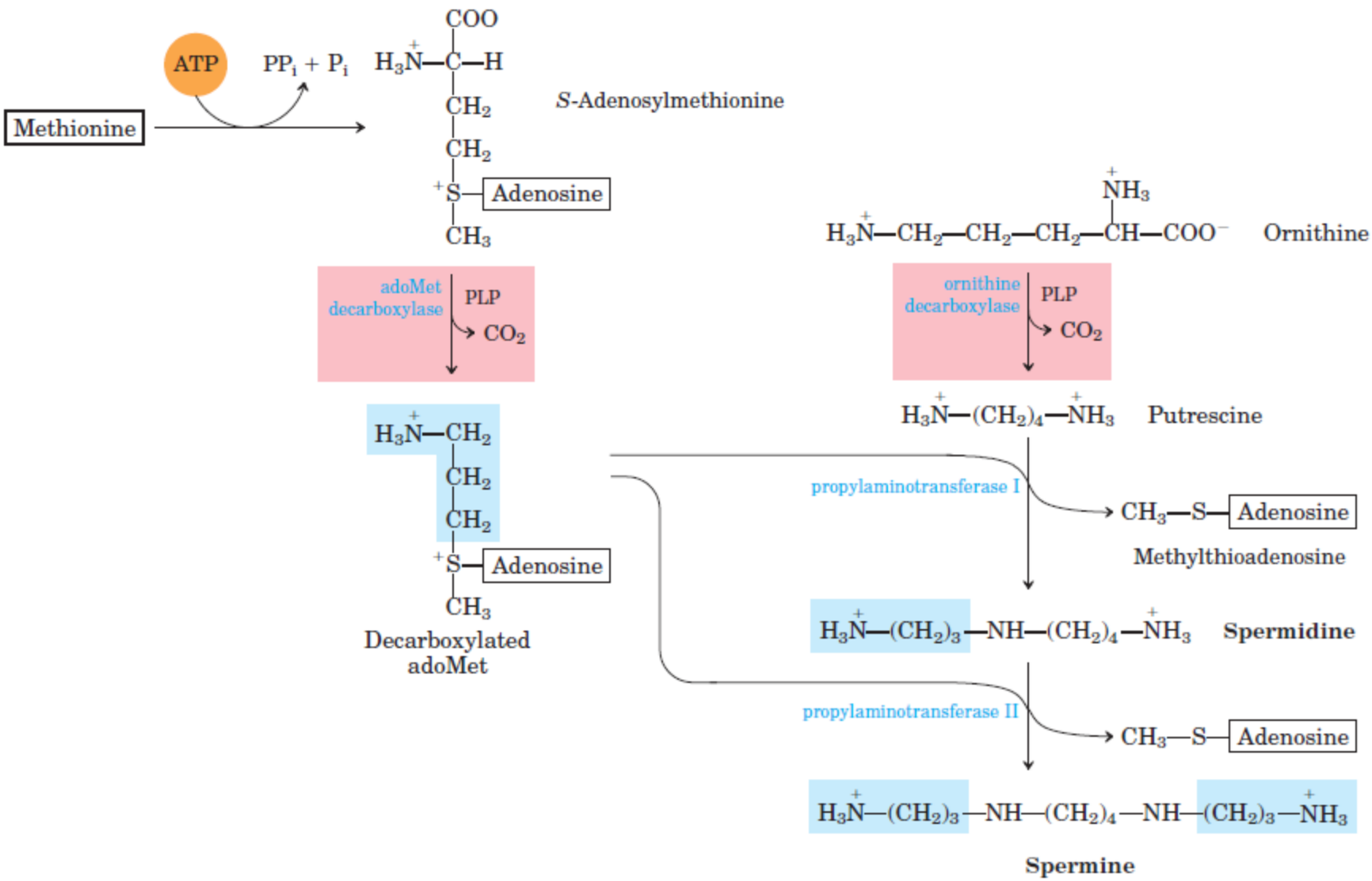
- Biotin (vit. B8 or vit. H) transfers carbon in the most oxidized state (CO_2).
- H4 Folate transfers carbon with multiple oxidation states.
- adoMet transfers carbon in the most reduced state (CH_3)



As with carbohydrates and lipids, the degradation of amino acids leads to the release of reducing equivalents (NADH and $FADH_2$) through the action of the citric acid cycle. These reducing equivalents are then used in mitochondrial respiration to generate energy.



