

Metabolism: Amino Acids and the Urea Cycle



Amino acid metabolism

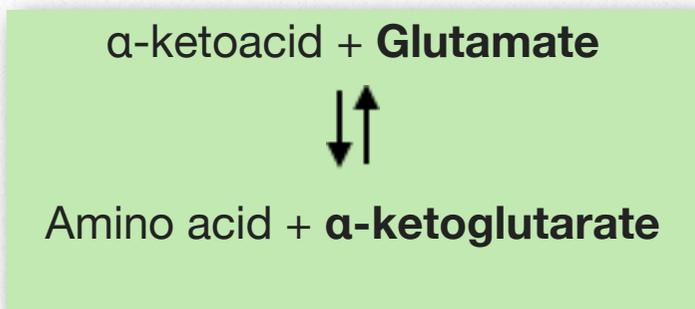
In contrast to some of the metabolic pathways described to this point, amino acid metabolism is not a single pathway. The 20 amino acids have some parts of their metabolism that overlap with each other, but others are very different from the rest. In discussing amino acid metabolism, we will group metabolic pathways according to common metabolic features they possess (where possible). First, we shall consider the anabolic pathways.

Transamination

Before beginning discussion of the pathways, it is worthwhile to discuss a reaction common to the metabolism of most of the amino acids and other nitrogen-containing compounds and that is transamination.

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In cells, nitrogen is a nutrient that moves from one molecule to another in a sort of hand-off process. A common transamination reaction is shown on the next page.



A specific reaction of this type is shown in [Figure 6.134](#).

Glutamate and glutamine play central roles in transamination, each containing one more amine group than α -ketoglutarate and glutamate, respectively. Transamination reactions, as noted earlier, occur by a ping-pong mechanism and involve swaps of amines and oxygens in Schiff base reactions. Two amino acids, glutamine and asparagine are the products of gaining an amine in their respective R-groups in reactions involving ammonium ion.

Synthesis varies

It is also important to recognize that organisms differ considerably in the amino acids that they can synthesize. Humans, for example, cannot make 9 of the 20 amino acids needed to make proteins, and the number of these that can be synthesized in needed amounts varies between adults and children.

Amino acids that cannot be made by an organism must be in the diet and are called essential amino acids. Non-essential amino acids are those an organism can make in sufficient quantities ([Figure 6.135](#)). Though amino acids do not have a common pathway

of metabolism, they are often organized in "families" of amino acids with overlapping metabolic reactions common to members of each group. To designate amino acid families in the text we will use a blue font for headings to distinguish them.

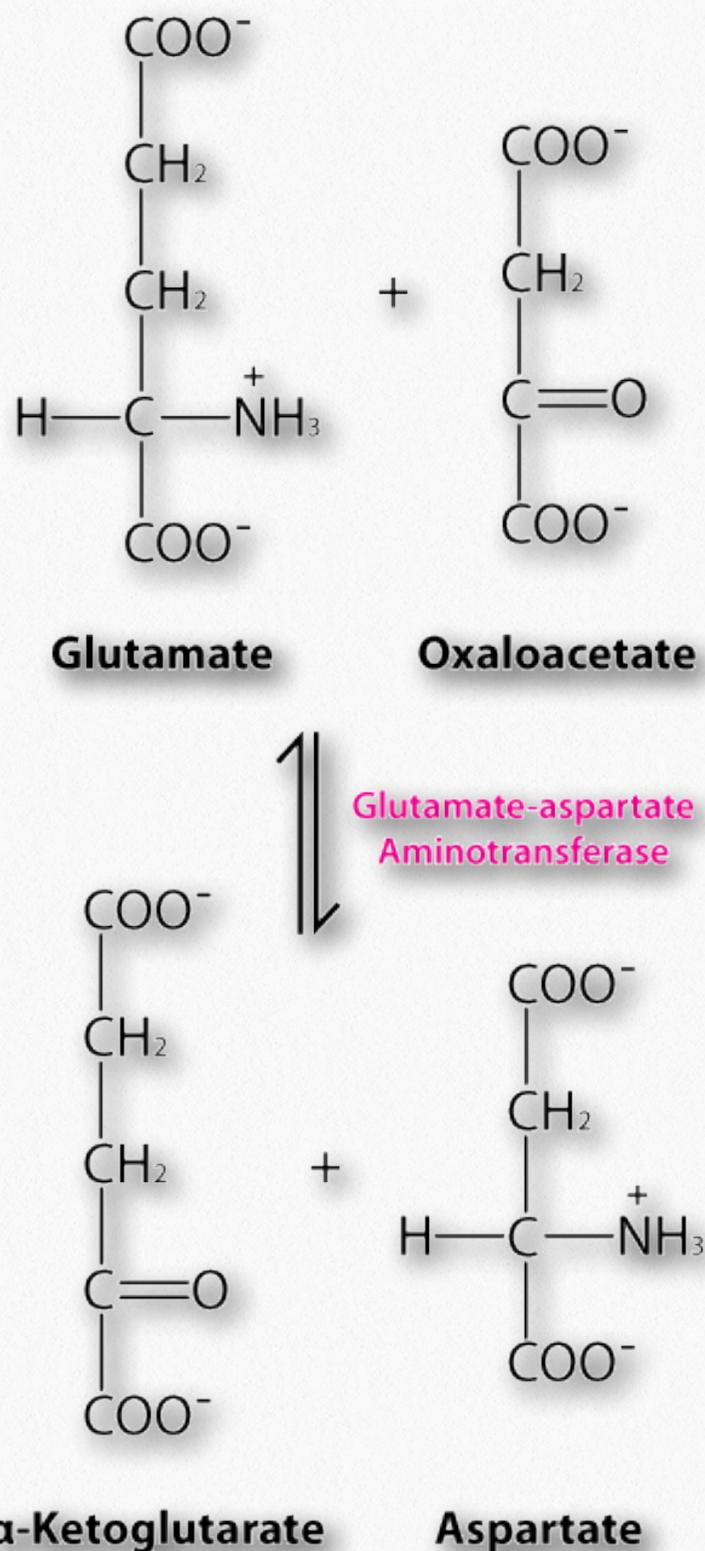
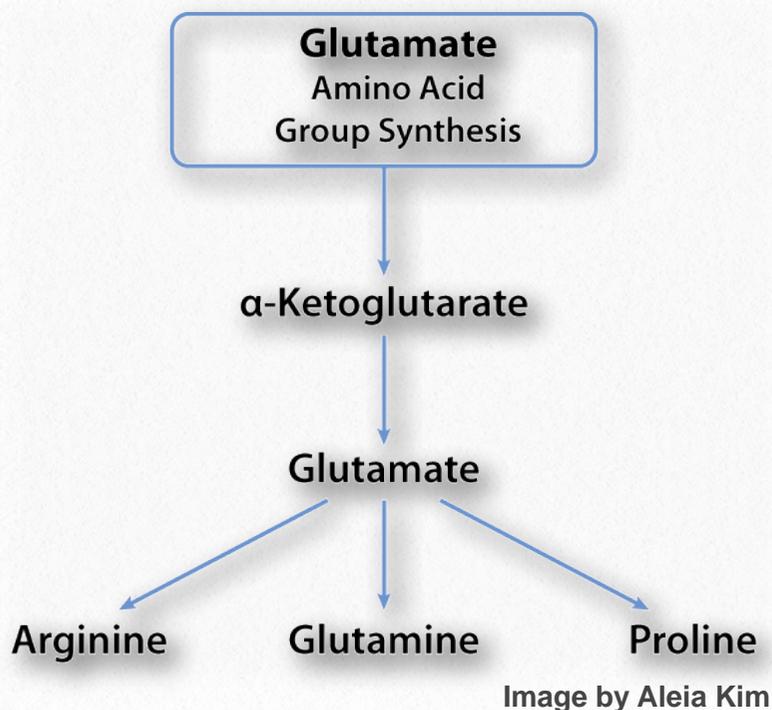


Figure 6.134 - Example of a transaminase (aminotransferase) reaction

Image by Aleia Kim

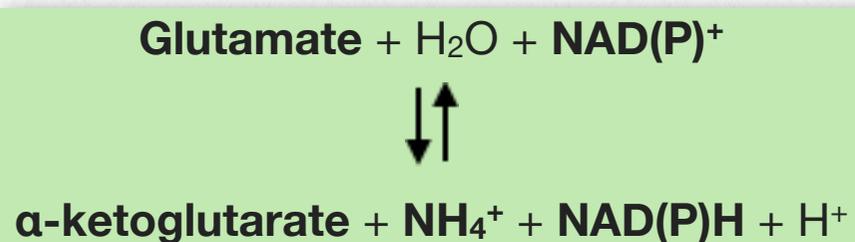
α -ketoglutarate family

This family of amino acids arises from α -ketoglutarate of the citric acid cycle. It includes the amino acids glutamic acid, glutamine, proline, and arginine. It is also called the glutamate family, since all the amino acids in it derive from glutamate.



Glutamate

α -ketoglutarate is readily converted to glutamate in transamination reactions, as noted above. It can also be produced by the enzyme glutamate dehydrogenase, which catalyzes the reaction below (in reverse) to make glutamate.



Essential

Histidine
Isoleucine
Leucine
Lysine
Methionine
Phenylalanine
Threonine
Tryptophan
Valine

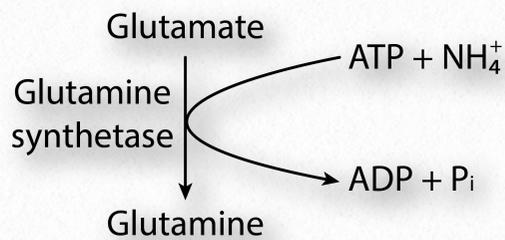
Non-Essential

Alanine
Arginine
Asparagine
Aspartic acid
Cysteine
Glutamic acid
Glutamine
Glycine
Proline
Selenocysteine
Serine
Tyrosine

Figure 6.135 - Essential and non-essential amino acids

Image by Pehr Jacobson

In the forward direction, the reaction is a source of ammonium ion, which is important both for the urea cycle and for glutamine metabolism. Because it is a byproduct of a citric acid cycle intermediate, glutamate can therefore trace its roots to any of the intermediates of the cycle. Citrate and isocitrate, for example, can be thought of as precursors of glutamate. In addition, glutamate can be made by transamination from α -ketoglutarate in numerous transamination reactions involving other amino acids.



Inhibitors of Glutamine Synthetase		
Amino acids	Nucleotides	Other
Glycine		
Alanine	AMP	Carbamoylphosphate
Serine	CTP	Glucosamine-6-phosphate
Histidine		
Tryptophan		

Figure 6.136 Action and inhibitors of glutamine synthetase

Image by Pehr Jacobson

catalyzed by glutamate synthetase commonly arises from nitrite reduction, amino acid breakdown, or photorespiration. Because it builds ammonia into an amino acid, glutamine synthetase helps reduce the concentration of toxic ammonia - an important consideration in brain tissue. Some inhibitors of glutamine synthetase are, in fact, the products of glutamine metabolism. They include histidine, tryptophan, carbamoyl phosphate, glucosamine-6-phosphate, CTP, and AMP. The gluta-

Glutamine

Synthesis of glutamine proceeds from glutamate *via* catalysis of the enzyme glutamine synthetase, one of the most important regulatory enzymes in all of amino acid metabolism (Figure 6.136).

Regulation of the enzyme is complex, with many allosteric effectors. It can also be controlled by covalent modification by adenylation of a tyrosine residue in the enzyme (Figure 6.137). In the figure, P_A and P_D are regulatory proteins facilitating conversion of the enzyme.

Ammonia used in the reaction

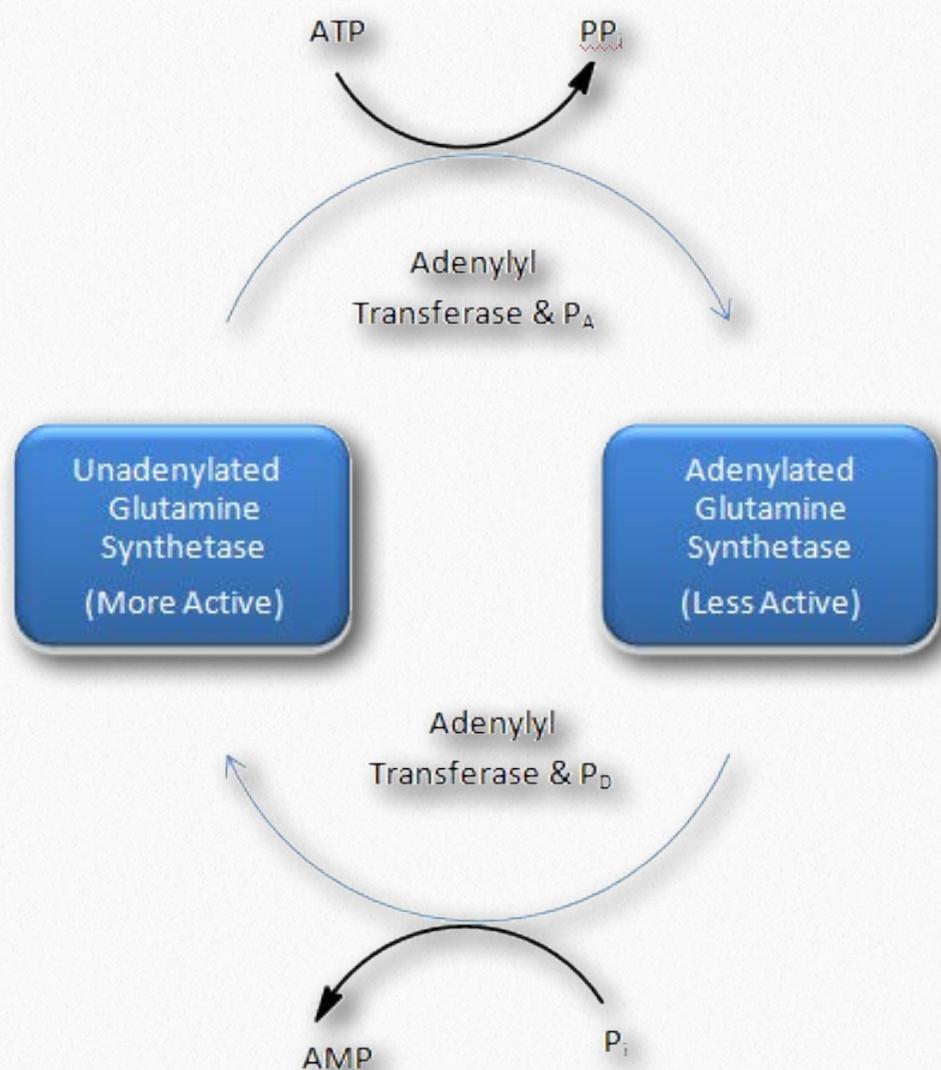


Figure 6.137 - Regulation of glutamine synthetase by adenylation

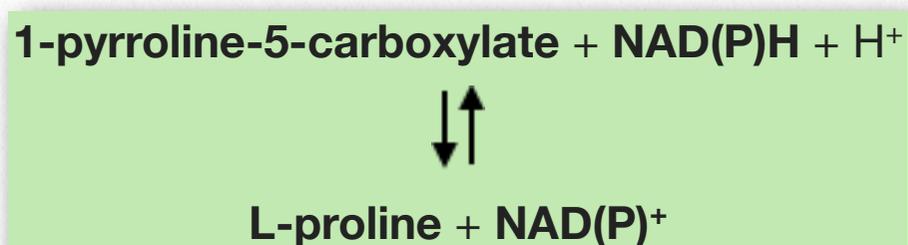
mate substrate site is a target for the inhibitors alanine, glycine, and serine. The ATP substrate site is a target for the inhibitors GDP, AMP, and ADP. Complete inhibition of the enzyme is observed when all of the substrate sites of the multi-subunit enzyme are bound by inhibitors. Lower levels of inhibitors results in partial or full activity, depending on the actual amounts.

Proline

Synthesis of proline starts with several reactions acting on glutamate. They are shown below in the green text box.

The L-glutamate-5-semialdehyde, so produced, is a branch point for synthesis of proline or ornithine. In the path to make proline, spontaneous cyclization results in formation of 1-pyrroline-5-carboxylic acid ([Figure 6.138](#)).

This, in turn, is reduced to form proline by pyrroline-5-carboxylate reductase.



1. ATP + L-glutamate



2. L-glutamate 5-phosphate + NADPH + H⁺



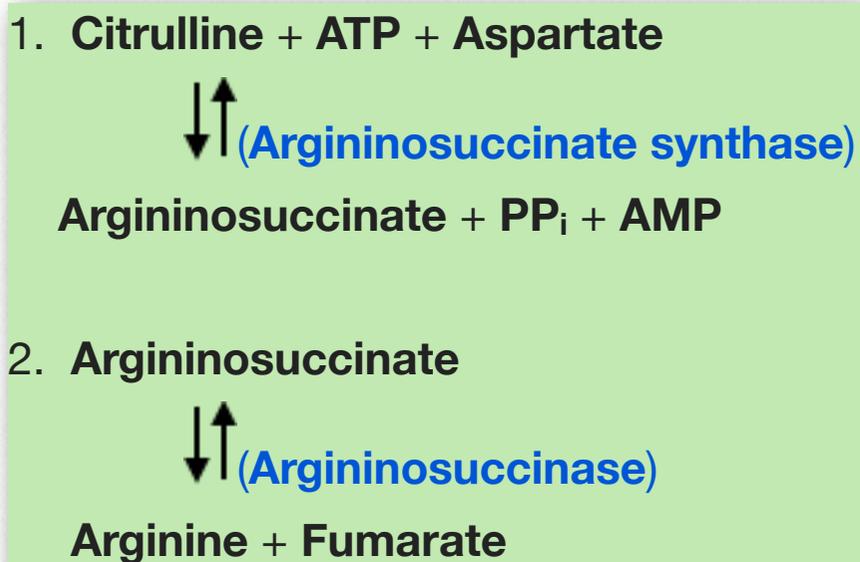
Arginine

Arginine is a molecule synthesized in the urea cycle and, thus, all urea cycle molecules can be considered as precursors. Starting with citrulline, synthesis of arginine can proceed as shown on the next page. The urea cycle can be seen [HERE](#).



Figure 6.138 - Spontaneous cyclization of L-glutamate-5-semialdehyde (left) to 1-pyrroline-5-carboxylic acid (right)

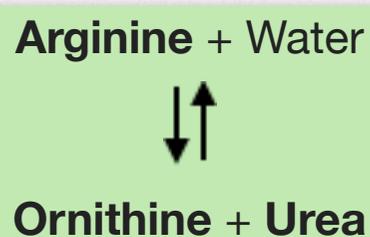
Image by Aleia Kim



An alternate biosynthetic pathway for making arginine from citrulline involves reversing the reaction catalyzed by nitric oxide synthase. It catalyzes an unusual five electron reduction reaction that proceeds in the following manner



Yet another way to synthesize arginine biologically is by reversal of the arginase reaction of the urea cycle



Arginine can also be made starting with glutamate. This 5 step pathway leading to ornithine is illustrated at the top of the next page (enzymes in blue). Ornithine, as noted above can readily be converted to arginine.

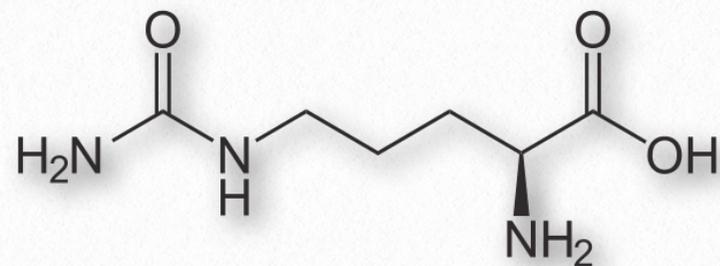


Figure 6.139 - **Citrulline**

The last means of making arginine is by reversing the methylation of asymmetric dimethylarginine (ADMA - Figure 6.140). ADMA is a metabolic byproduct of protein modification. It interferes with production of nitric oxide and may play a role in cardiovascular disease, diabetes mellitus, erectile dysfunction, and kidney disease.