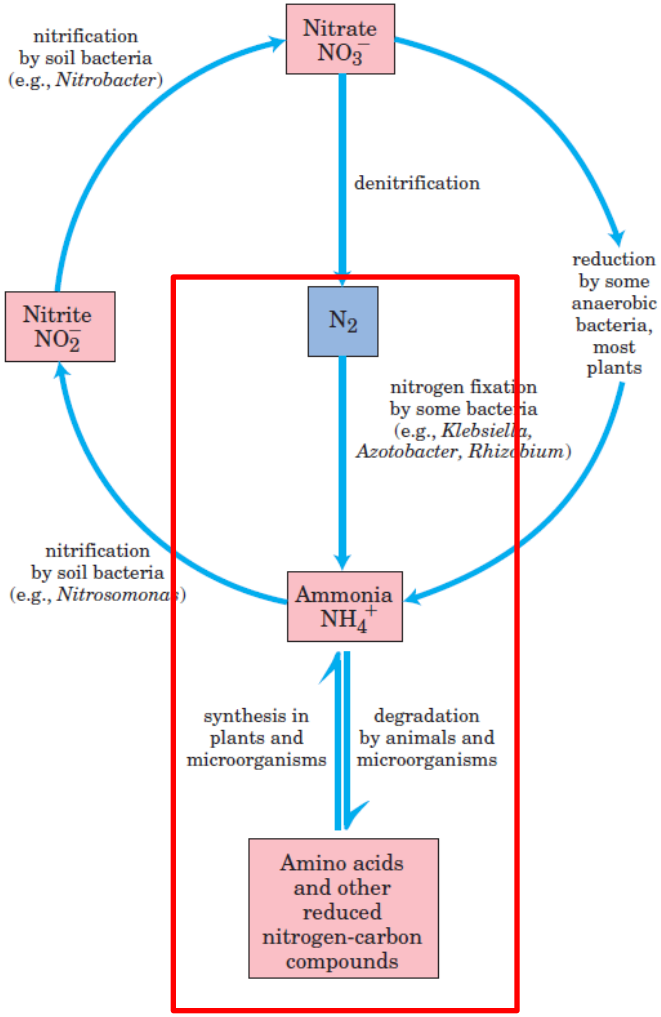




Nitrogen is the fourth most abundant element in living organisms, after carbon, hydrogen, and oxygen.

Nitrogen is predominantly present in amino acid and nucleotide molecules, so the biosynthesis of the former is closely interconnected with that of the latter.

Soluble nitrogen compounds are not very abundant in nature, so free amino acids, purines and pyrimidines formed by metabolism are largely recovered and reused.



The nitrogen cycle

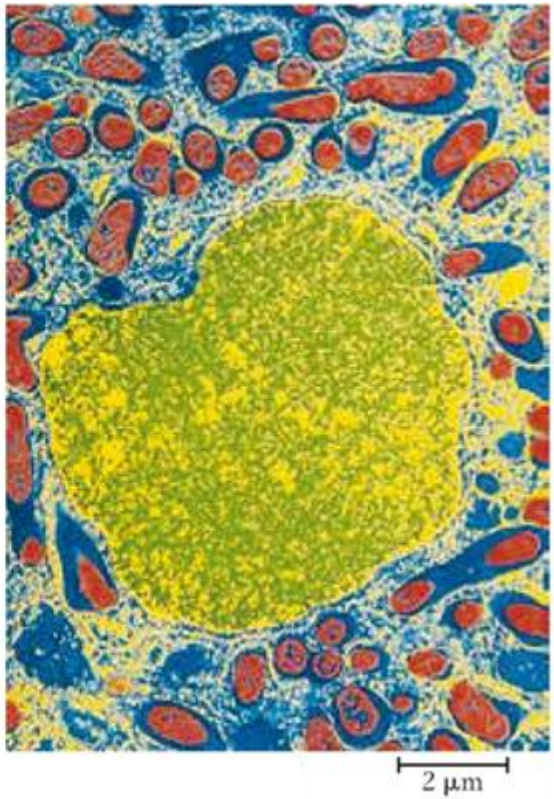
The total amount of nitrogen fixed* annually in the biosphere exceeds 10^{11} kg.

*Fixation (reduction) of atmospheric nitrogen by nitrogen-fixing bacteria to yield ammonia (NH_3 or NH_4^+).