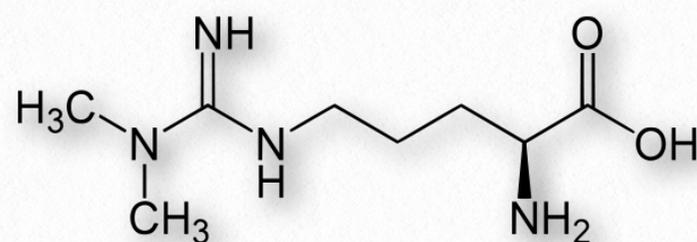


Figure 6.140 - **Asymmetric dimethyl arginine (ADMA)**

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1. **Glutamate + Acetyl-CoA**
 $\downarrow \uparrow$ (**Acetylglutamate synthetase**)
N-acetylglutamate + CoA-SH
2. **N-acetylglutamate + ATP**
 $\downarrow \uparrow$ (**N-acetylglutamate kinase**)
N-acetyl- γ -glutamyl phosphate
3. **N-acetyl- γ -glutamyl phosphate + NAD(P)H**
 $\downarrow \uparrow$ (**N-acetylglutamate dehydrogenase**)
N-acetylglutamate- γ -semialdehyde + NAD(P)⁺
4. **N-acetylglutamate- γ -semialdehyde + Glutamate**
 $\downarrow \uparrow$ (**Transaminase**)
N-acetylornithine + α -ketoglutarate
5. **N-acetylornithine + H₂O**
 $\downarrow \uparrow$ (**N-acetylornithinase**)
Ornithine + Acetate

Serine family

Serine is a non-essential amino acid synthesized from several sources. One starting point is the glycolysis intermediate, 3-phosphoglycerate, (3-PG) in a reaction

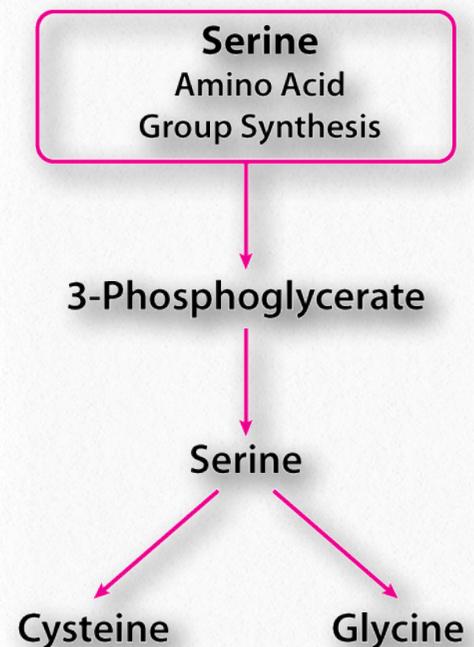
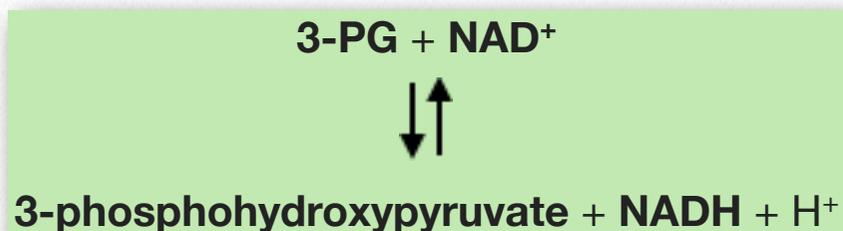


Image by Aleia Kim

catalyzed by 3-PG dehydrogenase.

Transamination by phosphoserine aminotransferase produces O-phosphoserine. The phosphate is then removed by phosphoserine phosphatase, to make serine.

These reactions are shown below. Phosphoserine phosphatase is missing in the genetic disease known as Williams-Beuren syndrome.

1. **3-phosphohydroxypyruvate + Glutamate**
 $\downarrow \uparrow$
O-phosphoserine + α -ketoglutarate
2. **O-phosphoserine + H₂O**
 $\downarrow \uparrow$
Serine + P_i

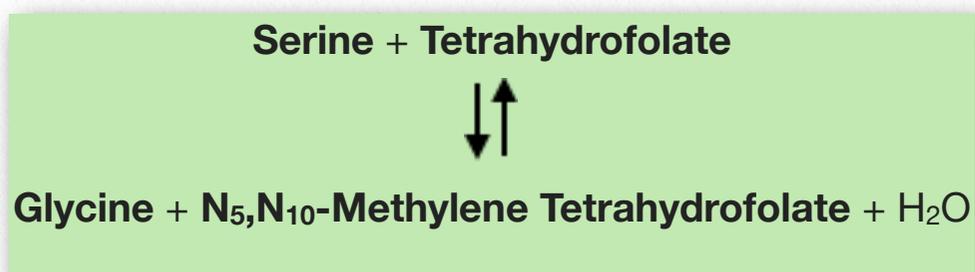
Serine can also be derived from glycine and *vice versa*. Their metabolic paths are intertwined as will be seen below. Serine is important for metabolism of purines and pyrimidines, and is the precursor for glycine, cysteine, and tryptophan in bacteria, as well as for sphingolipids and folate. Serine in the active site of serine proteases is essential for catalysis. A serine in the active site of acetylcholinesterases is the target of nerve gases and insecticides.

Covalent modification target

Serine in proteins can be the target of glycosylation or phosphorylation. D-serine is the second D-amino acid known to function in humans. It serves as a neuromodulator for NMDA receptors, by serving as a co-agonist, together with glutamate. D-serine is being studied as a schizophrenia treatment in rodents and as a possible biomarker for Alzheimers.

Glycine

As noted, glycine's metabolism is intertwined with that of serine. This is apparent in the reaction catalyzed by serine hydroxymethyltransferase.



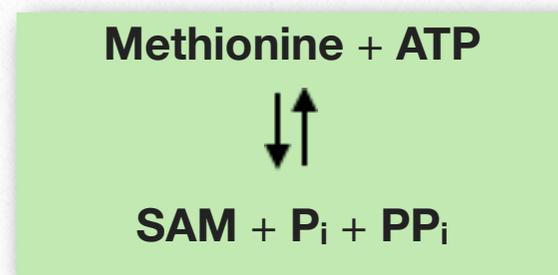
Notably, the previous reaction is also needed for recycling of folate molecules, which are important for single carbon reactions in nucleotide synthesis.

Vertebrates can also synthesize glycine in their livers using the enzyme glycine synthase.

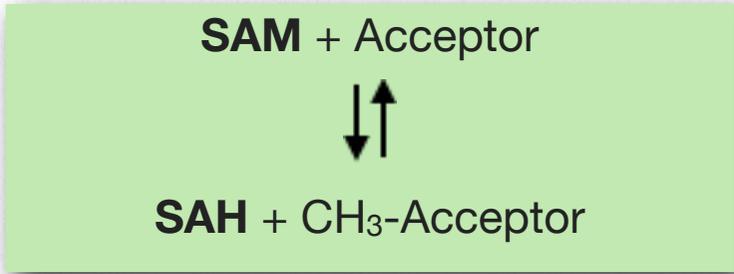
Glycine is a very abundant component of collagen. It is used in the synthesis of purine nucleotides and porphyrins. It is an inhibitory neurotransmitter and is a co-agonist of NMDA receptors with glutamate. Glycine was detected in material from Comet Wild 2.

Cysteine

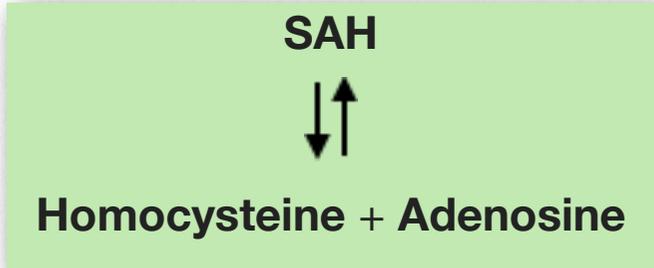
Cysteine can be synthesized from several sources. One source is the metabolism of the other sulfur-containing amino acid, methionine. This begins with formation of S-Adenosyl-Methionine (SAM), catalyzed by methionine adenosyltransferase.



SAM is a methyl donor for methyl transfer reactions and that is the next step in the pathway - donation of a methyl group (catalyzed by transmethylase)

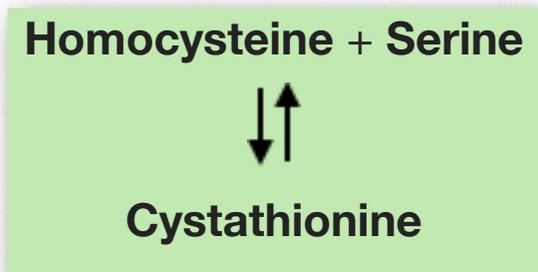


SAH (S-Adenosylhomocysteine) is cleaved by S-adenosylhomocysteine hydrolase,

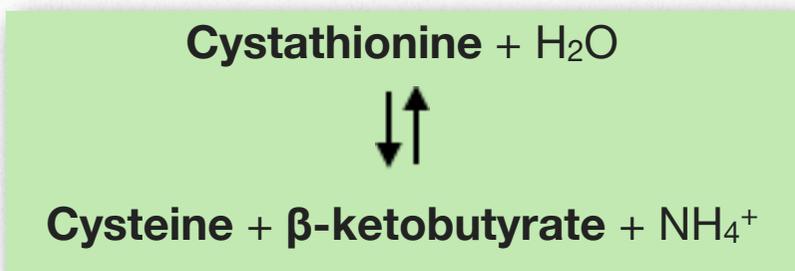


Homocysteine can be recycled back to methionine by action of methionine synthase

On the path to making cysteine, homocysteine reacts as follows (catalyzed by cystathionine β -synthase).

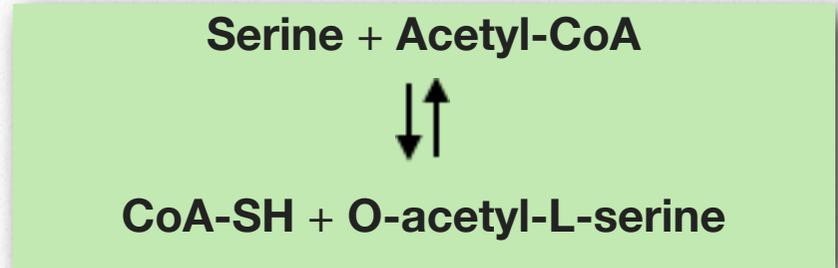


Last, cystathionase catalyzes release of cysteine

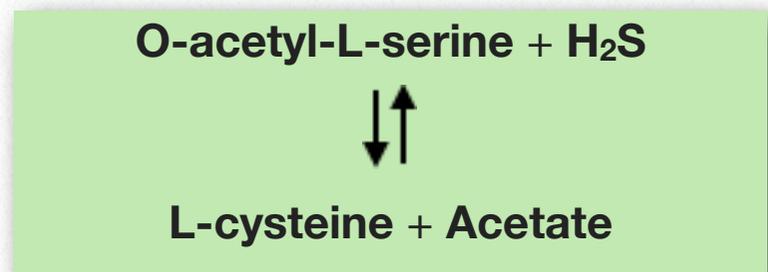


β -ketobutyrate can be metabolized to propionyl-CoA and then to succinyl-CoA to be used ultimately in the citric acid cycle.

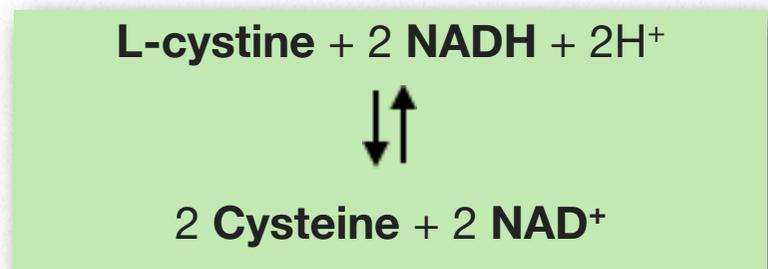
Another route to making cysteine is a two-step process that begins with serine, catalyzed first by serine-O-acetyltransferase



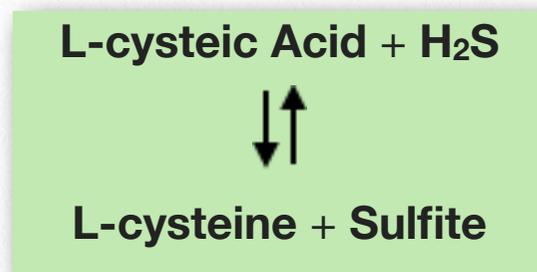
and then by cysteine synthase

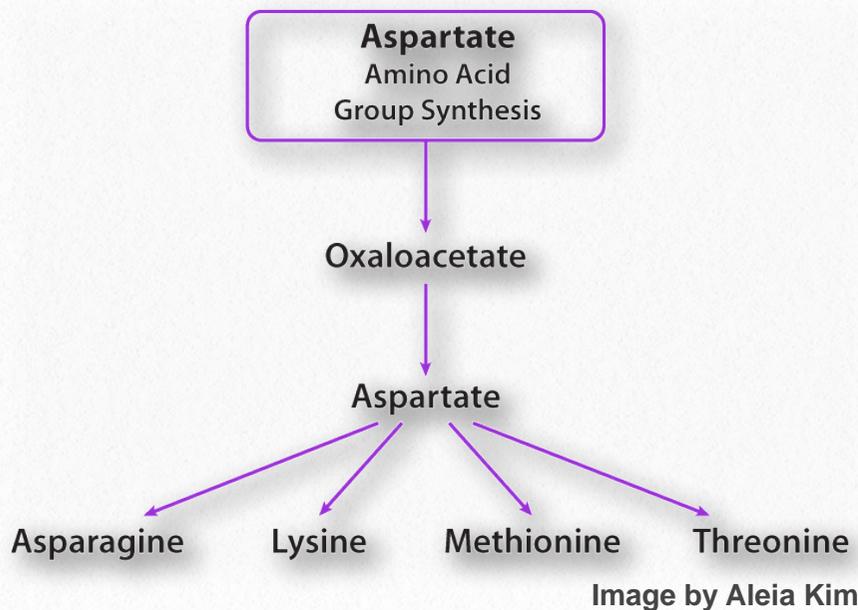


Cysteine can be also released from cystine by cystine reductase



Finally, cysteine can be made from cysteic acid by action of cysteine lyase

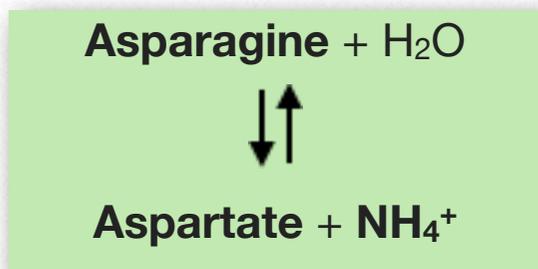




Aspartate family

Metabolism of aspartic acid is similar to that of glutamate. Aspartic acid can arise from transamination of a citric acid cycle intermediate (oxaloacetate).

Aspartate can also be generated from asparagine by the enzyme asparaginase.



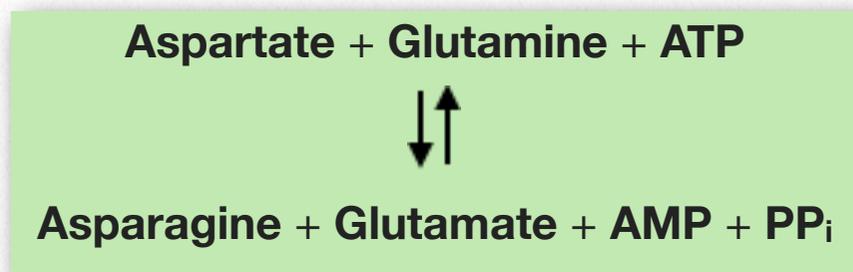
Further, aspartate can be produced by reversal of a reaction in the urea cycle (see [HERE](#))

Aspartate is also a precursor to four amino acids that are essential in humans. They are methionine, isoleucine, threonine, and lysine. Because oxaloacetate can be produced from aspartate, aspartate is an im-

portant intermediate for gluconeogenesis when proteins are the energy source.

Asparagine

Asparagine, too, is an amino acid produced in a simple transamination reaction. In this case, the precursor is aspartate and the amine donor is glutamine (catalyzed by asparagine synthetase)



Methionine

Metabolism of methionine overlaps with metabolism of the other sulfur-containing amino acid, cysteine. Methionine is not made in humans (essential) so the pathway shown in [Figure 6.141](#) is from bacteria.

The process begins with phosphorylation of aspartate. Numbers for each catalytic step in the figure are for the enzymes that follow:

- 1 - Aspartokinase
- 2 - Aspartate-semialdehyde dehydrogenase
- 3 - Homoserine dehydrogenase
- 4 - Homoserine O-transsuccinylase
- 5 - Cystathionine- γ -synthase
- 6 - Cystathionine- β -lyase
- 7 - Methionine synthase

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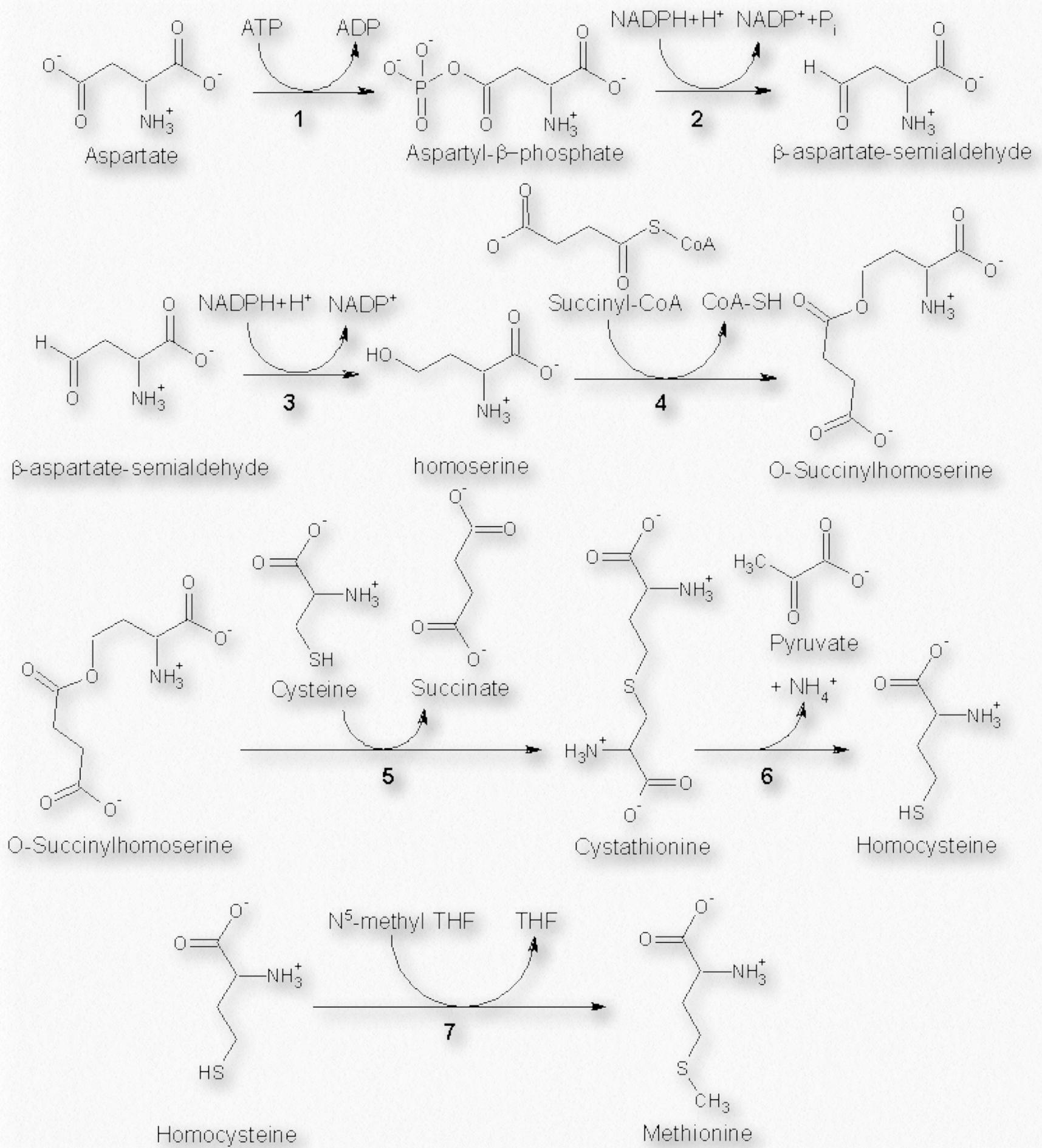
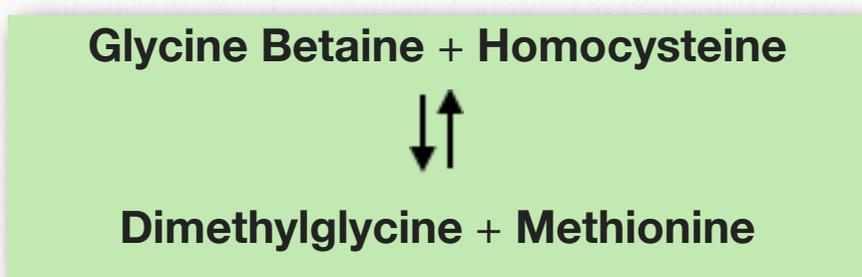


Figure 6.141 - Synthesis of methionine from aspartic acid

Wikipedia

Though humans cannot make methionine by the pathway shown in the figure, they can recycle methionine from homocysteine (a product of S-adenosylmethionine metabolism). This reaction requires the enzyme methionine synthase and Vitamin B₁₂ as a co-factor.

An alternative pathway of converting homocysteine to methionine involves a prominent liver enzyme, betaine-homocysteine methyltransferase. This enzyme catalyzes the reaction below.



In this reaction, a methyl group is transferred to homocysteine from glycine betaine to make the methionine. Glycine betaine is a trimethylated amine of glycine found in plants. It is a byproduct of choline metabolism.

Bacteria, mitochondria, and chloroplasts use a modified form of methionine, N-formylmethionine (Figure 6.142), as the first amino acid incorporated into their proteins. Formylation of methionine occurs only after methionine has been attached to its tRNA for translation. Addition of the formyl group is catalyzed by the enzyme methionyl-tRNA formyltransferase

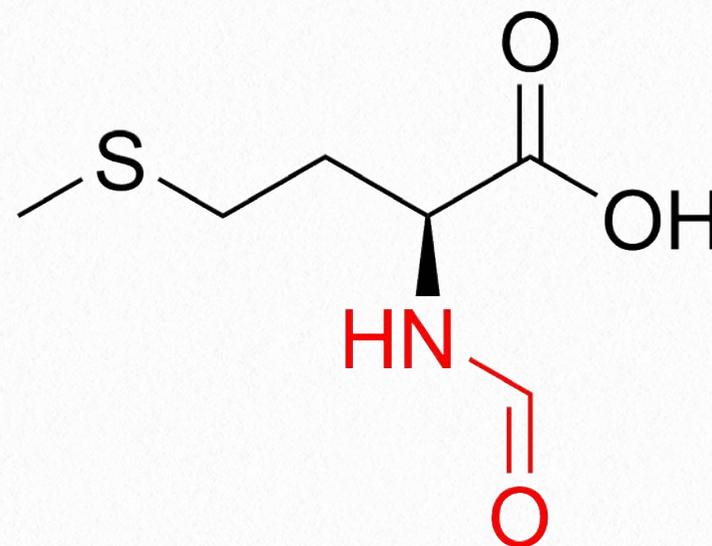


Figure 6.142 - **N-formyl-methionine**

Threonine

Though threonine is chemically similar to serine, the metabolic pathway leading to threonine does not overlap with that of serine. As seen in the figure, aspartate is a starting point for synthesis. Two phosphorylations/dephosphorylations and two reductions with electrons from NADPH result in production of threonine.

Enzymes in Figure 6.143 are as follows:

- 1 Aspartokinase
- 2 β -aspartate semialdehyde dehydrogenase
- 3 Homoserine dehydrogenase
- 4 Homoserine kinase
- 5 Threonine synthase

Breakdown of threonine produces acetyl-CoA and glycine. It can also produce α -ketobutyrate, which can be converted to succinyl-CoA for oxidation in the citric acid cycle.

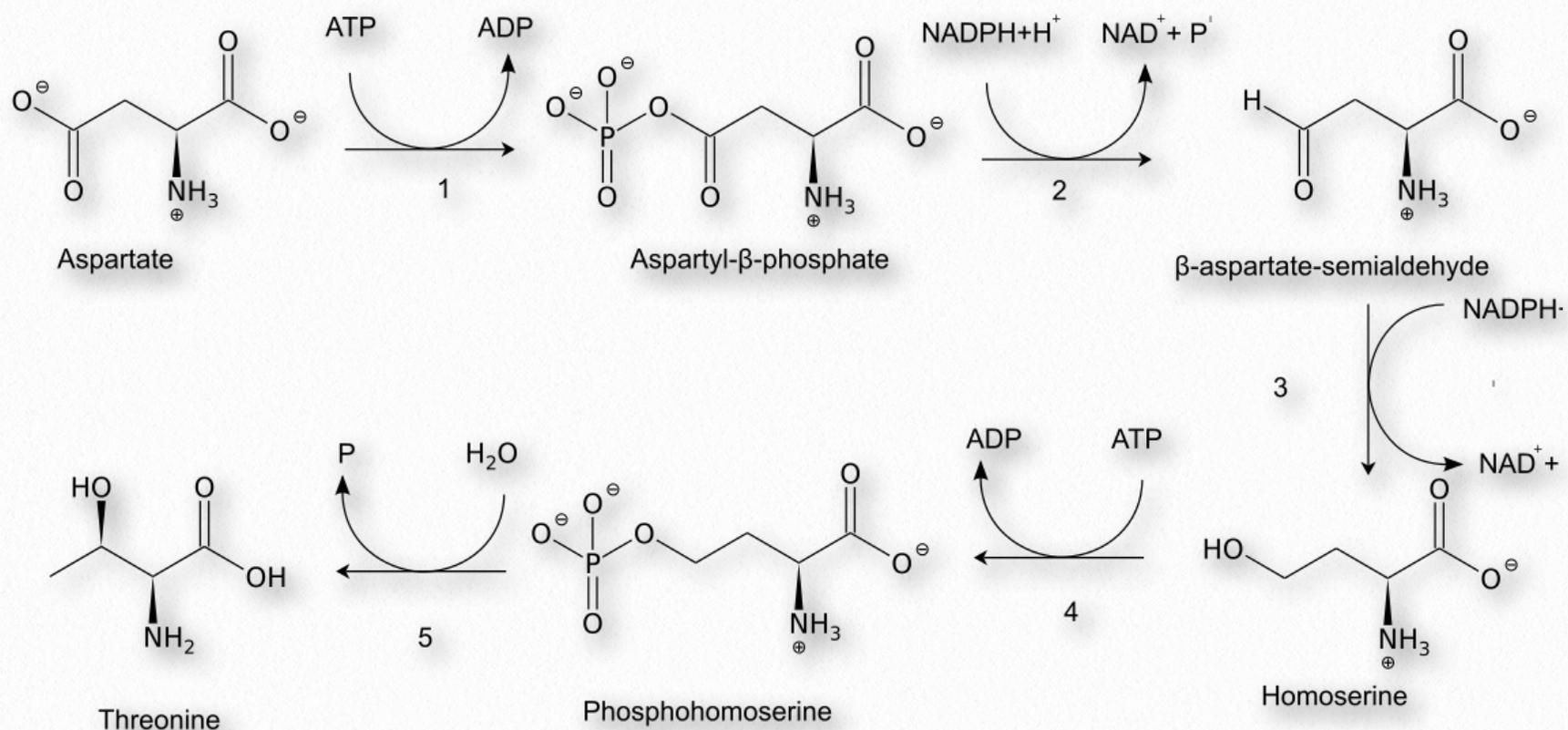


Figure 6.143 - Synthesis of threonine from aspartate

Wikipedia

Lysine

To get from aspartate to lysine, nine reactions and two non-enzymatic steps are involved, as seen in [Figure 6.144](#). Enzymes involved in lysine biosynthesis include (numbers correspond to numbered reactions in [Figure 6.144](#)):

- 1 - Aspartokinase
- 2 - Aspartate-semialdehyde dehydrogenase
- 3 - 4-hydroxy-tetrahydrodipicolinate synthase
- 4 - 4-hydroxy-tetrahydrodipicolinate reductase
- 5 - 2,3,4,5-tetrahydropyridine-2,6-dicarboxylate N-succinyltransferase
- 6 - Succinyl-diaminopimelate transaminase

- 7 - Succinyl-diaminopimelate desuccinylase
- 8 - Diaminopimelate epimerase
- 9 - Diaminopimelate decarboxylase

Low in cereal grains

Lysine is the essential amino acid found in the smallest quantity in cereal grains, but is found abundantly in legumes. Besides its synthesis and breakdown, lysine can be methylated, acetylated, hydroxylated, ubiquitinated, sumoylated, neddylated, biotinylated, pupylated, and carboxylated within proteins containing it. Hydroxylation of lysine is important for strengthening collagen and acetylation/methylation of lysine in histone proteins play roles in control of gene expression and epigenetics. Besides being used to make proteins, lysine is impor-

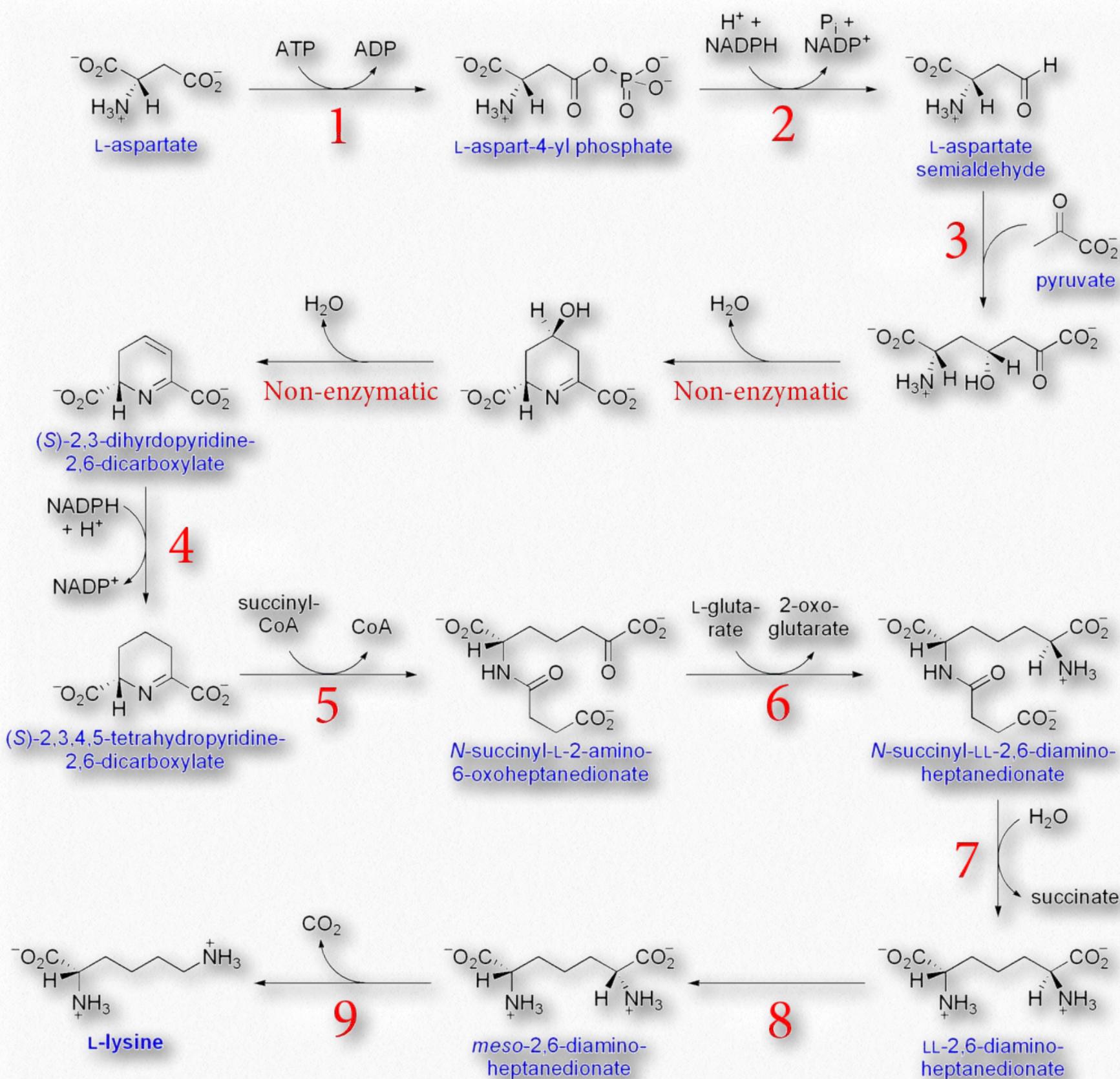


Figure 6.144 - Synthesis of Lysine from Aspartic Acid

tant for calcium absorption, recovery from injuries, and for production of hormones.

Oral lysine has been used as a treatment for herpes infections (cold sores) but its efficacy

is not established and it is not clear by what mechanism it would reduce the duration of the infection or reduce the number of outbreaks of viral infection..

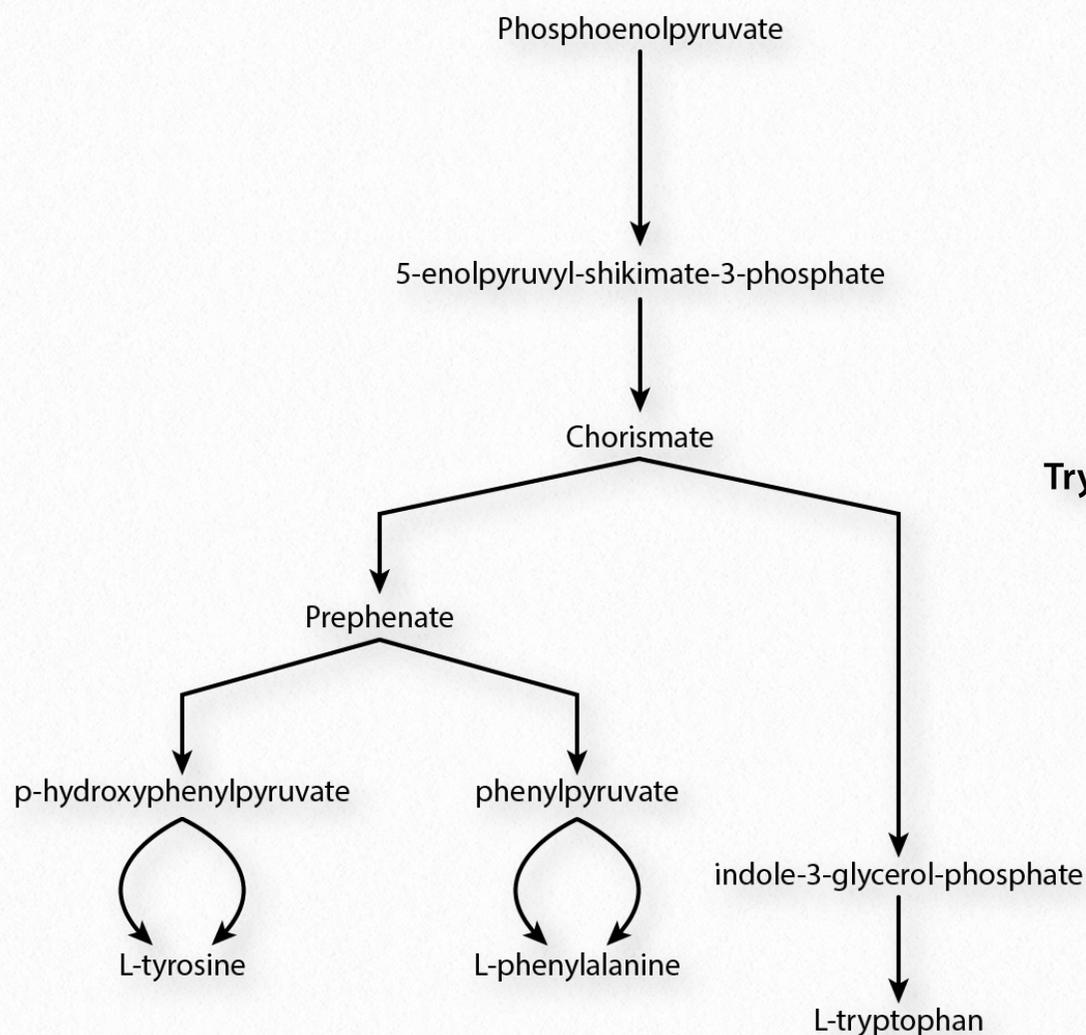


Figure 6.145 - Schematic pathway from PEP to aromatic amino acids

Image by Pehr Jacobson

Aromatic amino acids

The aromatic amino acids, tryptophan, phenylalanine, and tyrosine can all be made starting with two simple molecules - PEP and erythrose-4-phosphate (Figure 6.145). All three aromatic amino acids are also important sources of hormones, neurotransmitters, and even the skin pigment melanin.

Tryptophan synthesis

The proteogenic amino acid with the largest R-group, tryptophan is an essential

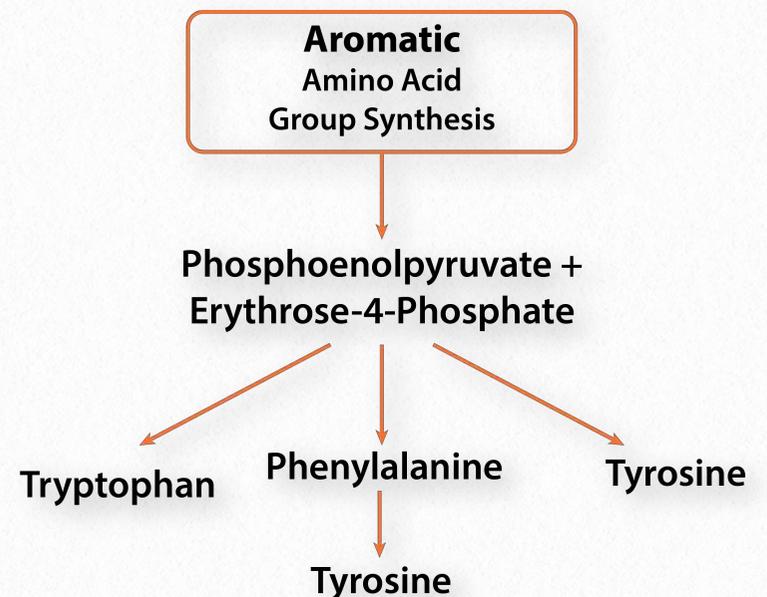


Image by Aleia Kim

amino acid distinguished structurally by its indole group. The amino acid is made in bacteria and plants from shikimic acid or anthranilate and serine is used in its synthesis.

Erythrose-4-phosphate and phosphoenolpyruvate (PEP) also serve as building blocks of tryptophan. The pathway of its synthesis is shown in Figures 6.146 to 6.148.

Erythrose-4-phosphate and phosphoenolpyruvate (PEP) are joined and then, after one hydrolysis, one dehydration, one oxidation and one reduction, the product is shikimic acid (Figure 6.147).

Shikimic acid is converted to chorismic acid in three steps, as shown in Figure 6.147. Finally, synthesis of tryptophan from chorismic acid is shown in Figure 6.148.