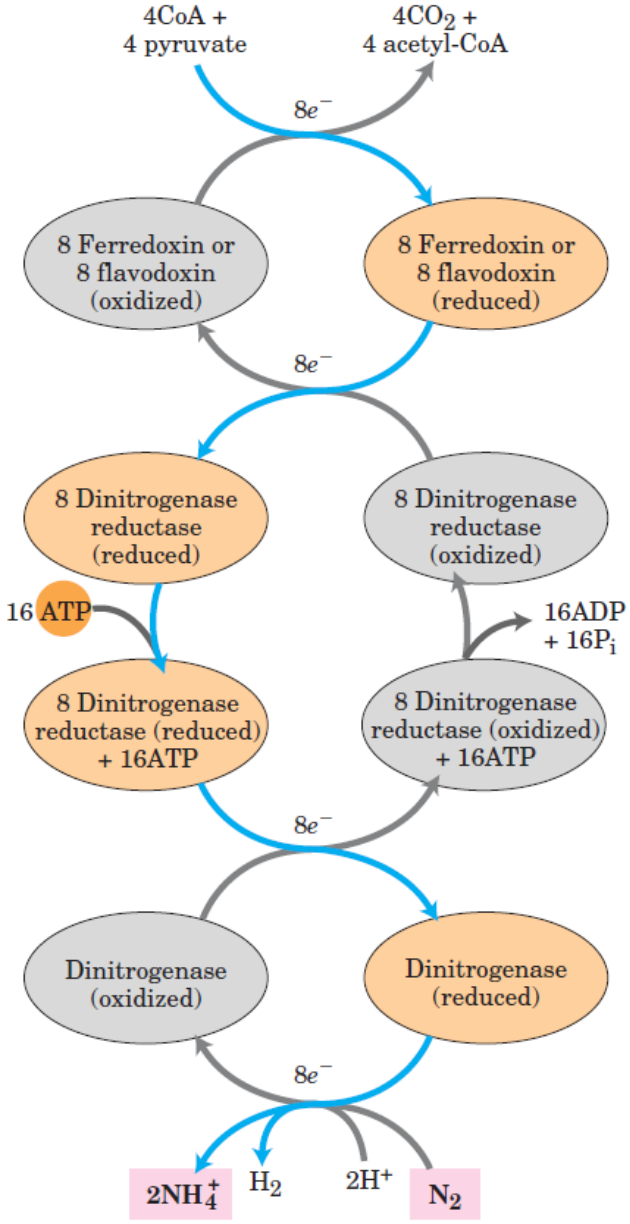
Nitrogen-fixing nodules

Bacteroids produce the nitrogenase complex that converts atmospheric nitrogen (N_2) to ammonium (NH_4^+); without the bacteroids, the plant is unable to utilize N_2. The infected root cells provide some factors essential for nitrogen fixation, including leghemoglobin; this heme protein has a very high binding affinity for oxygen, which strongly inhibits nitrogenase.

Root nodules of bird's-foot trefoil, a legume.



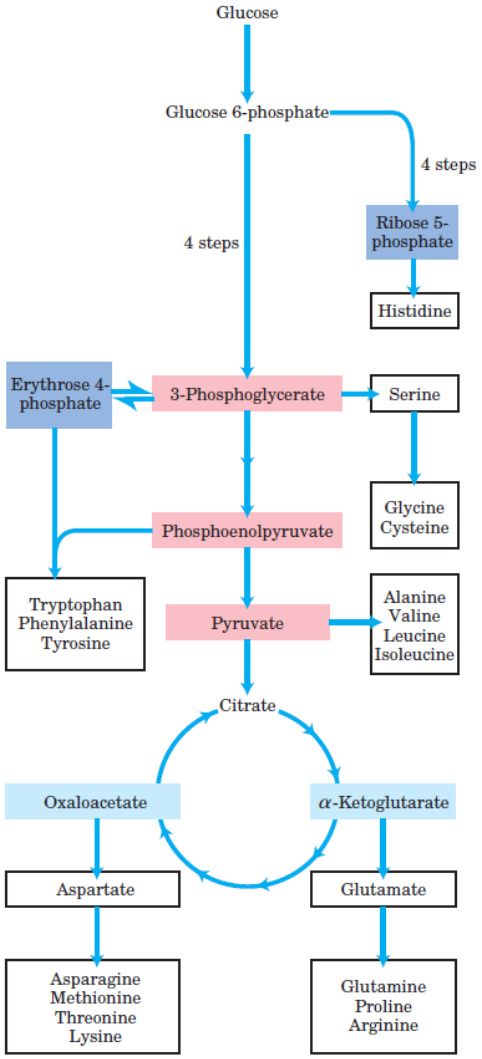
Artificially colorized electron micrograph of a thin section through a pea root nodule. Symbiotic nitrogen-fixing bacteria, or bacteroids (red), live inside the nodule cells, surrounded by the peribacteroid membrane (blue). The cell nucleus is shown in yellow/green.



Conversion of atmospheric N_2 into ammonium ion NH_4^+ (ionized NH_3 in solution at neutral pH) is carried out by bacteria equipped with the enzyme nitrogenase.

The so-called nitrogen fixation is an energetically expensive process: for the production of 2 molecules of NH_3, 16 molecules of ATP and 8 pairs of electrons are needed.

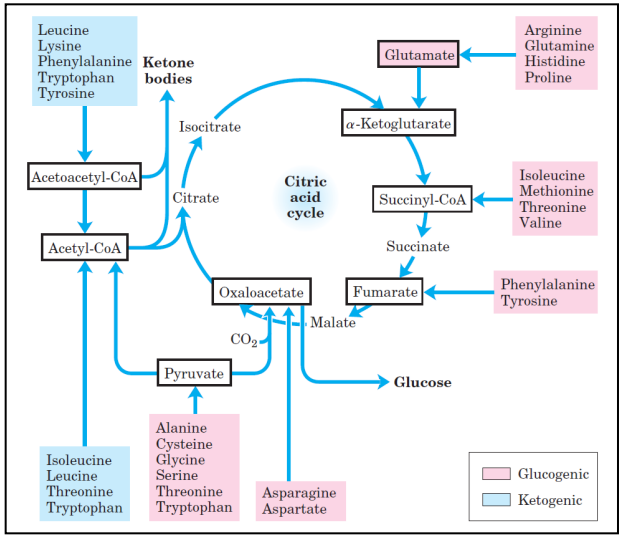
NH_4^+ can then be used by plants for biosynthesis.



Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

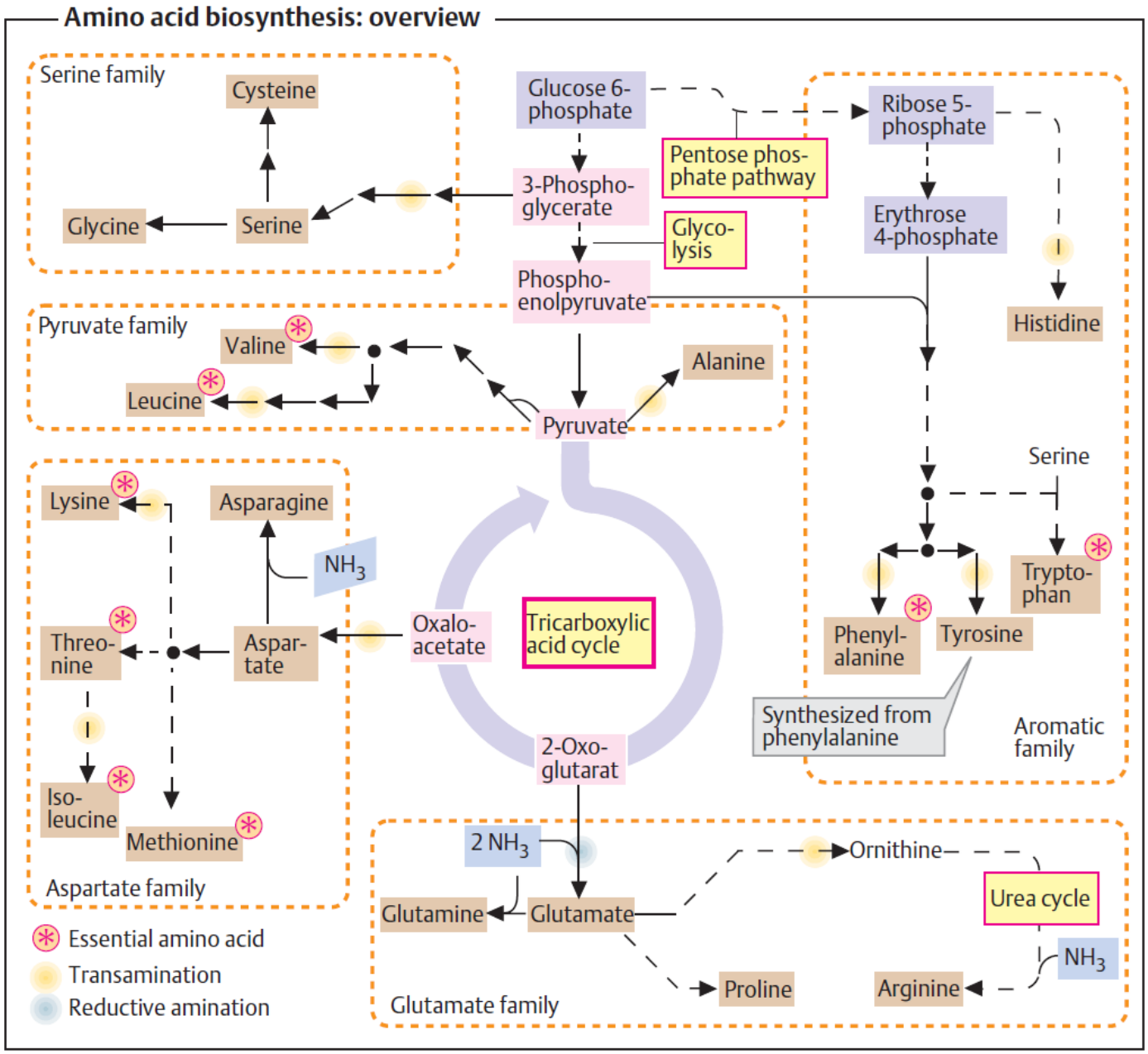
α-Ketoglutarate	**Pyruvate**
Glutamate	Alanine
Glutamine	Valine*
Proline	Leucine*
Arginine	Isoleucine*
3-Phosphoglycerate	**Phosphoenolpyruvate and erythrose 4-phosphate**
Serine	Tryptophan*
Glycine	Phenylalanine*
Cysteine	Tyrosine†
Oxaloacetate	**Ribose 5-phosphate**
Aspartate	Histidine*
Asparagine	
Methionine*	
Threonine*	
Lysine*	

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



Overview of amino acid biosynthesis

The carbon skeleton precursors derive from three sources: glycolysis (pink), the citric acid cycle (blue), and the pentose phosphate pathway (purple).



Nonessential and Essential Amino Acids for Humans

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.