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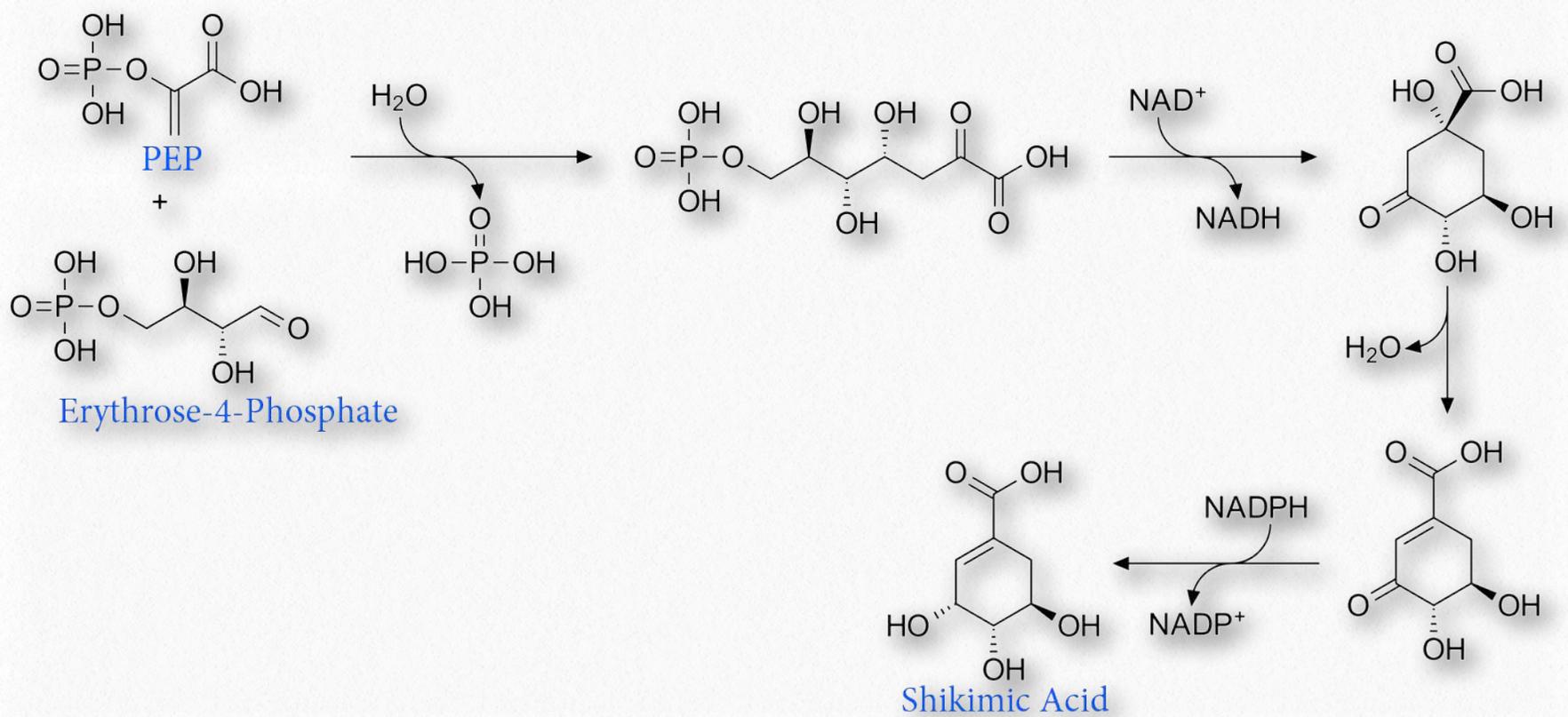


Figure 6.146 - Synthesis of shikimic acid from PEP and erythrose-4-phosphate

Wikipedia

Regulation

Regulation of tryptophan synthesis in bacteria

occurs partly via a process called attenuation that operates through the *trp* operon. In this mechanism, low levels of tryptophan slow ribosomal movement (and translation) through the operon. This is particularly important because bacteria can have transcription and translation occurring simultaneously. Slowing translation due to low tryptophan levels allows a tran-

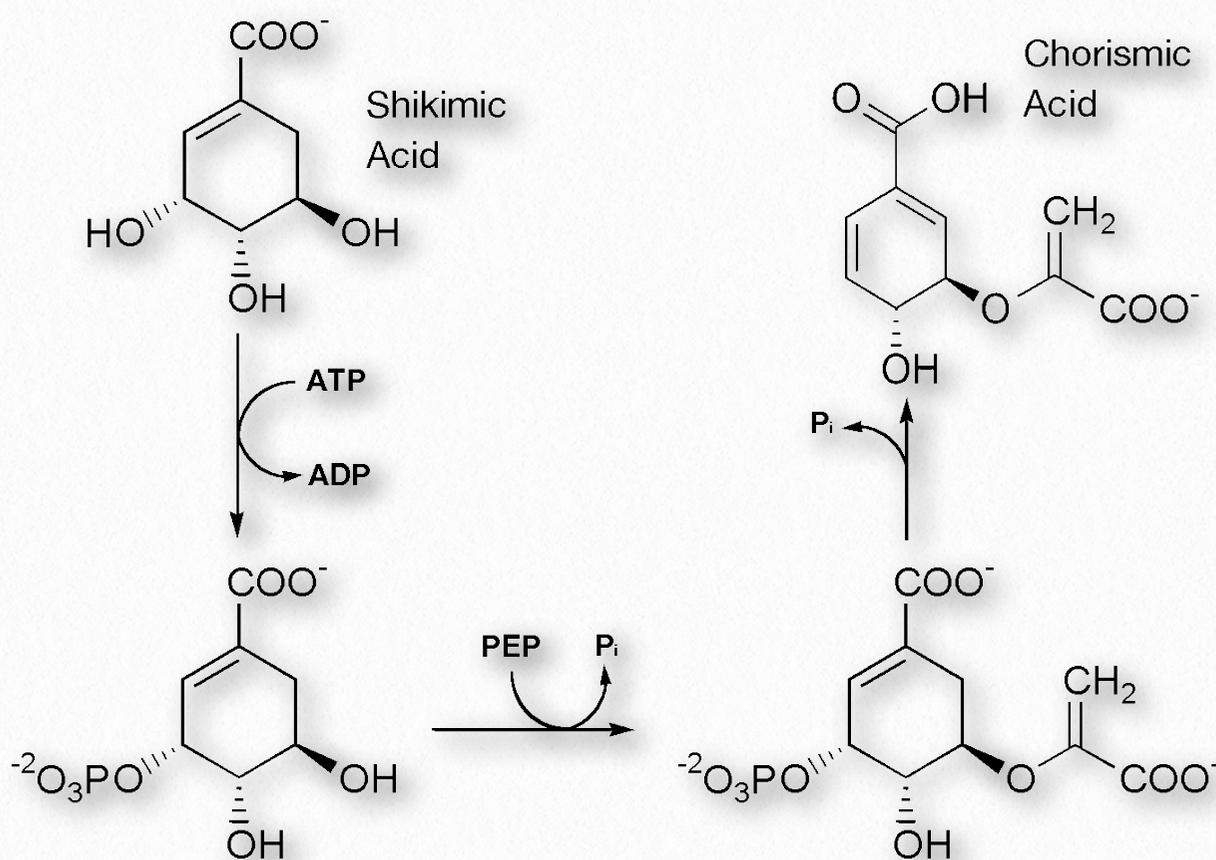


Figure 6.147 - The route to tryptophan - making chorismic acid from shikimic acid

Wikipedia

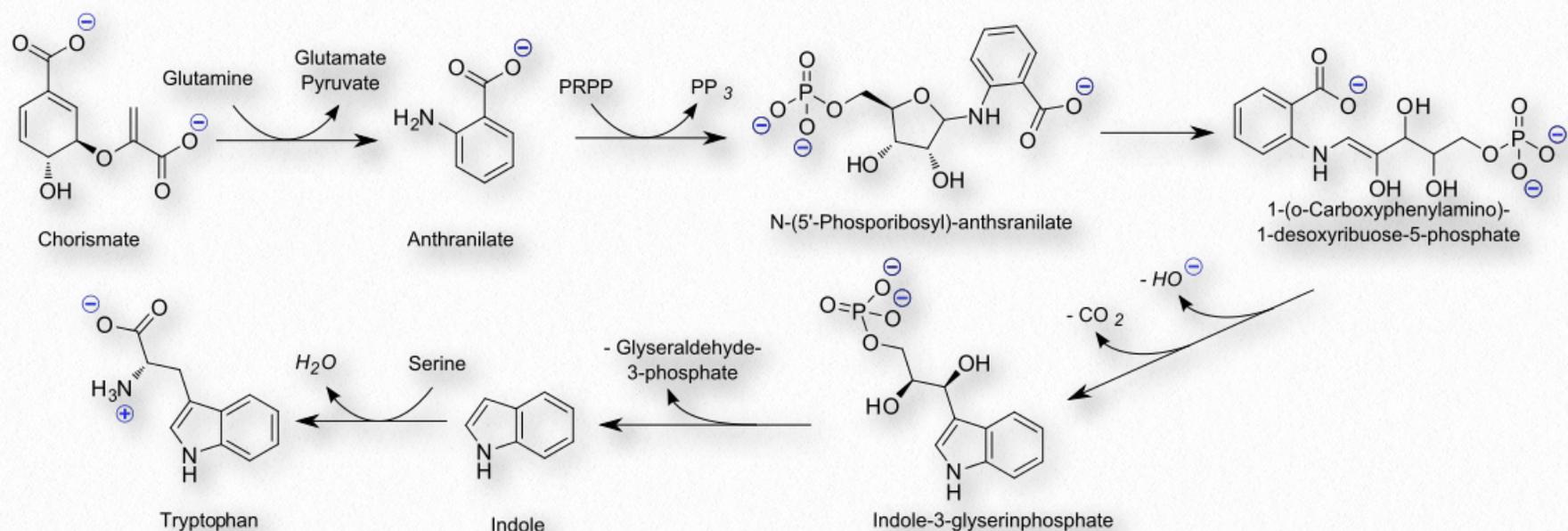


Figure 6.148 - Synthesis of tryptophan from chorismic acid

scription termination mechanism to be inhibited. Since translation only slows when tryptophan is in short supply, premature termination of transcription occurs when tryptophan is abundant (see also [HERE](#)).

Besides its importance for making proteins, tryptophan is an important precursor of serotonin (neurotransmitter), melatonin (hormone), niacin (vitamin), and auxin (plant hormone). The two pathways leading from tryptophan to three of these molecules is shown in [Figure 6.149](#).

Melatonin

Melatonin is a compound made from tryptophan that is found in a wide spectrum of biological systems, including plants, animals, fungi, and bacteria. In animals, it acts as a hormone for circadian rhythm synchronization, signaling the onset of darkness each day. It has effects on the timing of sleep, seasonal

effects, and can affect blood pressure, among other physiological phenomena. It can cross cell membranes, as well as the blood-brain barrier. Melatonin is a potent anti-oxidant and provides protective functions for nucleic acids. It is used sometimes to help in treatment of sleep disorders. Some reports have indicated that children with autism have abnormal melatonin pathways with low levels of the hormone.

Blue light

Melatonin production is affected by blue light and may be linked to sleep abnormalities for people using computer monitors after dark. To protect against this, some computer programs are available that reduce the screen's blue light output in the evenings. Special eyeglasses that block blue light are also available. Though melatonin is linked to sleep in some animals (including humans), noctur-

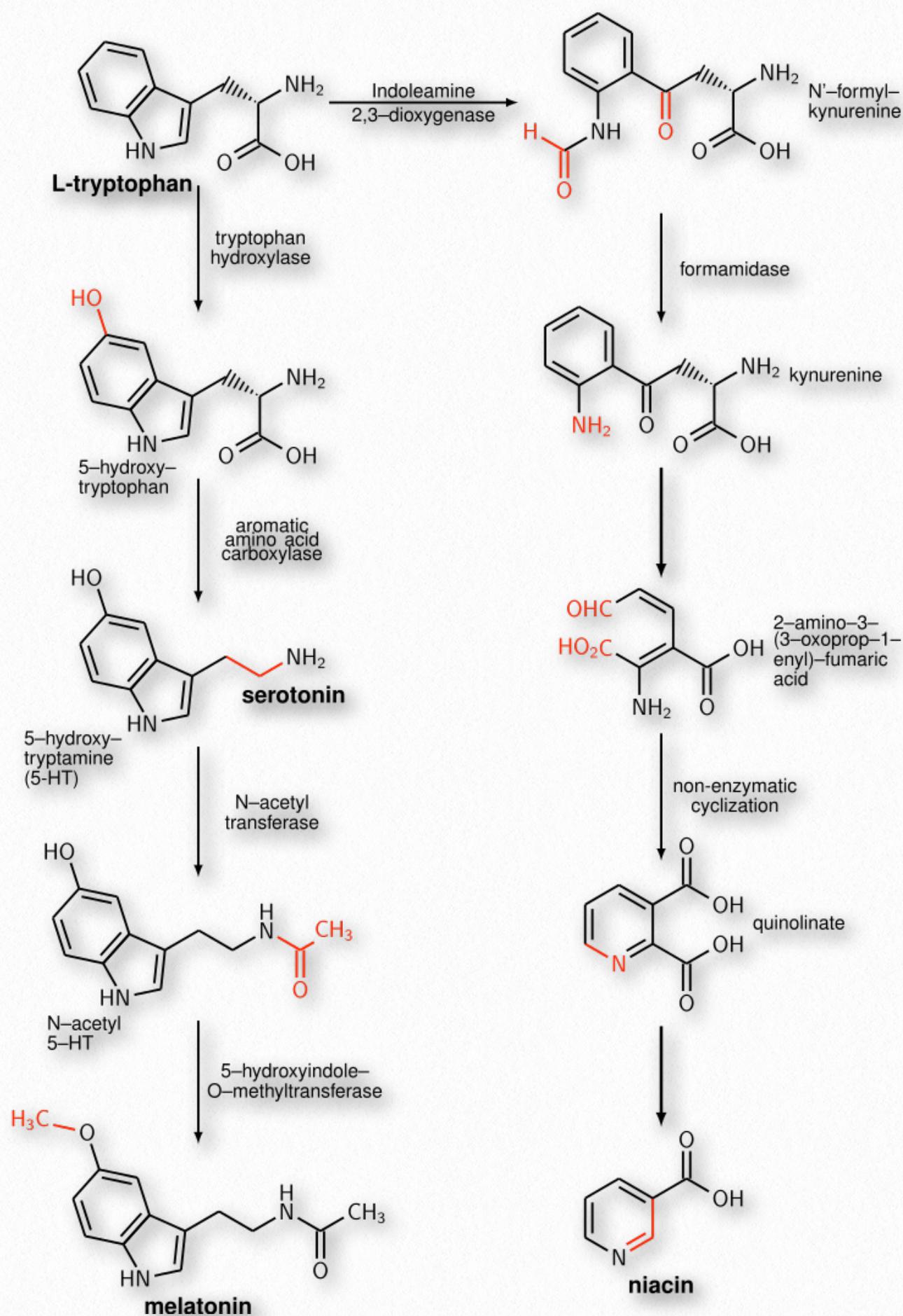


Figure 6.149 - Tryptophan is a precursor of serotonin, melatonin, and niacin

nal animals are activated by increasing melatonin levels. Varying day/night lengths during the year alter melatonin production and provide biological signals of the seasons. These are especially important in the seasonal coloring and breeding habits of some animals. Melatonin is present in cherries, bananas, grapes, rice, cereals, olive oil, wine, and beer.

Serotonin

Serotonin, or 5-hydroxytryptamine, is a monoamine neurotransmitter derived from tryptophan. Blood platelets store serotonin and release it when they bind to a clot, causing vasoconstriction. Serotonin plays a role in cognitive functions and enhances memory and learning. Serotonin is widely thought to be a contributor to feelings of happiness and well-

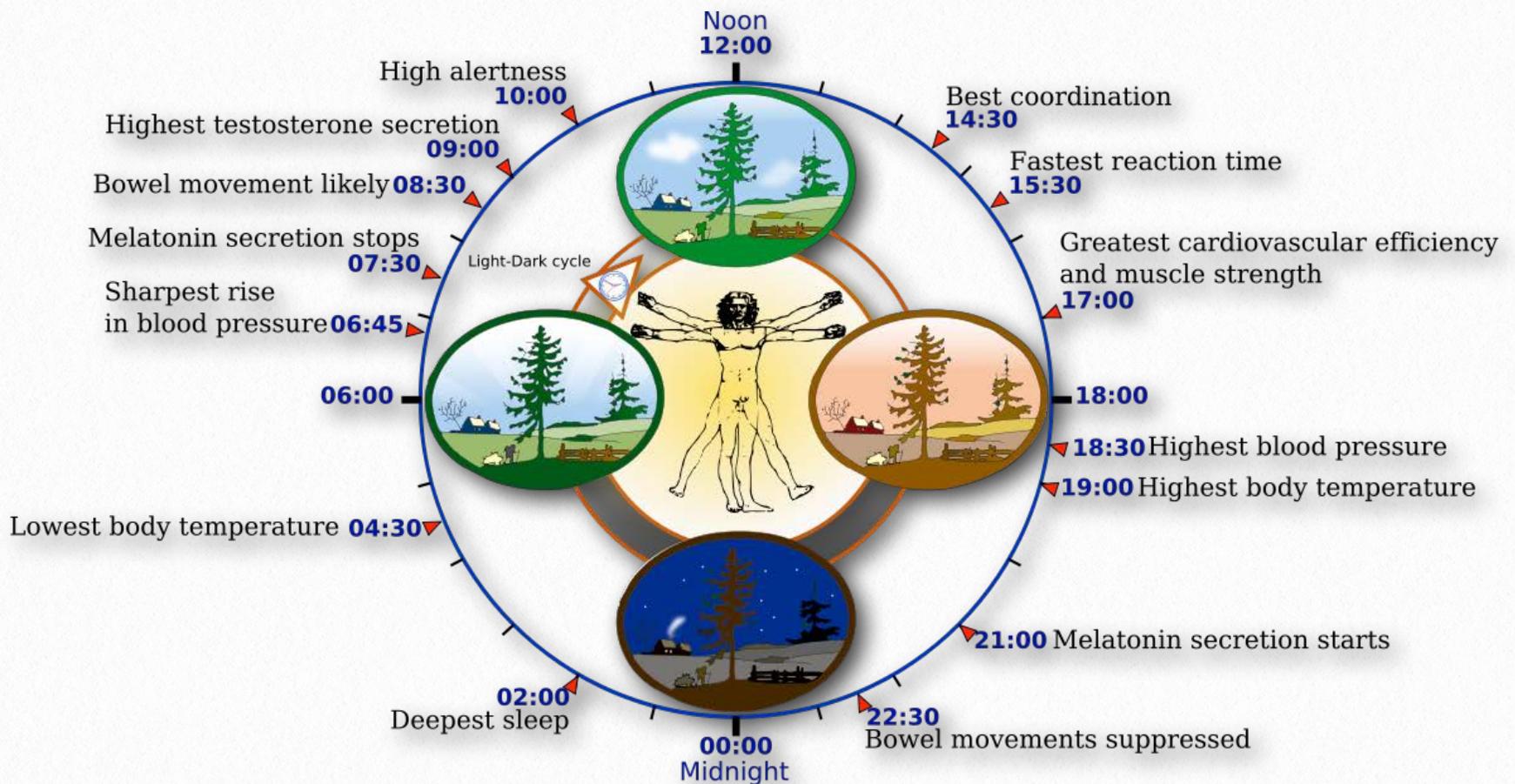


Figure 6.150 - Melatonin and human circadian rhythms

Wikipedia

being. Some common anti-depressant drugs, including Prozac, Paxil and Zoloft, act to modulate action of serotonin at synapses.

Niacin

Niacin is also known as Vitamin B₃ and nicotinic acid. Niacin can be made from tryptophan and people who have the inability to absorb tryptophan in the digestive system exhibit symptoms similar to niacin deficiency.

Extreme deficiency of niacin in the diet leads to the disease known as pellagra, while insufficient amounts of niacin in the diet are linked with nausea, anemia, headaches, and tiredness. A diet that is primarily composed of

grains like corn can lead to niacin deficiency, because the niacin in these sources is not readily bioavailable. Treatment of the grain with alkali, as in the traditional Mexican practice of soaking corn in lime, can make the niacin more easily absorbed from food.

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Niacin is related to pyridine and the amide form of it is nicotinamide, an important component of NAD⁺/NADH and NADP⁺/NADPH. The last pairs of molecules are essential as electron acceptors/carriers for most cellular oxidation-reduction reactions.

Auxins

Auxins are plant growth hormones derived from tryptophan. The most important of these

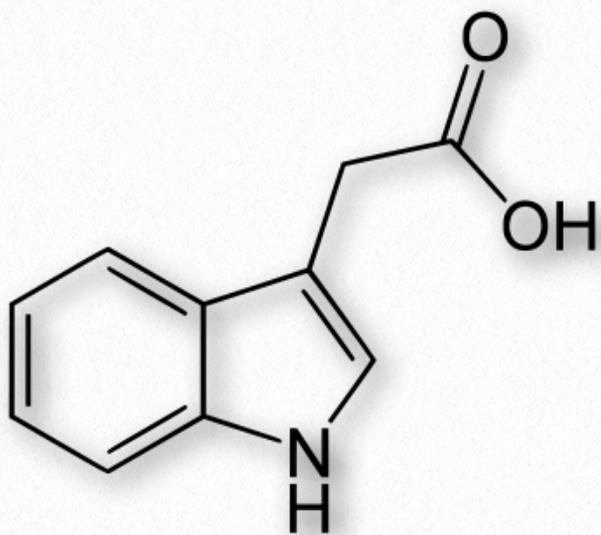


Figure 6.151 - Auxin - indole-3-acetic acid

is indole-3-acetic acid (Figure 6.151). Auxins are involved in almost every aspect of plant growth and development. They activate proteins, such as expansins and various en-



Figure 6.152 - Wild type *Arabidopsis* (left) and a mutant unable to transmit auxin signals (right)

Wikipedia

zymes that modify the structure of cell wall components, to loosen the cell walls of a plant and stimulate elongation of cells. In the presence of cytokinins, auxins stimulate cell division. Auxins are also involved in the maintenance of meristems and in cell patterning and organogenesis. Auxins are crucial for establishing root primordia as well as for elongation of root hairs. Auxins play important roles in organizing the xylem and phloem of plants, and it has long been known that plant callus tissue can be made to differentiate into shoots or roots, depending on the relative concentrations of auxins and cytokinins supplied in the medium.