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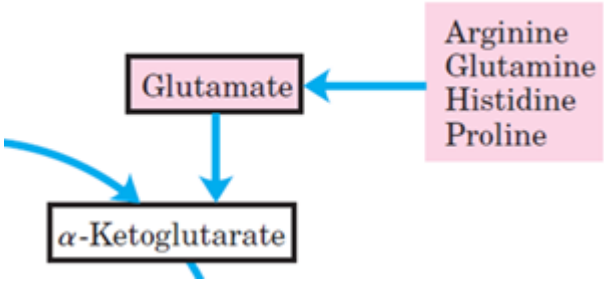
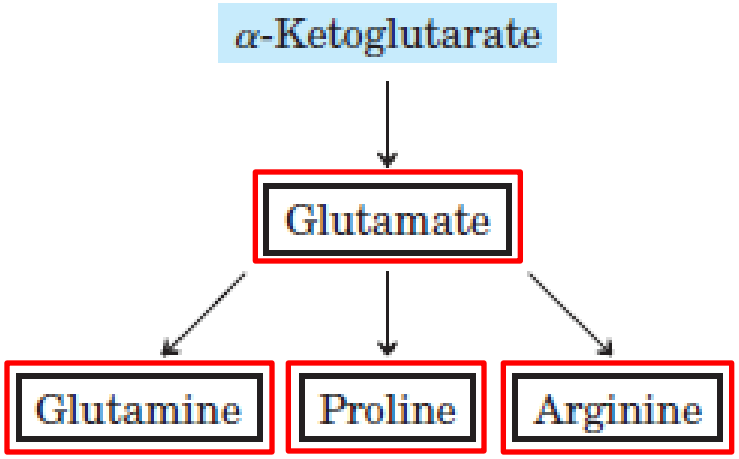
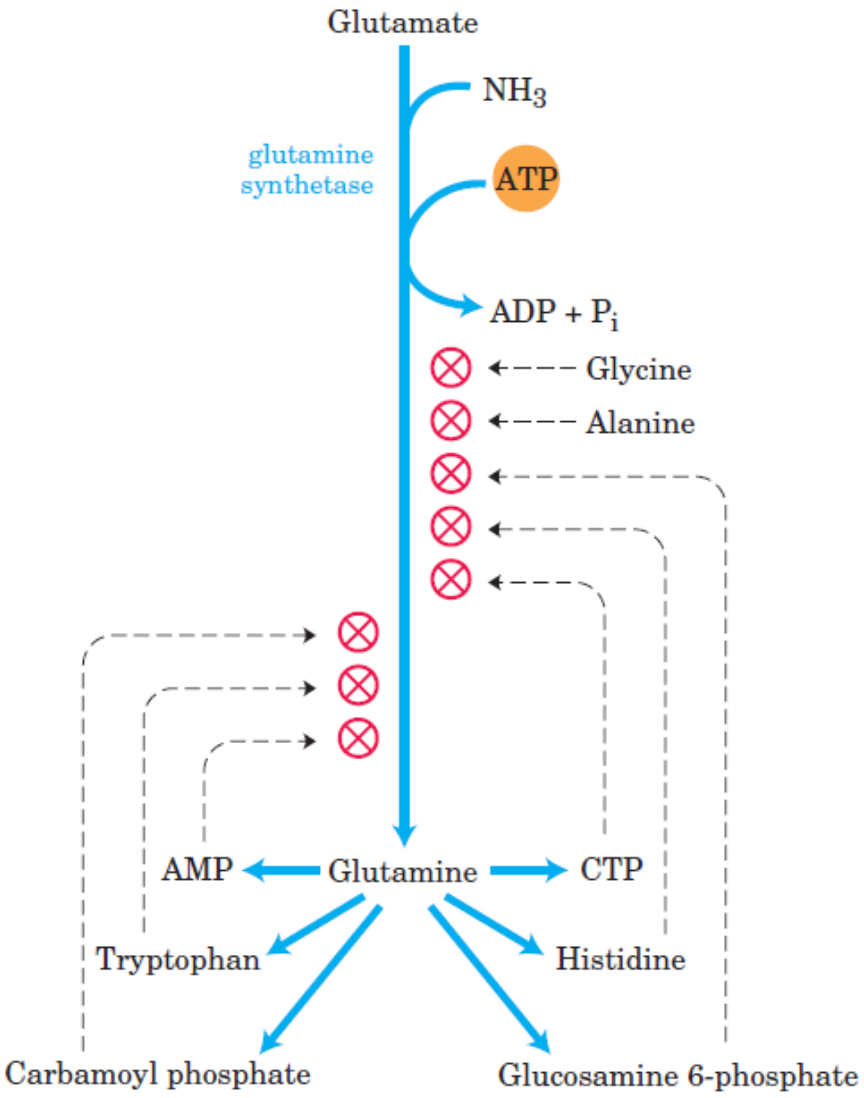