Figure 6.153 Crown gall on a rose

Wikipedia

Agrobacterium tumefaciens, a bacterium which infects a wide variety of plants, inserts its own DNA, including genes necessary for the synthesis of plant hormones, into its host's cells. The subsequent overproduction of auxins stimulates the growth of tumors (called crown galls) on the plant (Figure 6.153).

Phenylalanine

Phenylalanine is an essential, hydrophobic amino acid in humans that is a precursor of tyrosine and since tyrosine is a precursor of several important catecholamines, phenylalanine is, thus, a precursor of them as well.

PKU

Phenylalanine is linked to the genetic disease phenylketonuria (PKU) which arises from an inability to metabolize the amino acid in people lacking (or deficient in) the enzyme phenylalanine hydroxylase. If left untreated, the disease can cause brain damage and even death, but if detected early, it can be easily managed by carefully monitoring dietary intake of the amino acid. Because of this, newborns are routinely tested for PKU. Phenylalanine is a component of the artificial sweetener known as aspartame (NutraSweet - [Figure 6.154](#)) and is consequently dangerous for people suffering from this disorder.

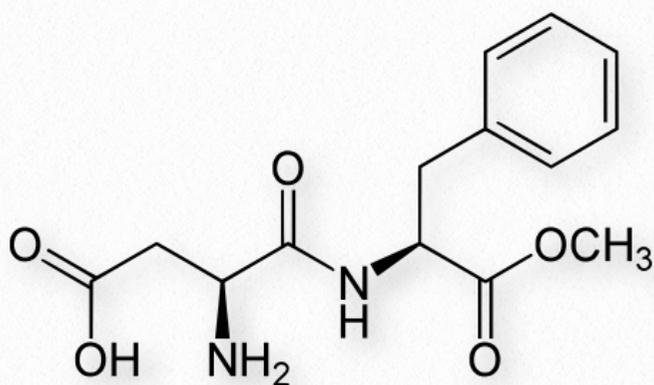
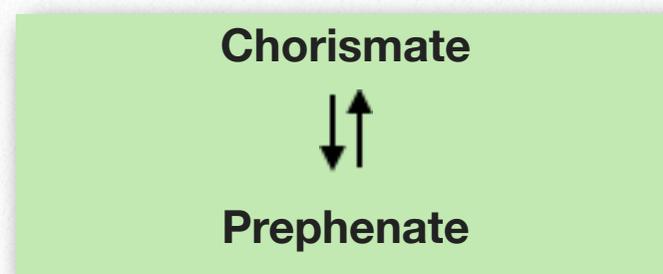
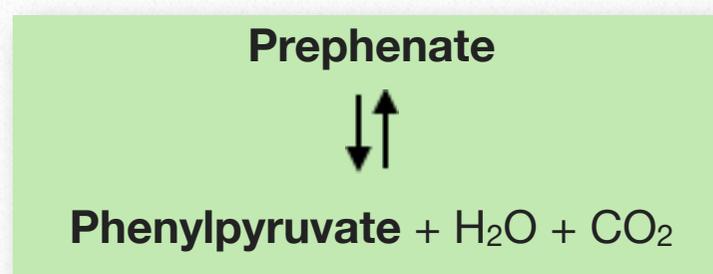


Figure 6.154 - Aspartame - a methyl ester of the aspartic acid-phenylalanine dipeptide

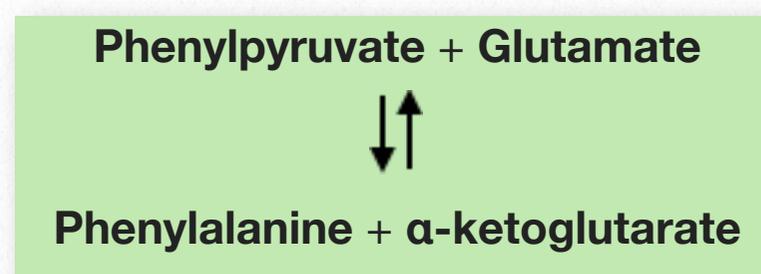
Biosynthesis of phenylalanine in bacteria overlaps with synthesis of tryptophan. The branch occurs at chorismic acid where the enzyme chorismate mutase catalyzes a molecular rearrangement to produce prephenate.



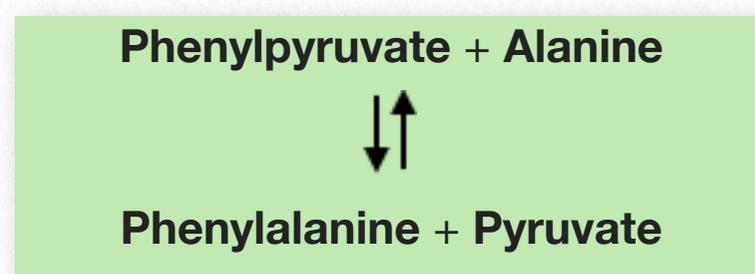
Proton attack on prephenate results in loss of water and carbon dioxide to yield phenylpyruvate.



Transamination of phenylpyruvate yields phenylalanine.



Alternatively, phenylalanine can obtain its amine group in a transamination reaction from alanine.



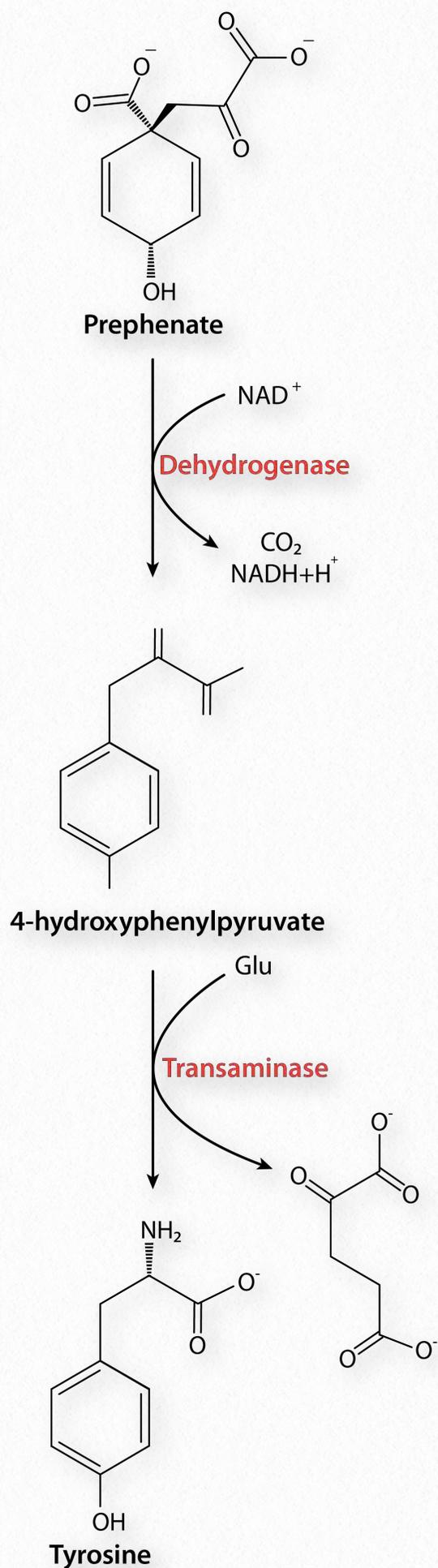


Figure 6.155 - Synthesis of tyrosine from prephenate

Image by Pehr Jacobson

Hydroxylation of phenylalanine by aromatic amino acid hydroxylase (phenylalanine hydroxylase) yields tyrosine.

Tyrosine

Because tyrosine is made from phenylalanine and the latter is an essential amino acid in humans, it is not clear whether to classify tyrosine as essential or non-essential. Some define it as a conditionally essential amino acid. Others simply categorize it as non-essential.

As noted above, tyrosine can arise as a result of hydroxylation of phenylalanine. In addition, plants can synthesize tyrosine by oxidation of prephenate followed by transamination of the resulting 4-hydroxyphenylpyruvate (Figure 6.155).

The hydroxyl group on tyrosine is a target for phosphorylation by protein kinase enzymes involved in signal transduction path-

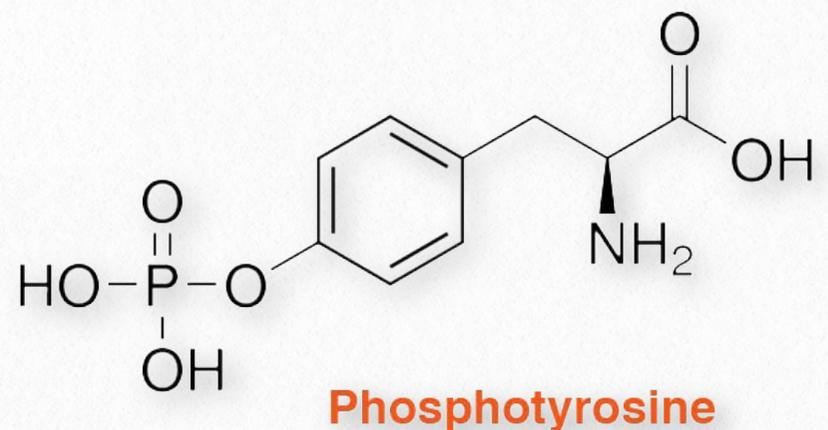


Figure 6.156 - The phosphorylated form of tyrosine

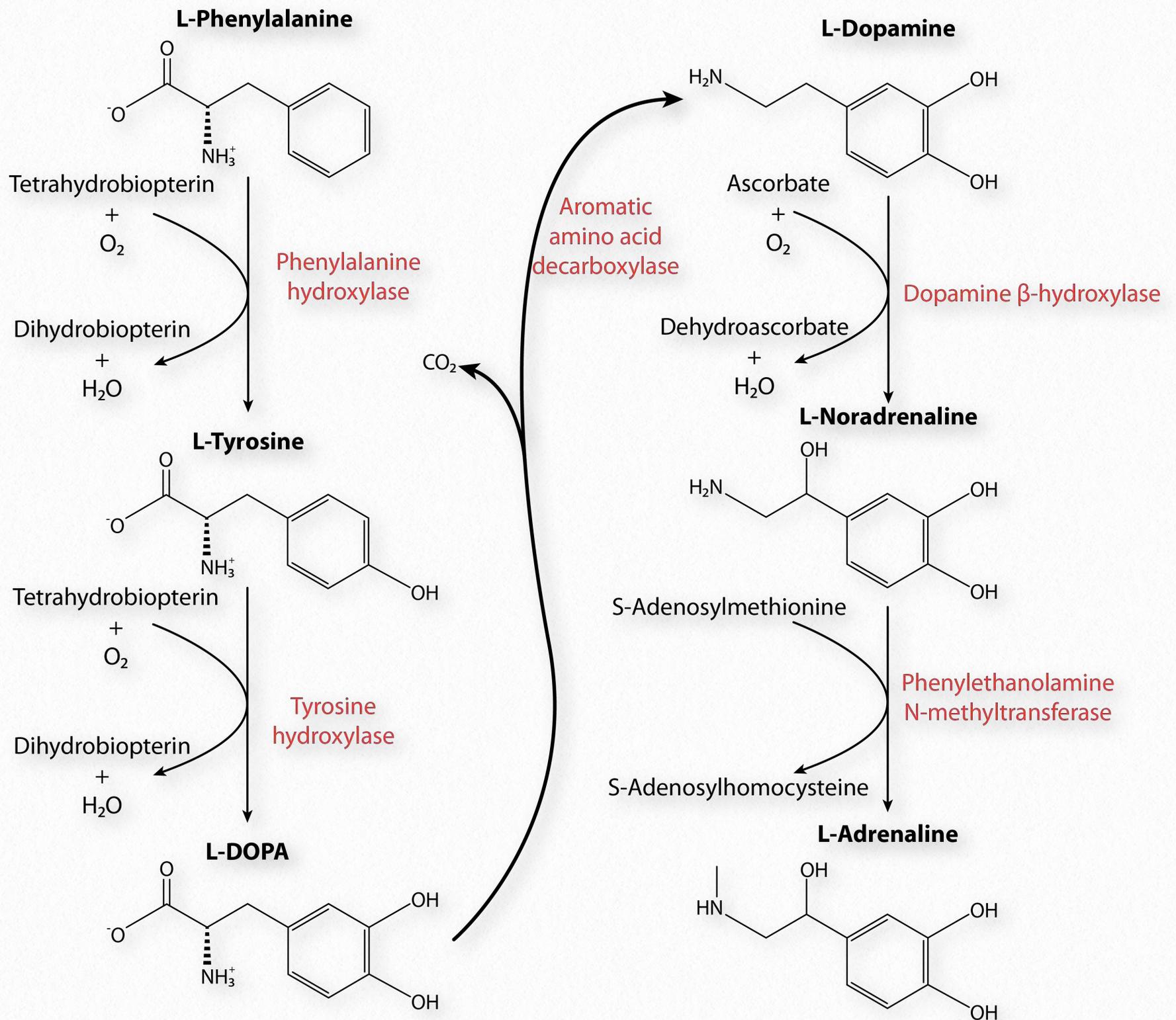


Figure 6.157 - Conversion of phenylalanine and tyrosine to catecholamines

Image by Pehr Jacobson

ways (Figure 6.156). When located in membranes, these enzymes are referred to as receptor tyrosine kinases and they play important roles in controlling cellular behavior/response.

In photosystem II of chloroplasts, tyrosine, at the heart of the system, acts as an elec-

tron donor to reduce oxidized chlorophyll. The hydrogen from the hydroxyl group of tyrosine is lost in the process, requiring re-reduction by four core manganese clusters.

Tyrosine is also important in the small subunit of class I ribonucleotide reducta-

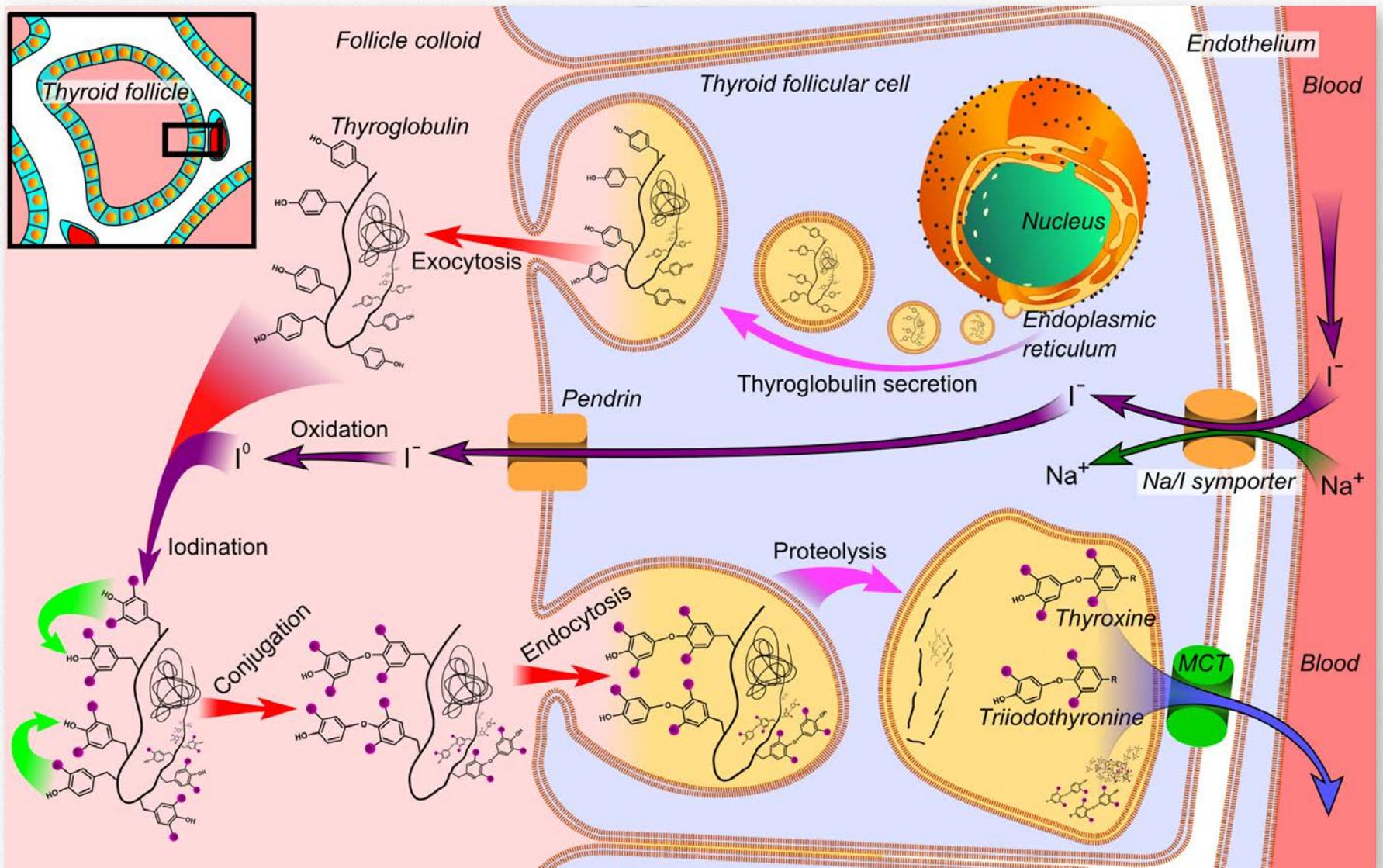


Figure 6.158 - Synthesis of thyroid hormones from tyrosine and movement in the body

Wikipedia

ses where it forms a stable radical in the catalytic action of the enzyme (see [HERE](#)).

Tyrosine metabolites

Tyrosine is a precursor of catecholamines, such as L-dopa, dopamine, norepinephrine, and epinephrine ([Figure 6.157](#)).

The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are also synthesized from tyrosine. As shown in [Figure 6.158](#), this involves a series of iodinations of tyrosines side-chains of a protein known as thyroglobulin. Combinations of iodi-

nated tyrosines give rise to thyroxine and triiodothyronine. These are subsequently cleaved from the protein and released into the bloodstream.

Oxidation and polymerization of tyrosine is involved in synthesis of the family of melanin pigments. Tyrosine is involved in the synthesis of at least two types - eumelanin and pheomelanin ([Figure 6.159](#)).

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Another molecule derived from tyrosine is the benzoquinone portion of Coenzyme Q (CoQ). This

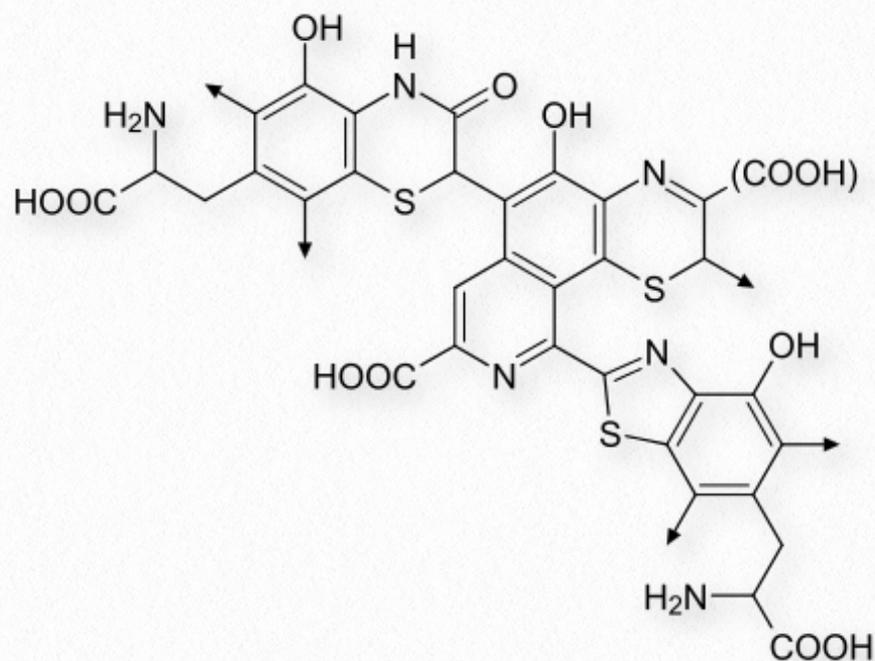


Figure 6.159 - A portion of pheomelanin - Arrows show directions of polymer extension

pathway requires the enzyme HMG-CoA Reductase and since this enzyme is inhibited by cholesterol-lowering statin drugs, CoQ can be limited in people being treated for high cholesterol levels.

Dopamine

Dopamine plays several important roles in the brain and body. A member of the catecholamine and phenethylamine families, its name comes from the fact that it is an amine made by removing a carboxyl group from L-DOPA. Dopamine is synthesized in the brain and kidneys. It is also made in plants, though its function in plants is not clear. Conversion of dopamine to norepinephrine (Figure 6.157) requires vitamin C.

Dopamine is a neurotransmitter, being released by one nerve cell and then traveling across a synapse to signal an adjacent nerve

cell. Dopamine plays a major role in the brain's reward-mediated behavior. Rewards, such as food or social interaction, increase dopamine levels in the brain, as do addictive drugs. Other brain dopamine pathways are involved in motor control and in managing the release of various hormones.

Chemical messenger

Outside the nervous system, dopamine is a local chemical messenger. In blood vessels, it inhibits norepinephrine release and causes vasodilation. In the kidneys, it increases sodium excretion and urine output. It reduces gastrointestinal motility and protects intestinal mucosa in the digestive system and in the immune system, it reduces lymphocyte activity. The effect dopamine has on the pancreas is to reduce insulin production. With the exception of the blood vessels, dopamine is synthesized locally and exerts its effects near the cells that release it.

Epinephrine

Epinephrine (also called adrenalin) is a catecholamine chemically related to norepinephrine that is a hormone with medical applications. It is used to treat anaphylaxis, cardiac arrest, croup, and, in some cases, asthma, when other treatments are not working, due to its ability to favor bronchodilation.

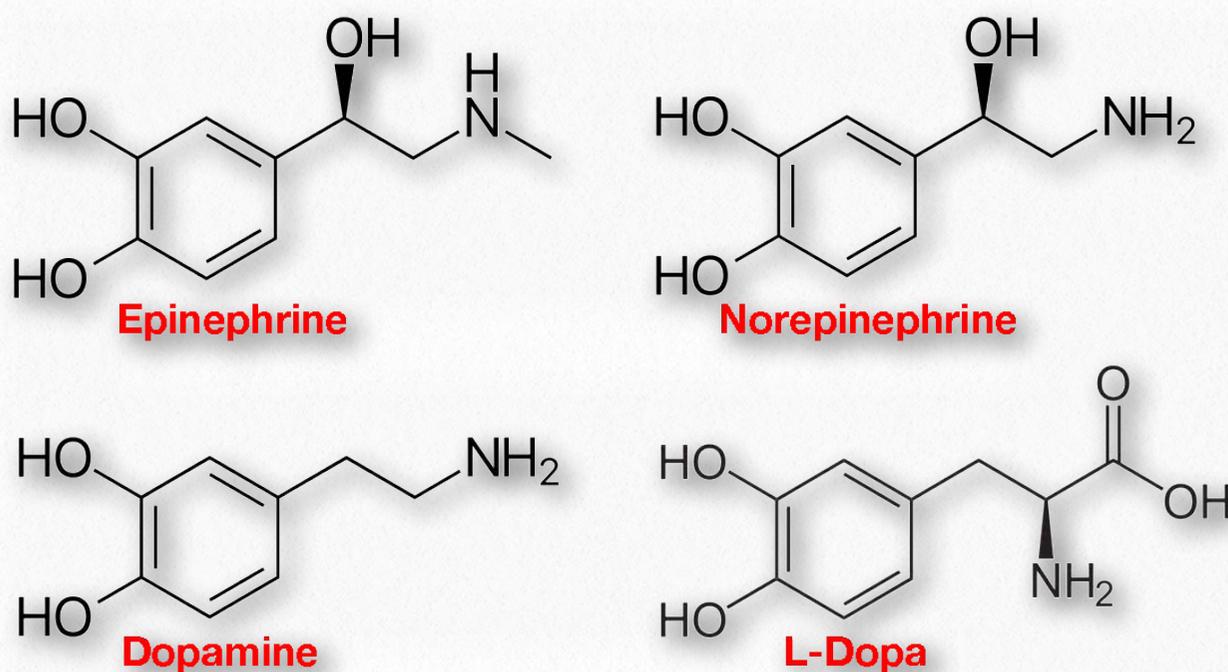


Figure 6.160 - Four catecholamines made from tyrosine

Epinephrine is the drug of choice for treating anaphylaxis. The compound may be given through inhalation, by intravenous injection, or subcutaneous injection and exerts effects through the α - and β -adrenergic receptors. In the body, it is produced and released by adrenal glands and some neurons.

Effects

Physiological effects of epinephrine may include rapid heart beat, increased blood pressure, heart output, pupil dilation, blood sugar concentration and increased sweating. Other physical effects may include shakiness, increased anxiety, and an abnormal heart rhythm.

Norepinephrine

Norepinephrine (also called noradrenalin) is a catecholamine molecule that acts as a

hormone and neurotransmitter. It is chemically similar to epinephrine, differing only in the absence of a methyl group on its amine. Norepinephrine is made and released by the central nervous system (*locus coeruleus* of the brain) and the sympathetic nervous system. The compound is released into the blood

stream from adrenal glands and affects α - and β -adrenergic receptors.

Norepinephrine is at its lowest levels during sleep and at its highest levels during stress (fight or flight response). The primary function of norepinephrine is to prepare the body for action. It increases alertness, enhances memory functions, and helps to focus attention. Norepinephrine increases heart rate and blood pressure, increases blood glucose and blood flow to skeletal muscle and decreases flow of blood to the gastrointestinal system.

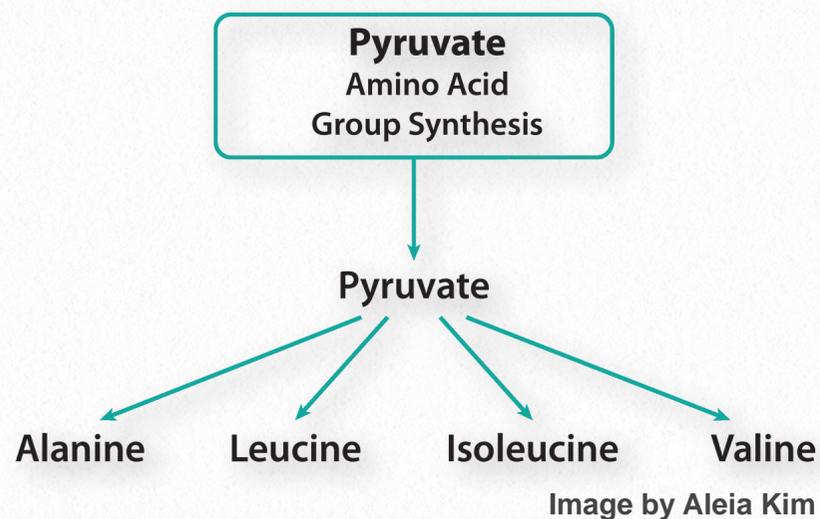
Medical considerations

Norepinephrine may be injected to overcome critically low blood pressure and drugs countering its effects are used to treat heart conditions. α -blockers, for example, are used to battle cardiovascular and psychiatric disor-

ders. β -blockers counter a different set of norepinephrine's effects than α -blockers and are used to treat glaucoma, migraine headaches and other cardiovascular problems.

Pyruvate family

The family of amino acids derived from pyruvate has four members, each with a simple aliphatic side chain no longer than four carbons. The simplest of these is alanine.



Alanine

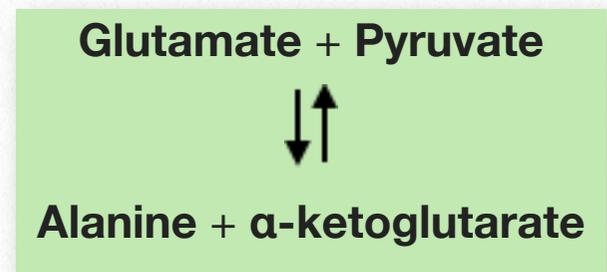
Alanine is the amino acid that is most easily produced from pyruvate. The simple transamination catalyzed by alanine transaminase produces alanine from pyruvate.

Alternative pathways for synthesis of alanine include catabolism of valine, leucine, and isoleucine.

Glucose-alanine cycle

The glucose-alanine cycle is an important nitrogen cycle related to the Cori cycle that occurs between muscle and liver cells in the body (see

[HERE](#)). In it, breakdown of glucose in muscles leads to pyruvate. When nitrogen levels are high, pyruvate is transaminated to alanine, which is exported to hepatocytes.



In the liver cells, the last transamination of the glucose-alanine cycle occurs. The amine group of alanine is transferred to α -ketoglutarate to produce pyruvate and glutamate. Glucose can then be made by gluconeogenesis from pyruvate. Importantly, breakdown of glutamate yields ammonium ion, which can be made into urea for excretion, thus reducing the body's load of potentially toxic amines. This pathway may be particularly important in the brain.

Another way of removing excess ammonium from a tissue is by attaching it to glutamate to make glutamine. Glutamate is a neurotransmitter, so having an alternative way of removing amines (glucose-alanine cycle) is important, especially in the brain.

Leucine

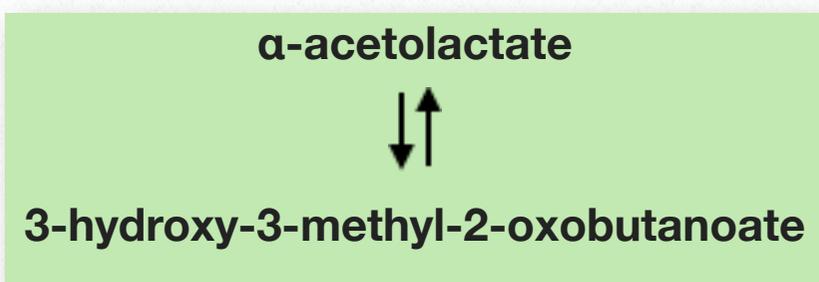
Like valine and isoleucine, leucine is an essential amino acid in humans. In adipose tissue and muscle, leucine is used in sterol synthesis. It is the only amino acid to stimulate muscle protein synthesis, and as a dietary supple-

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ment in aged rats, it slows muscle degradation. Leucine is an activator of mTOR, a protein which, when inhibited, has been shown to increase life span in *Saccharomyces cerevisiae*, *C. elegans*, and *Drosophila melanogaster*.

Metabolism of leucine, valine, and isoleucine (also called Branched Chain Amino Acids - BCAAs) starts with decarboxylation of pyruvate and attachment of the two-carbon hydroxyethyl fragment to thiamine pyrophosphate (Figure 6.161). Metabolism of isoleucine proceeds with attachment of the hydroxylated two carbon piece (hydroxyethyl-TPP) to α -ketobutyrate and is covered in the section describing that amino acid (see [HERE](#)).

Metabolism of valine and leucine proceeds with attachment of the hydroxyethyl piece from TPP to another pyruvate to create α -acetolactate. Rearrangement of α -acetolactate by acetolactate mutase makes 3-hydroxy-3-methyl-2-oxobutanoate.



Reduction with NAD(P)H by aceto-

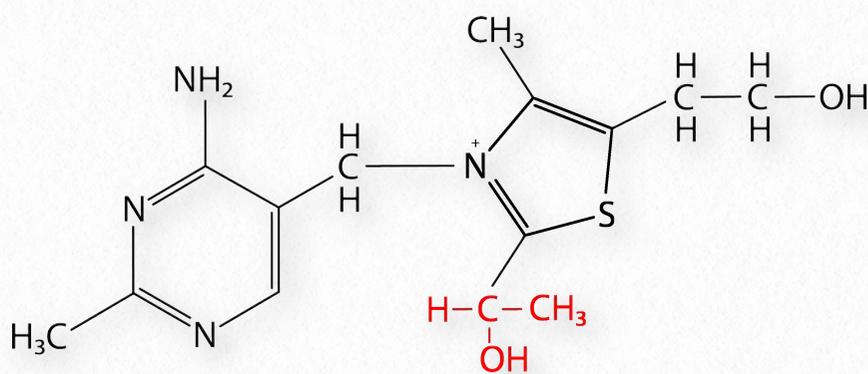
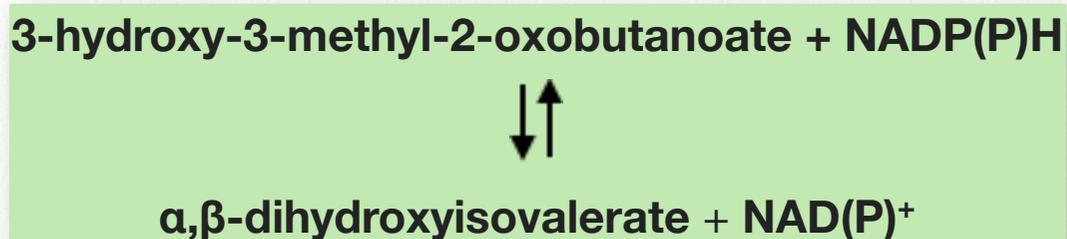


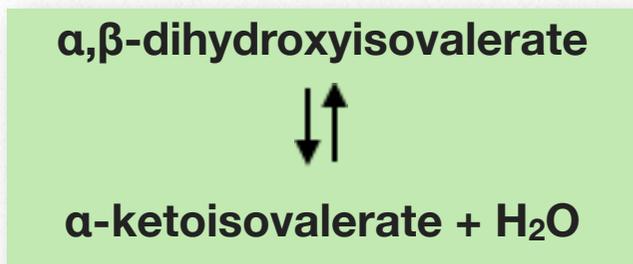
Figure 6.161 - Hydroxyethyl fragment (in red) attached to thiamine pyrophosphate

Image by Pehr Jacobson

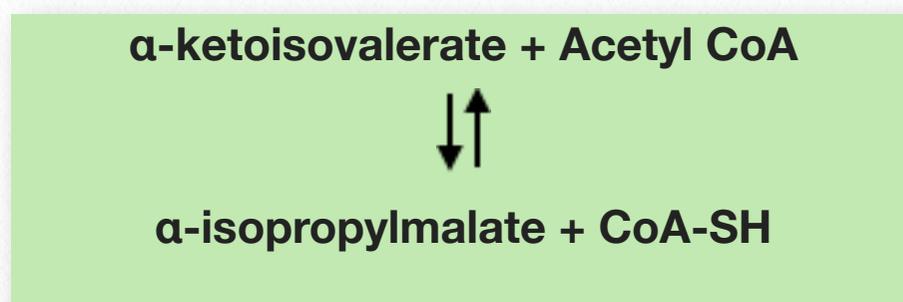
hydroxy acid isomeroreductase yields α,β -dihydroxyisovalerate.



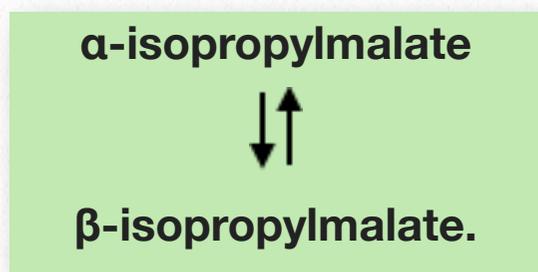
Loss of water, catalyzed by dihydroxyacid dehydratase produces α -ketoisovalerate.



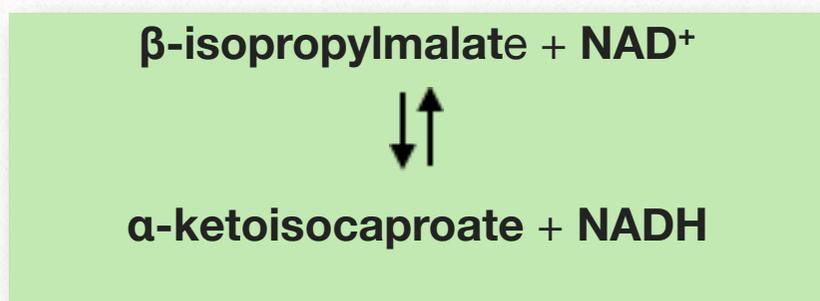
This molecule is a branch point for synthesis of leucine and valine. Addition of an acetyl group from acetyl-CoA yields α -isopropylmalate (catalyzed by α -isopropylmalate synthase).



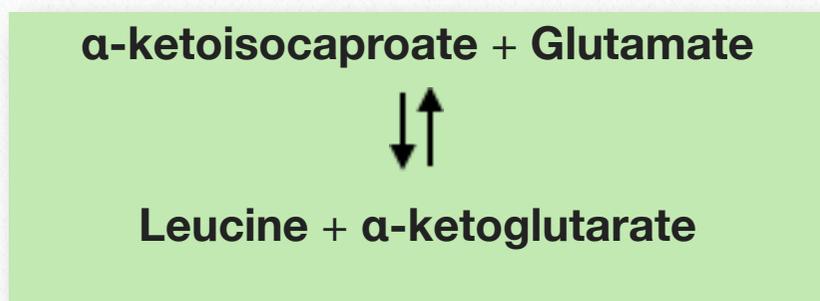
Rearrangement, catalyzed by isopropylmalate dehydratase, gives rise to β -isopropylmalate.



Oxidation by isopropylmalate dehydrogenase and NAD^+ , gives α -ketoisocaproate.



Transamination of it (catalyzed by leucine aminotransferase and using glutamate) gives the final product of leucine (top of next column).

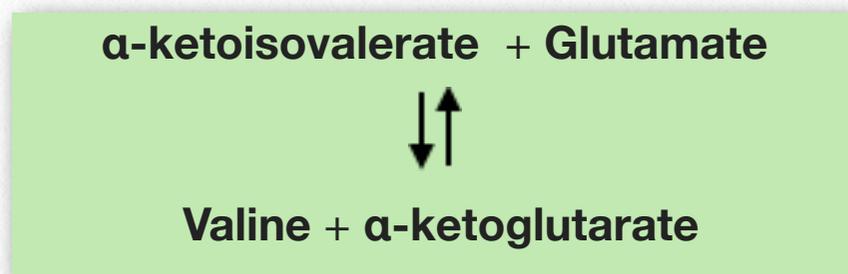


Valine

An essential amino acid in humans, valine is derived in plants from pyruvate and shares part of its metabolic synthesis pathway with leucine and a small slice of it with isoleucine. Metabolism of all three amino acids starts with decarboxylation of pyruvate and attachment of the two-carbon hy-

droxyethyl fragment to thiamine pyrophosphate (Figure 6.161), as noted above.

As seen earlier, α -ketoisovalerate is the molecule at the point in the metabolic pathway where synthesis of valine branches from that of leucine. In fact, α -ketoisovalerate is only one step away from valine. Transamination of α -ketoisovalerate catalyzed by valine isoleucine aminotransferase gives valine.



Isoleucine

Synthesis of isoleucine (an essential amino acid in humans) begins in plants and microorganisms with pyruvate and α -ketobutyrate (a byproduct of threonine metabolism - threonine deaminase - Figure 6.162).

Metabolism of isoleucine proceeds with attachment to α -ketobutyrate of the hydroxyethyl-TPP product of pyruvate decarboxylation to form α -aceto- α -hydroxybutyrate. The reaction is catalyzed by acetolactate synthase. Rearrangement and reduction by aceto-hydroxy acid isomeroreductase and NAD(P)H yields α, β -dihydroxy- β -methylvalerate. Shown on next page.