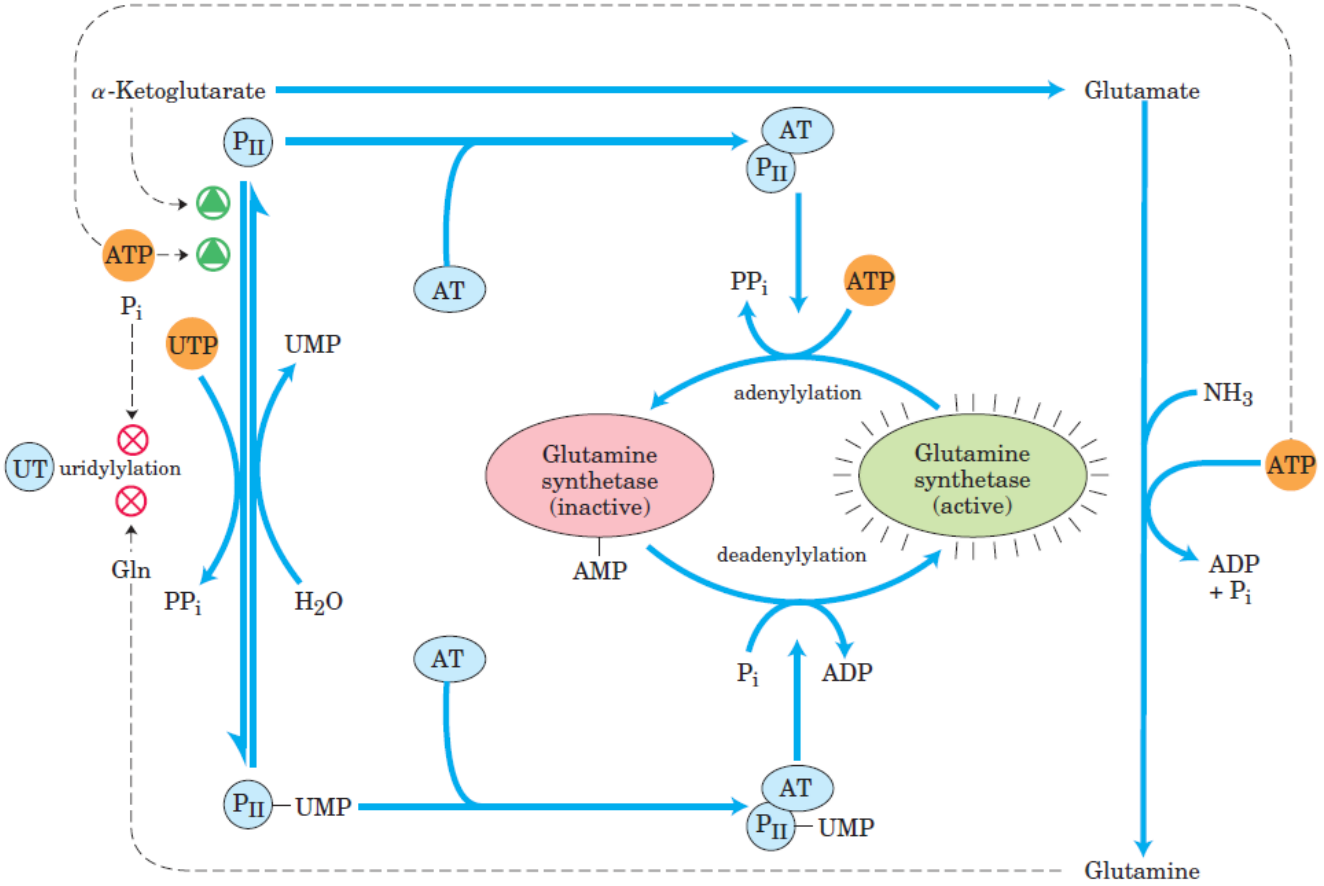




Allosteric regulation of glutamine synthetase

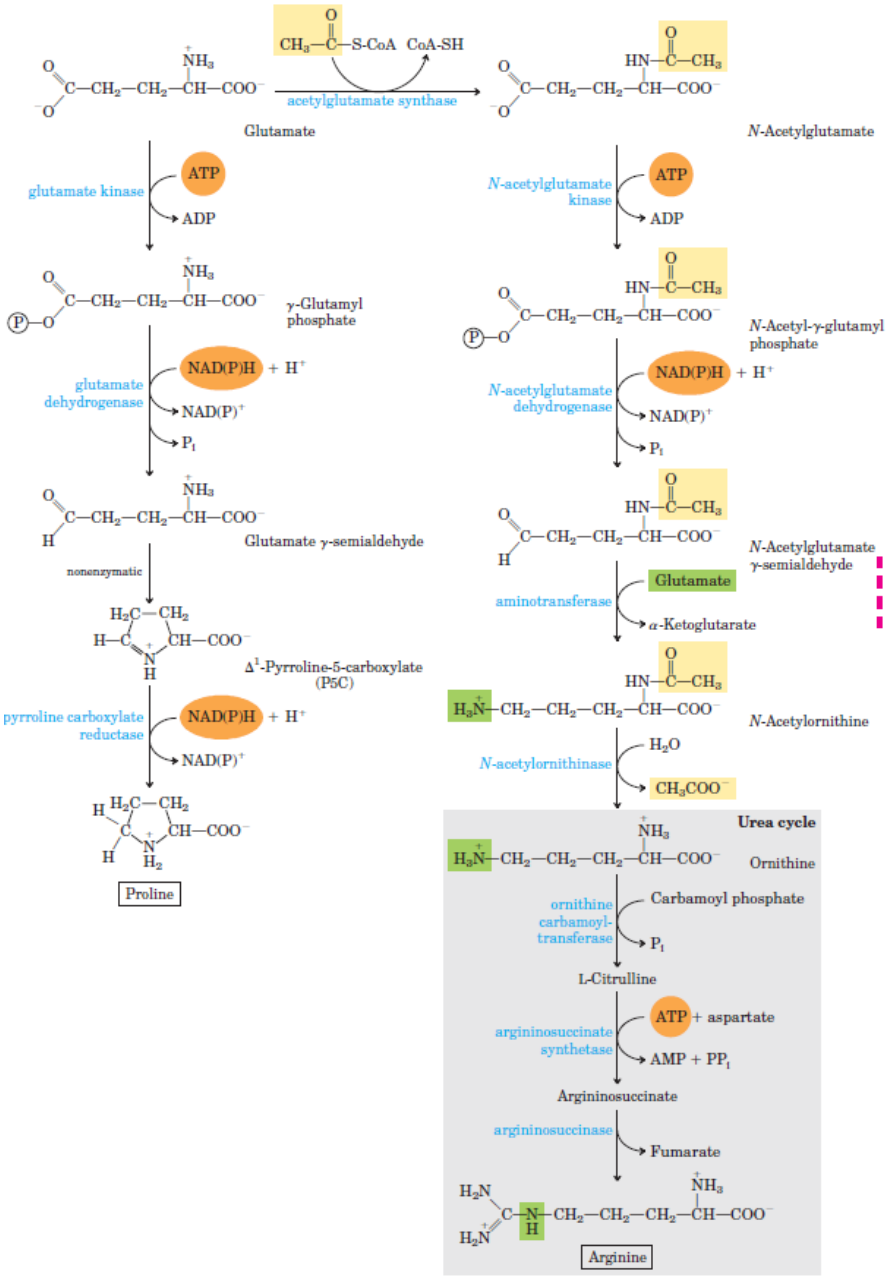
The enzyme undergoes cumulative regulation by six end products of glutamine metabolism.