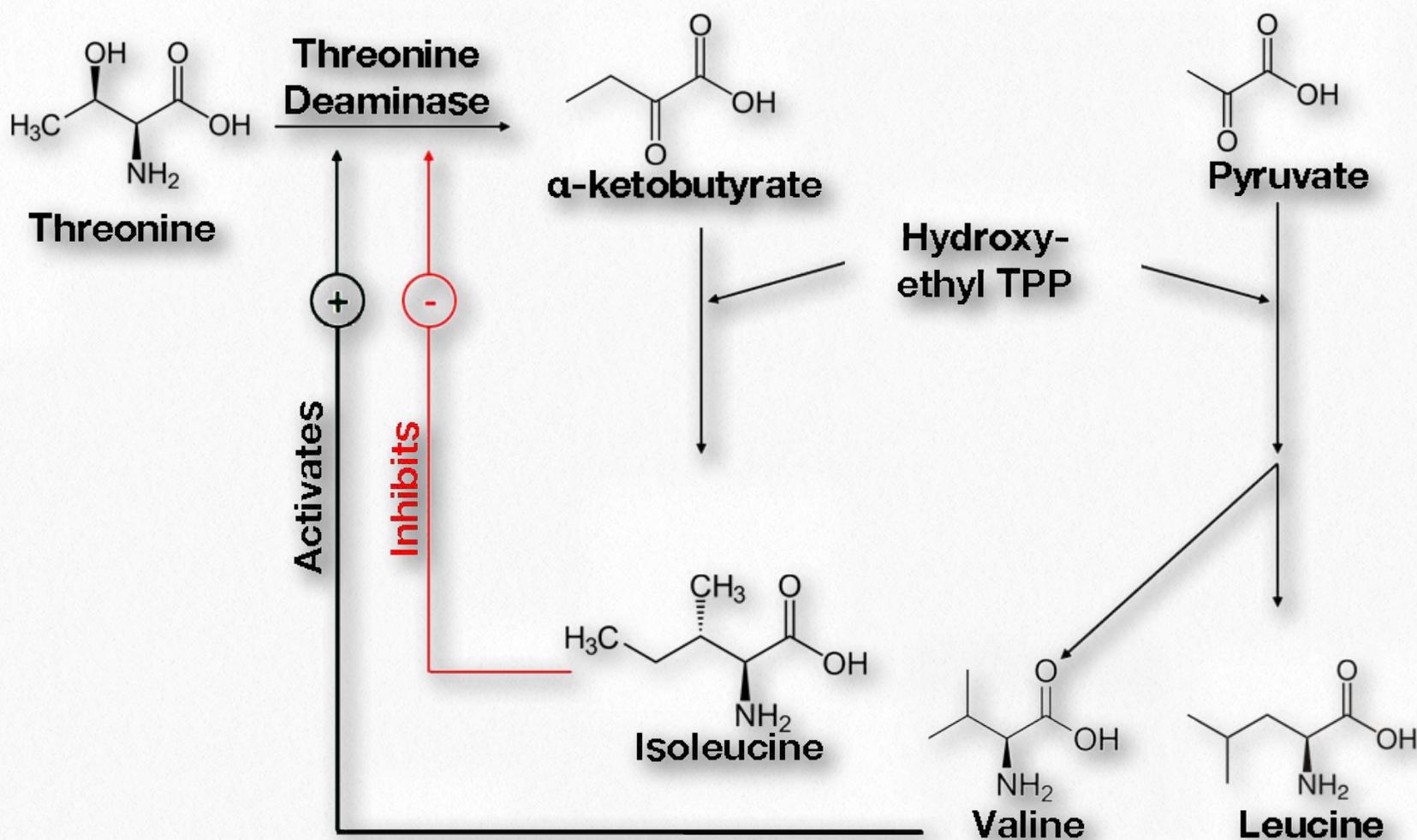
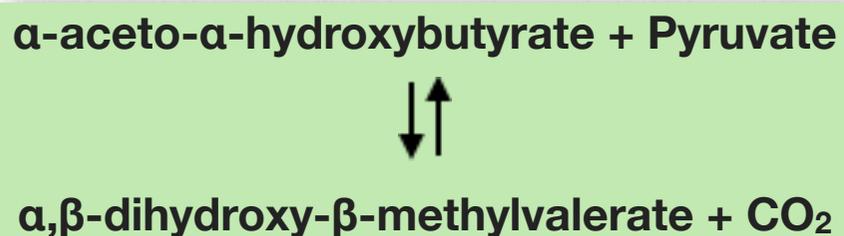
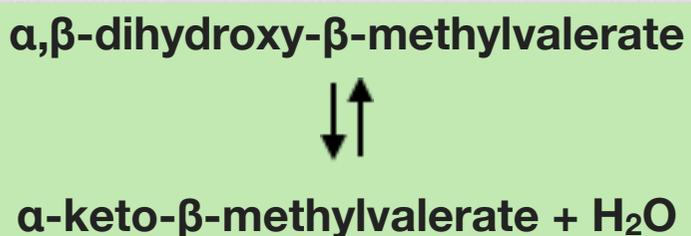


Figure 6.162 - Threonine deaminase and regulation of BCAA synthesis

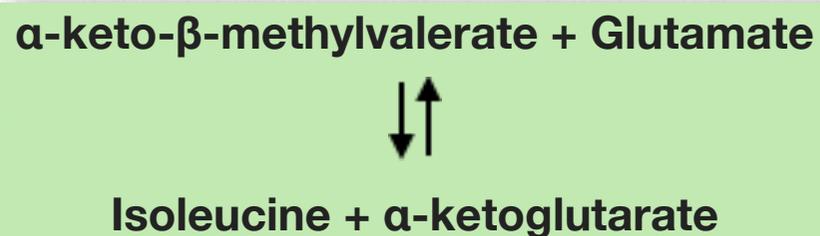
Wikipedia



Loss of water (catalyzed by dihydroxy acid dehydratase) gives α -keto- β -methylvalerate.



Transamination (using glutamate and valine isoleucine transaminase) yields isoleucine.



Interestingly, several of the enzymes of valine metabolism catalyze reactions in the isoleucine pathway. Though the substrates are slightly different, they are enough like the valine intermediates that they are recognized as substrates.

Isoleucine has a second asymmetric center within it, but only one isomeric form of the four possible ones from the two centers is found biologically.

Regulation of synthesis

Regulation of synthesis of the branched chain amino acids (BCAAs - valine, leucine, and isoleucine) is complex. The key molecule in the regulation is α -ketobutyrate, which is synthesized in cells as a breakdown product of threonine. The enzyme catalyzing its synthesis is threonine deaminase (Figure 6.162), which is allosterically regulated. The enzyme is inhibited by its own product (isoleucine) and activated by valine, a product of a parallel pathway.

Thus, when valine concentration is high, the balance shifts in favor of production of isoleucine and since isoleucine competes with valine and leucine for hydroxyethyl-TPP, synthesis of these two amino acids goes down. When isoleucine concentration increases, threonine deaminase is inhibited, shifting the balance back to production of valine and leucine.

Attenuation

Another control mechanism for regulation of leucine synthesis occurs in bacteria and is known as attenuation. In this method, accumulation of leucine speeds the process of translation of a portion of the mRNA copy of the leucine operon (coding sequences for enzymes necessary to make leucine). This, in turn, causes transcription of the genes of the leucine operon to terminate

prematurely, thus stopping production of the enzymes necessary to make leucine.

When leucine levels fall, translation slows, preventing transcription from terminating prematurely and allowing leucine metabolic enzymes to be made. Thus, leucine levels in the cell control the synthesis of enzymes necessary to make it.

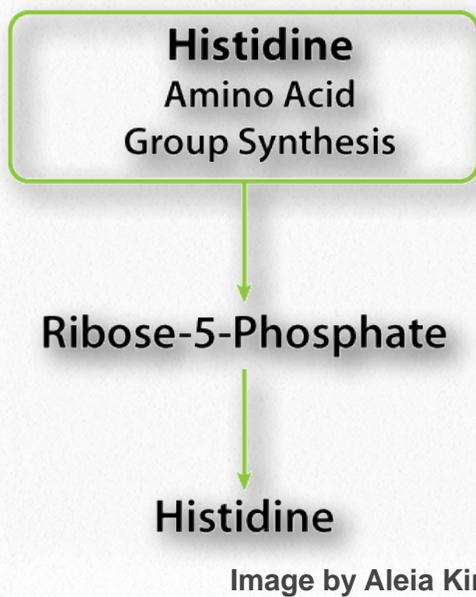
Histidine family

Synthesis of histidine literally occurs in a class by itself - there are no other amino acids in its synthesis family. The amino acid is made in plants (*Arabidopsis*, in this case) by a pathway that begins with ribose-5-phosphate. The overall pathway is shown in the green text boxes on the next two pages. Abbreviations used in the boxes are shown below.

Enzyme names

- 1 = Ribose-phosphate diphosphokinase
- 2 = ATP-phosphoribosyltransferase
- 3 = Phosphoribosyl-ATP pyrophosphohydrolase
- 4 = Phosphoribosyl-AMP cyclohydrolase
- 5 = ProFAR-I (N'-[(5'phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide ribonucleotide isomerase)
- 6 = Imidazole glycerol-phosphate syn-





thase (IGPS)

7 = **I**midazole glycerol-phosphate dehydrogenase

8 = **H**istidinol-phosphate aminotransferase

9 = **H**istidinol-phosphate phosphatase

10 = **H**istidinol dehydrogenase

Abbreviations used

1 - PRPP = Phosphoribosyl Pyrophosphate

2. PRATP = Phosphoribosyl ATP

3. PRAMP = Phosphoribosyl AMP

4. ProFAR = (N'-[(5'-phosphoribosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide

5. PRFAR = (N'-[(5-phosphoribulosyl)formimino]-5-aminoimidazole-4-carboxamide) ribonucleotide

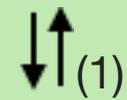
6. IGP = Imidazole glycerol-phosphate

7. AICAR = 5'-phosphoribosyl-4-carboximide-5-aminoimidazole

8. IAP = Imidazole acetol-phosphate

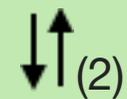
9. α -KG = α -ketoglutarate

Ribose-5-Phosphate + ATP



PRPP + AMP

PRPP + ATP



PRATP

PRATP



PRAMP + PP_i

PRAMP



ProFAR

ProFAR



PRFAR

PRFAR + Glutamine

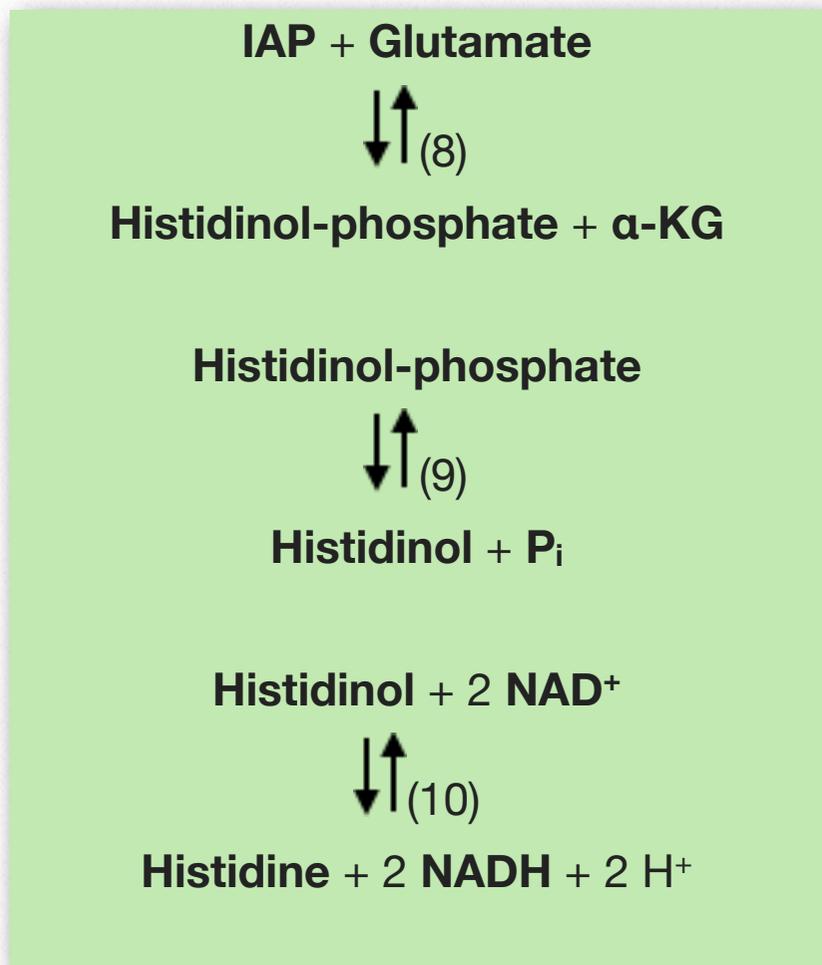


IGP + Glutamate + AICAR

IGP



IAP



Histidine is a feedback inhibitor of ATP-phosphoribosyltransferase and thus helps to regulate its own synthesis. Histidine is the only amino acid to contain an imidazole ring. It is ionizable and has a pKa of about 6. As a result, histidine's R-group can gain/lose a proton at pH values close to cellular conditions.

Selenocysteine

A cysteine analog commonly referred to as the 21st amino acid, selenocysteine (Figure 6.163) is an unusual amino acid occasionally found in proteins. Although it is rare, selenocysteine has been found in proteins in bacteria, archaea and eukaryotes.

In contrast to amino acids such as phosphoserine, hydroxyproline, or acetyl-lysine,

which arise as a result of post-translational modifications, selenocysteine is actually built into growing peptide chains in ribosomes during the process of translation.

No codon specifies selenocysteine, so to incorporate it into a protein, a tRNA carrying it must bind to a codon that normally specifies STOP (UGA). This alternative reading of the UGA is dependent on formation of a special hairpin loop structure in the mRNA encoding selenoproteins.

Selenium is rather toxic, so cellular and dietary concentrations are typically exceedingly

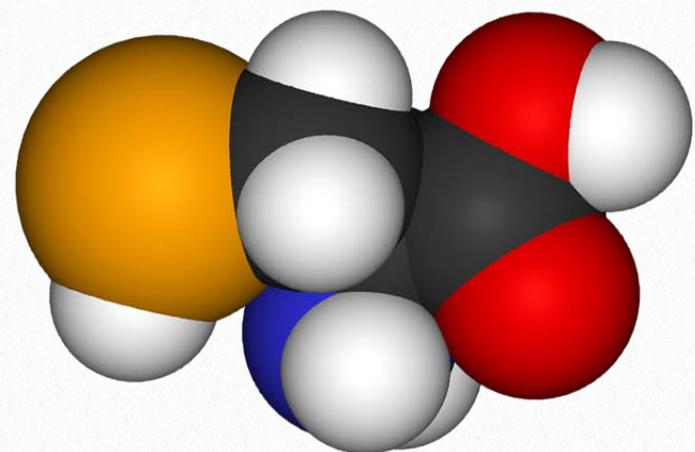
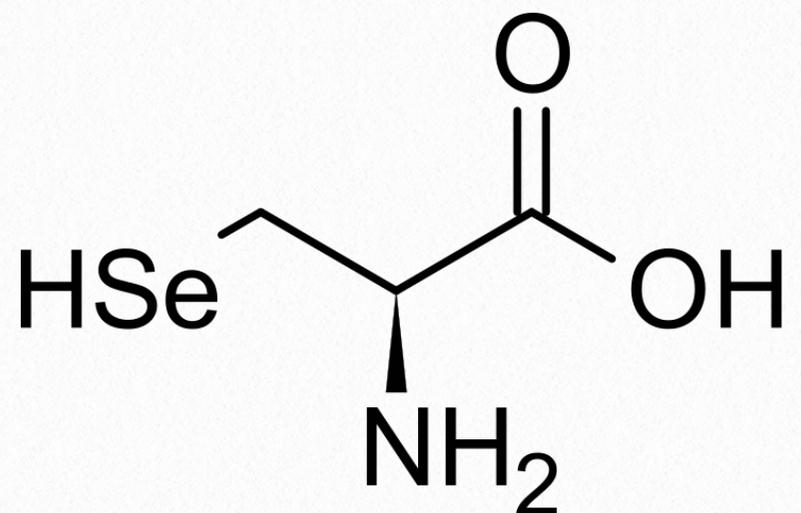


Figure 6.163 - Selenocysteine

low. About 25 human proteins are known to contain the amino acid. These include five glutathione peroxidases, and three thioredoxin reductases. Iodothyronine deiodinase, a key enzyme that converts thyroxine to the active T3 form, also contains selenocysteine in its active site. All of these proteins contain a single selenocysteine.

A eukaryotic protein known as selenoprotein P, found in the blood plasma of animals, contains ten selenocysteine residues and is thought to function as an antioxidant and/or in heavy metal detoxification. Besides selenocysteine, at least two other biological forms of a seleno-amino acid are known. These include 1) selenomethionine (Figure 6.164), a naturally occurring amino acid in Brazil nuts, cereal grains, soybeans, and grassland legumes and 2) methylated forms of selenocysteine, such as Se-methylselenocysteine, are found in *Astragalus*, *Allium*, and *Brassica* species.

Stop codon

The specifics of the process of translation will be described elsewhere in the book, but to get selenocysteine into a protein, the tRNA carrying selenocysteine pairs with a stop codon (UGA) in the mRNA in the ribosome. Thus, instead of stopping translation, selenocysteine can be incorporated into a growing protein and translation continues instead of stopping.

Four genes are involved in preparation of selenocysteine for incorporation into proteins. They are known as sel A, sel B, sel C, and sel D. Sel C codes for the special tRNA that carries selenocysteine. The amino acid initially put onto the selenocysteine tRNA is not selenocysteine, but rather serine. Action of sel A and sel D are necessary to convert the serine to a selenocysteine.

An intermediate in the process is selenophosphate, which is the selenium donor. It is derived from H_2Se , the form in which selenium is found in the cell. The tRNA carrying selenocysteine has a slightly different structure than other tRNAs, so it requires assistance in translation. The sel B gene encodes for an EF-Tu-like protein that helps incorporate the selenocysteine into the protein during translation.

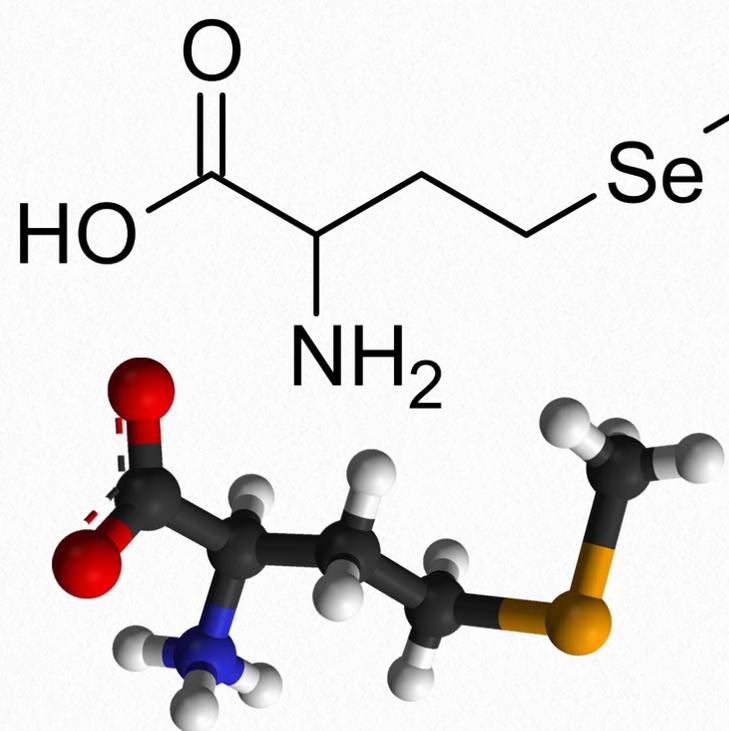


Figure 6.164 - **Selenomethionine**

Recoding the UGA

Using UGA codons to incorporate selenocysteine into proteins could wreak havoc if done routinely, as UGA, in fact, almost always functions as a stop codon and is only rarely used to code for selenocysteine. Fortunately, there is a mechanism to ensure that the reading of a UGA codon as selenocysteine occurs only when the mRNA encodes a selenoprotein.

Unusual structures in mRNAs

The mRNAs for selenocysteine-containing proteins form unusual mRNA structures around the UGA codon that make the ribosome “miss” it as a stop codon and permit the tRNA with selenocysteine to be incorporated instead.

Pyrrolysine

Like selenocysteine, pyrrolysine is a rare, unusual, genetically encoded amino acid found in some cells. Proteins containing it are enzymes involved in methane metabolism and so far have been found only in methanogenic archaeans and one species of bacterium. The amino acid is found in the active site of the enzymes containing it. It is sometimes referred to as the 22nd amino acid.

Synthesis of the amino acid biologically begins with two lysines. One is converted to (3R)-3-Methyl-D-ornithine, which is attached to the second lysine. Af-

ter elimination of an amine group, cyclization, and dehydration, L-pyrrolysine is produced. Pyrrolysine is attached to an unusual tRNA (pylT gene product) by action of the aminoacyl tRNA synthetase encoded by the pylS gene. This unusual tRNA can pair with the UAG stop codon during translation and allow for incorporation of pyrrolysine into the growing polypeptide chain during translation in a manner similar to incorporation of selenocysteine.

Urea cycle

The urea cycle holds the distinction of being the first metabolic cycle discovered - in 1932, five years before the citric acid cycle. It is an important metabolic pathway for balancing nitrogen in the bodies of animals and it takes place primarily in the liver and kidney.