Alanine and glycine probably serve as indicators of the general status of amino acid metabolism in the cell.



Second level of regulation of glutamine synthetase: covalent modifications

Cascade leading to adenylylation (inactivation) of glutamine synthetase. AT represents adenylyltransferase; UT, uridylyltransferase.



Biosynthesis of proline and arginine from glutamate

Nonessential and Essential Amino Acids for Humans

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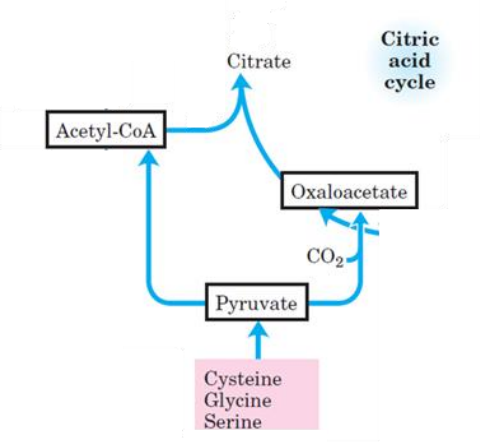
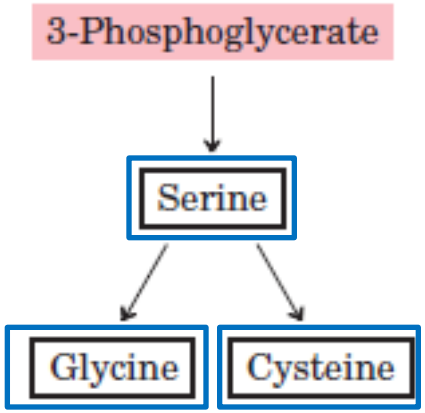
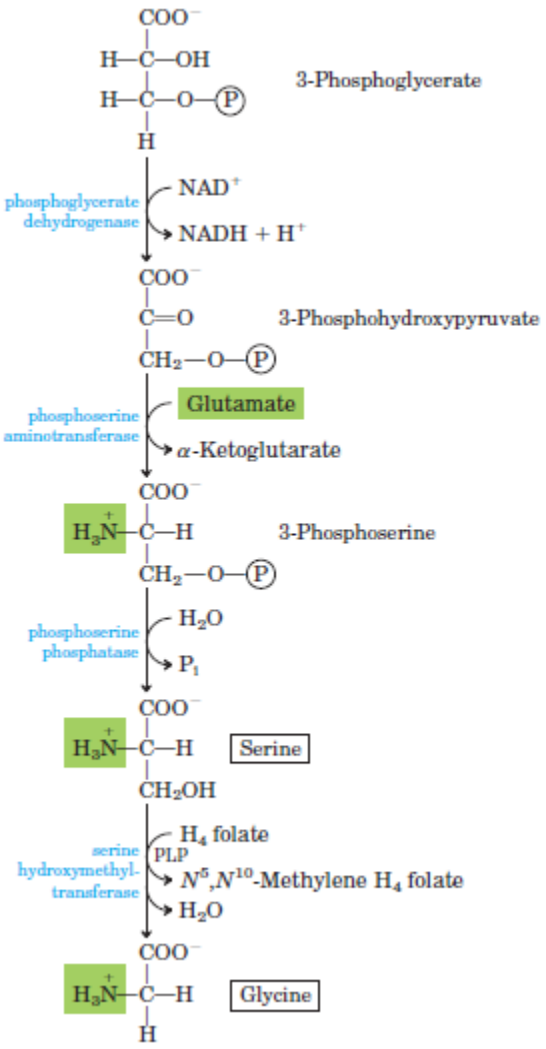
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

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

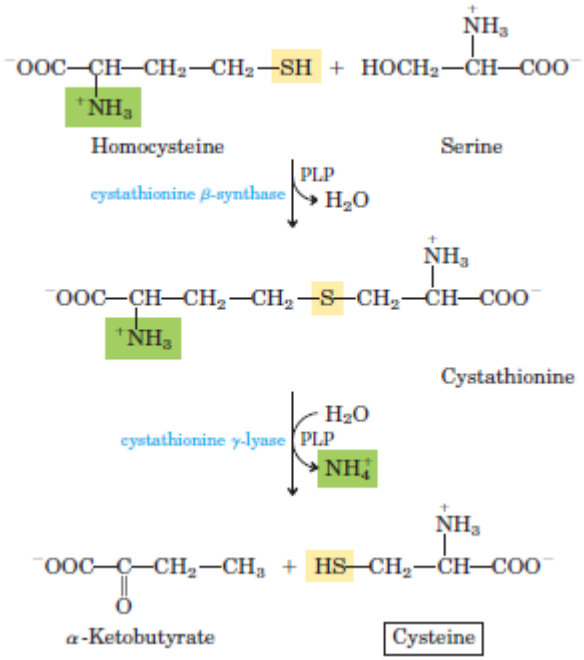






Biosynthesis of serine from 3-phosphoglycerate

and of glycine from serine



Biosynthesis of cysteine from homocysteine and serine in mammals

Nonessential and Essential Amino Acids for Humans

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

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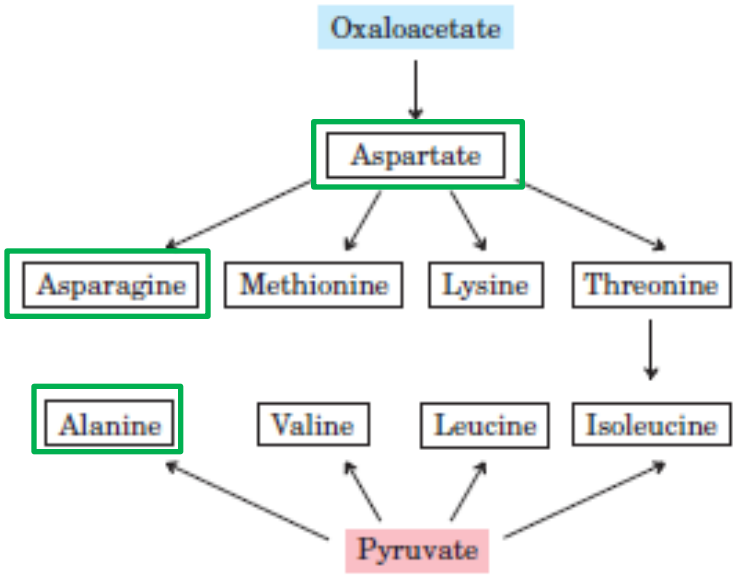
Asparagine is formed by amidation of aspartate (donor glutamine).



Aspartate and alanine are synthesized from oxaloacetate and pyruvate, respectively, by transamination with glutamate.

Nonessential and Essential Amino Acids for Humans

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

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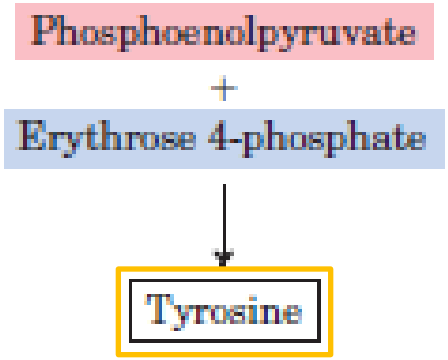

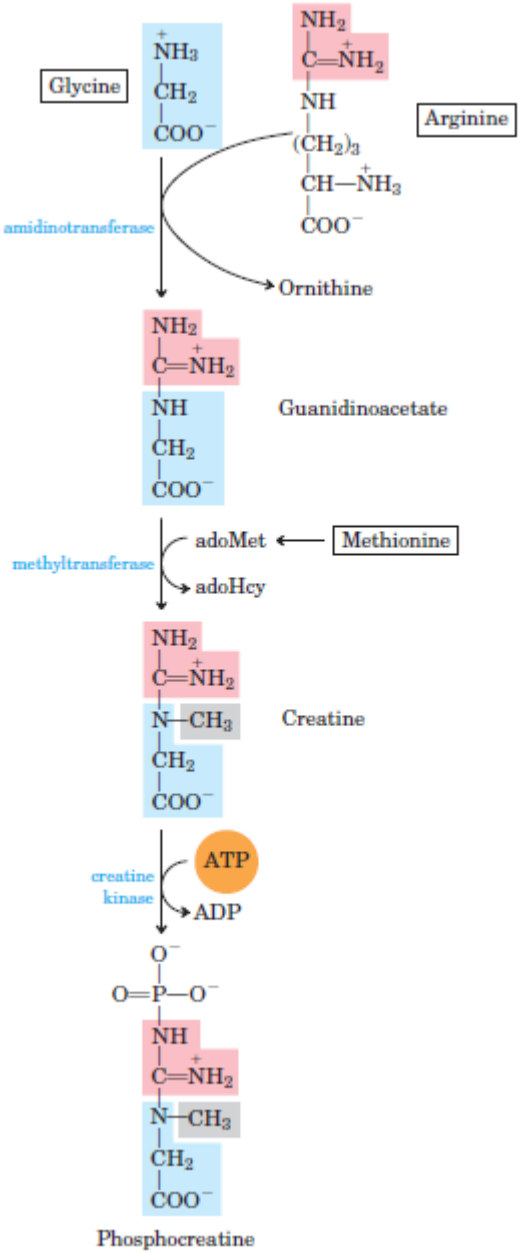

Biosynthesis of creatine and phosphocreatine

Creatine is made from three amino acids: glycine, arginine, and methionine.
This pathway shows the versatility of amino acids as precursors of other nitrogenous biomolecules.

Glutathione metabolism

(a) Biosynthesis of glutathione.
(b) Reduced form of glutathione.