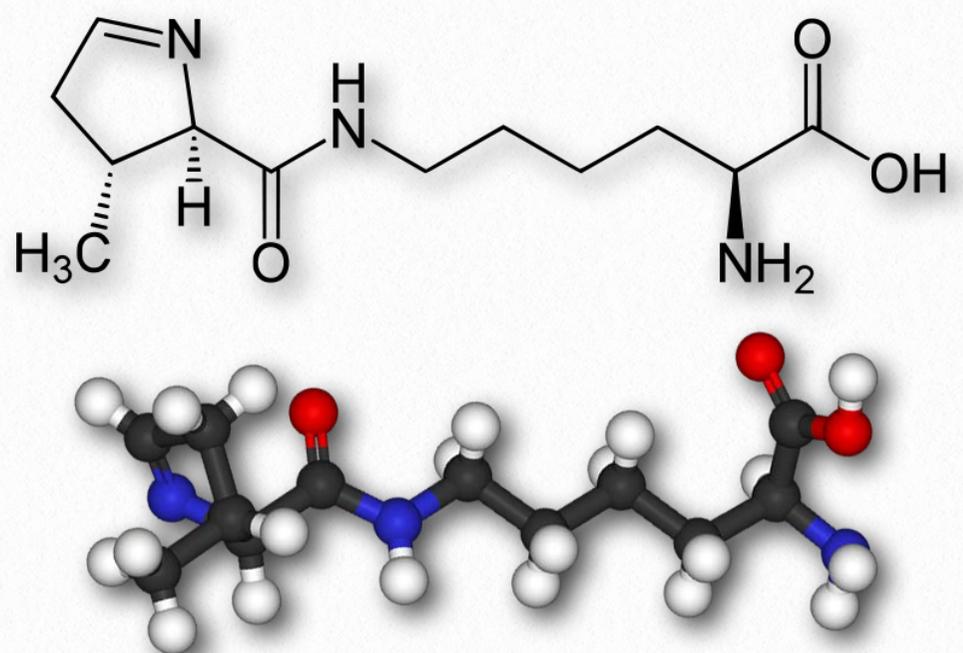


Figure 6.165 - Pyrrolysine

Organisms, like humans, that excrete urea are called ureotelic. Those that excrete uric acid (birds, for example) are called uricotelic and those that excrete ammonia (fish) are ammonotelic. Ammonia, of course, is generated by metabolism of amines and is toxic, so managing levels of it is critical for any organism. Excretion of ammonia by fish is one reason that an aquarium periodically requires cleaning and replacement of water.

Liver failure can lead to accumulation of nitrogenous waste and exacerbates the problem. As shown in [Figure 1.166](#), the cycle contains five reactions, with each turn of the cycle producing a molecule of urea. Of the five reactions, three occur in the cytoplasm and two take place in the mitochondrion. (The reaction making carbamoyl phosphate, catalyzed by carbamoyl phosphate synthetase is not shown in the figure.)

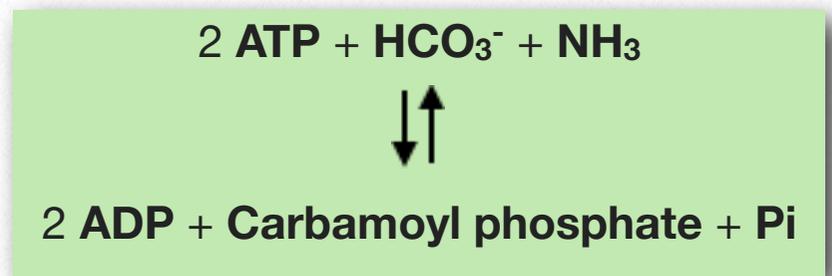
Ornithine synthesis

Though the cycle doesn't really have a starting point, a common place to begin discussion is with the molecule of ornithine. As discussed elsewhere in this book, ornithine intersects the metabolic pathways of arginine and proline.

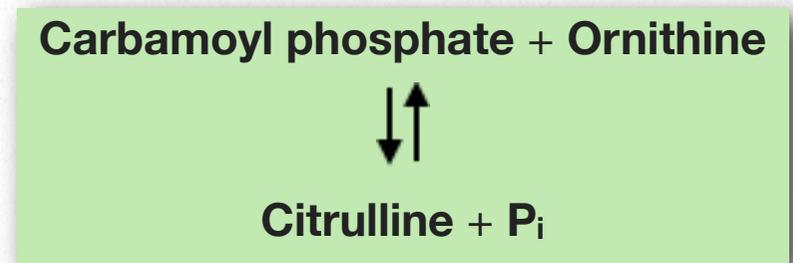
Ornithine is found in the cytoplasm and is transported into the mitochondrion by the ornithine-citrulline antiport of the inner



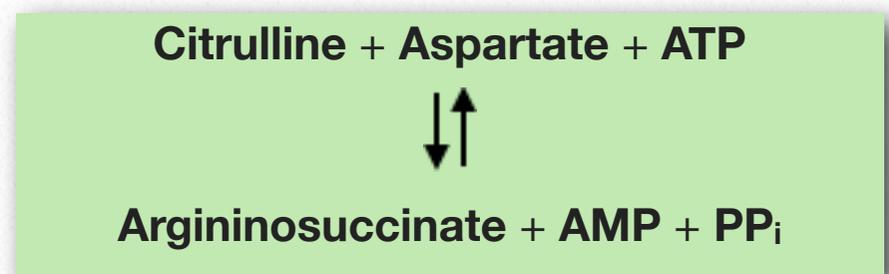
mitochondrial membrane. In the matrix of the mitochondrion, two reactions occur relevant to the cycle. The first is formation of carbamoyl phosphate from bicarbonate, ammonia, and ATP catalyzed by carbamoyl phosphate synthetase I.



Carbamoyl phosphate then combines with ornithine in a reaction catalyzed by ornithine transcarbamoylase to make citrulline.



The citrulline is transported out to the cytoplasm by the ornithine-citrulline antiport mentioned above. In the cytoplasm, citrulline combines with L-aspartate using energy of ATP to make citrullyl-AMP (an intermediate) followed by argininosuccinate. The reaction is catalyzed by argininosuccinate synthase.



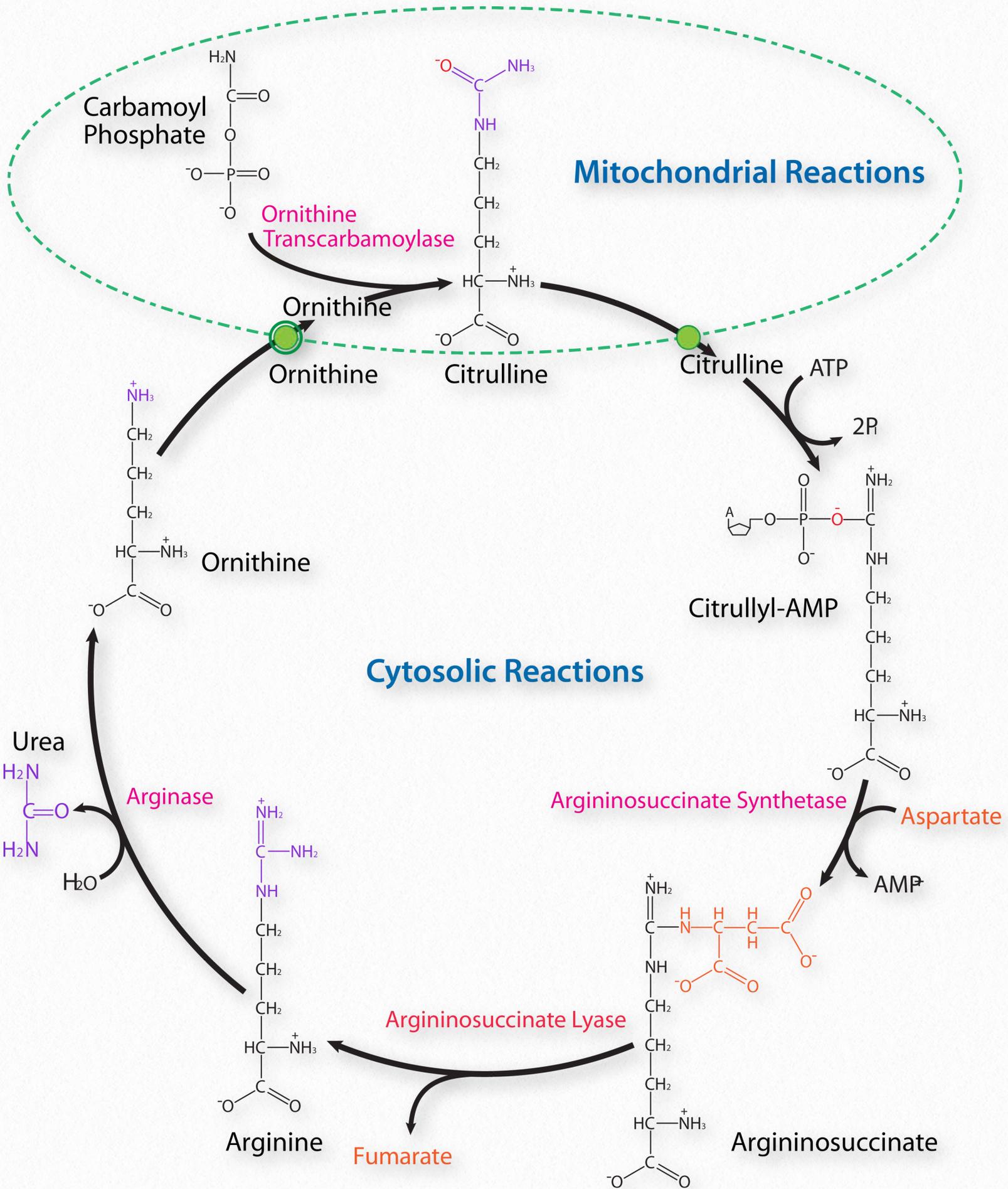
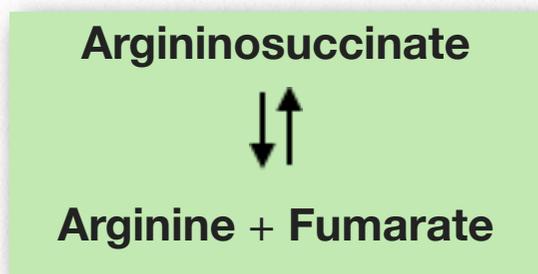


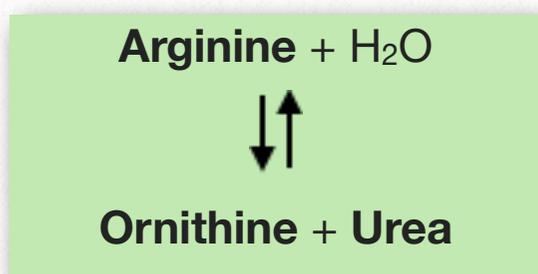
Figure 6.166 - The urea cycle

Image by Aleia Kim

Next, fumarate is split from argininosuccinate by argininosuccinate lyase to form arginine.



Water is used by arginase to cleave arginine into urea and ornithine, completing the cycle.



Urea is less toxic than ammonia and is released in the urine. Some organisms make uric acid for the same reason.

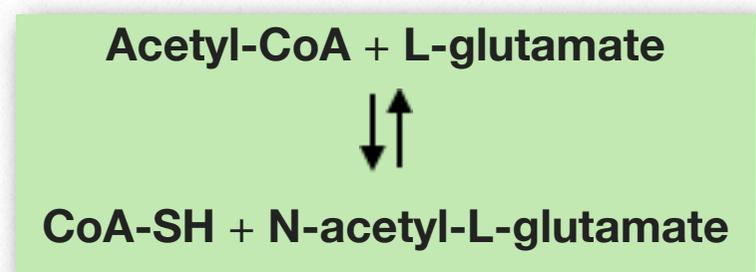
It is worth noting that aspartic acid, ammonia, and bicarbonate enter the cycle and fumarate and urea are produced by it. Points to take away include 1) ammonia is converted to urea using bicarbonate and the amine from aspartate; 2) aspartate is converted to fumarate which releases more energy than if aspartate were converted to oxaloacetate, since conversion of fumarate to malate to oxaloacetate in the citric acid cycle generates an NADH, but direct conversion of aspartate to oxaloacetate does not; and 3) glutamate and aspartate are acting as shuttles to funnel ammonia into the cycle.

Glutamate, as will be seen below, is a scavenger of ammonia.

Urea cycle regulation

The urea cycle is controlled both allosterically and by substrate concentration. The cycle requires N-acetylglutamate (NAG) for allosteric activation of carbamoyl phosphate synthetase I. The enzyme that catalyzes synthesis of NAG, NAG synthetase, is activated by arginine and glutamate. Thus, an indicator of high amine levels, arginine, and an important shuttler of amine groups, glutamate, stimulates the enzyme that activates the cycle.

The reaction catalyzed by NAG synthetase is



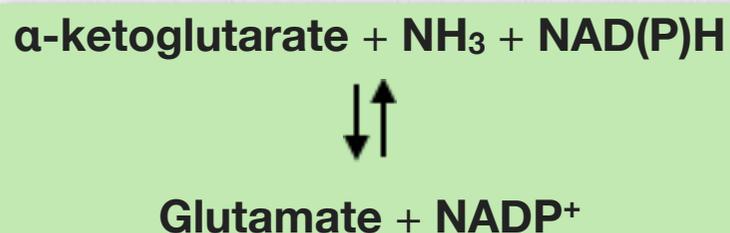
At the substrate level, all of the other enzymes of the urea cycle are controlled by the concentrations of substrates they act upon. Only at high concentrations are the enzymes fully utilized.

Complete deficiency of any urea cycle enzyme is fatal at birth, but mutations resulting in reduced expression of enzymes can have mixed effects. Since the enzymes are usually not limiting for these reactions, increasing substrate can often overcome reduced enzyme

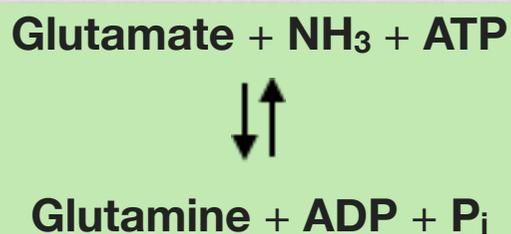
amounts to a point by simply fully activating enzymes present in reduced quantities.

Ammonia accumulation

However, if the deficiencies are sufficient, ammonium can accumulate and this can be quite problematic, especially in the brain, where mental deficiencies or lethargy can result. Reduction of ammonium concentration relies on the glutamate dehydrogenase reaction (named for the reverse reaction).



Additional ammonia can be taken up by glutamate in the glutamine synthetase reaction.



The result of these reactions is that α -ketoglutarate and glutamate concentrations will be reduced and the concentration of glutamine will increase. For the brain, this is a yin/yang situation. Removal of ammonia is good, but reduction of α -ketoglutarate concentration means less energy can be generated by the citric acid cycle. Further, glutamate is, itself, an important neurotransmitter and a precursor of another neurotransmitter - γ -aminobutyric acid (GABA).

Energy generation

From an energy perspective, the urea cycle can be said to break even or generate a small amount of energy, if one includes the energy produced in releasing ammonia from glutamate (one NADH). There are two NADHs produced (including the one for converting fumarate to oxaloacetate), which give 4-6 ATPs, depending on how efficiently the cell performs electron transport and oxidative phosphorylation.

The cycle takes in 3 ATPs and produces 2 ADPs and one AMP. Since AMP is equivalent to 2 ATP, the cycle uses 4 ATP. Thus, the cycle either breaks even in the worst case or generates 2 ATPs in the best case.

Amino acid catabolism

Amino acids are divided according to the pathways involved in their degradation. There are three general categories. Ones that yield intermediates in the glycolysis pathway are called glucogenic and those that yield intermediates of acetyl-CoA or acetoacetate are called ketogenic. Those that involve both are called glucogenic and ketogenic. These are shown in [Figures 6.167](#) and [6.168](#).

As seen in the two figures, amino acids largely produce breakdown products related to intermediates of the citric acid cycle or glycolysis, but this isn't the complete picture. Some amino acids, like tryptophan,

Glucogenic and Ketogenic Amino Acids

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

acetate and fumarate. Enzymes involved include 1) tyrosine transaminase; 2) p-hydroxylphenylpyruvate dioxygenase; 3) homogentisate dioxygenase; 4) maleylacetoacetate *cis-trans*-isomerase; and 5) 4-fumaryl acetoacetate hydrolase.

Breakdown of leucine is a multi-step process ultimately yielding the ketone body acetoacetate and acetyl-CoA. Branched chain amino acids (BCAAs - valine, leucine,

Figure 6.167 - Results of amino acid catabolism

Image by Aleia Kim

phenylalanine, and tyrosine yield hormones or neurotransmitters on further metabolism (as noted earlier). Others like cysteine and methionine must dispose of their sulfur and all of the amino acids must rid themselves of nitrogen, which can happen *via* the urea cycle, transamination, or both.

Tyrosine catabolism

Breakdown of tyrosine (Figure 6.169) is a five step process that yields acetoa-

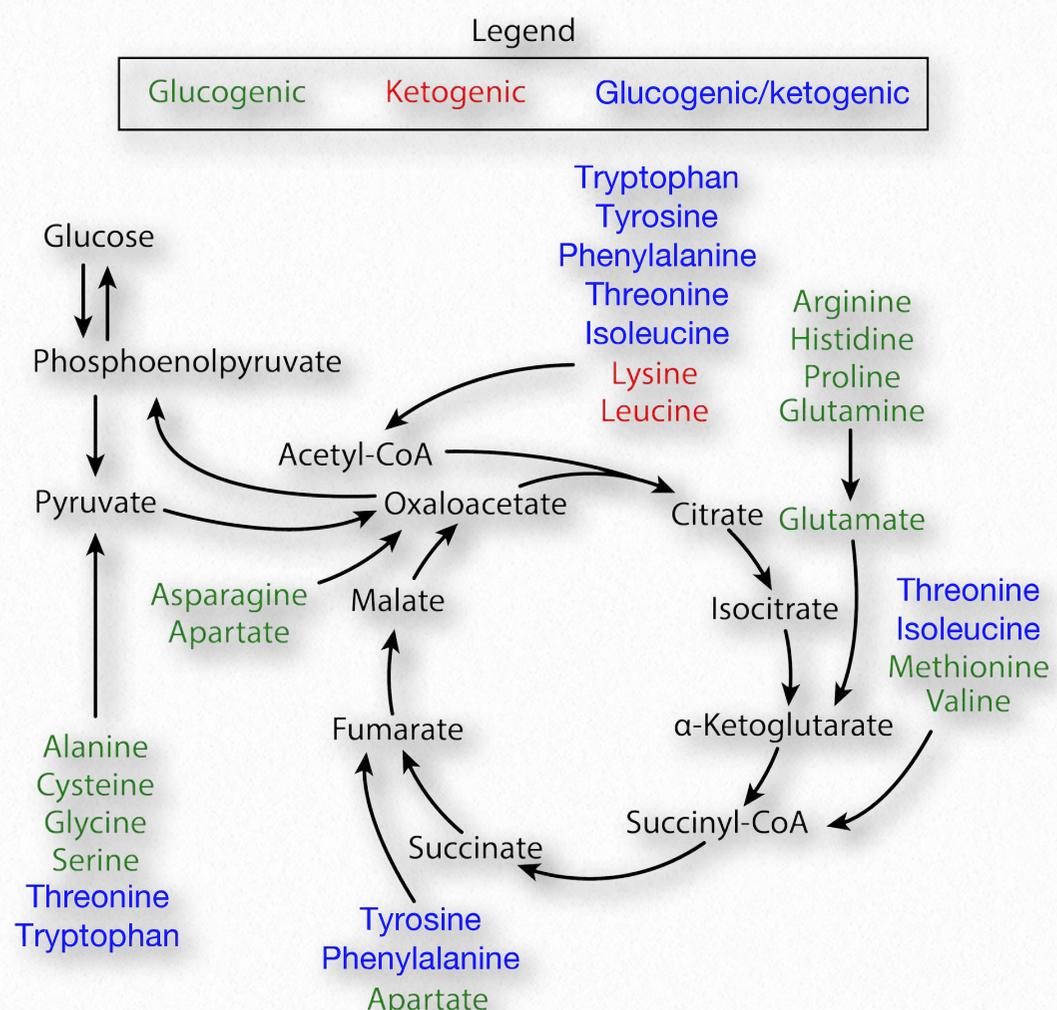


Figure 6.168 - Breakdown pathways for amino acids. Some yield more than one intermediate.

Image by Pehr Jacobson

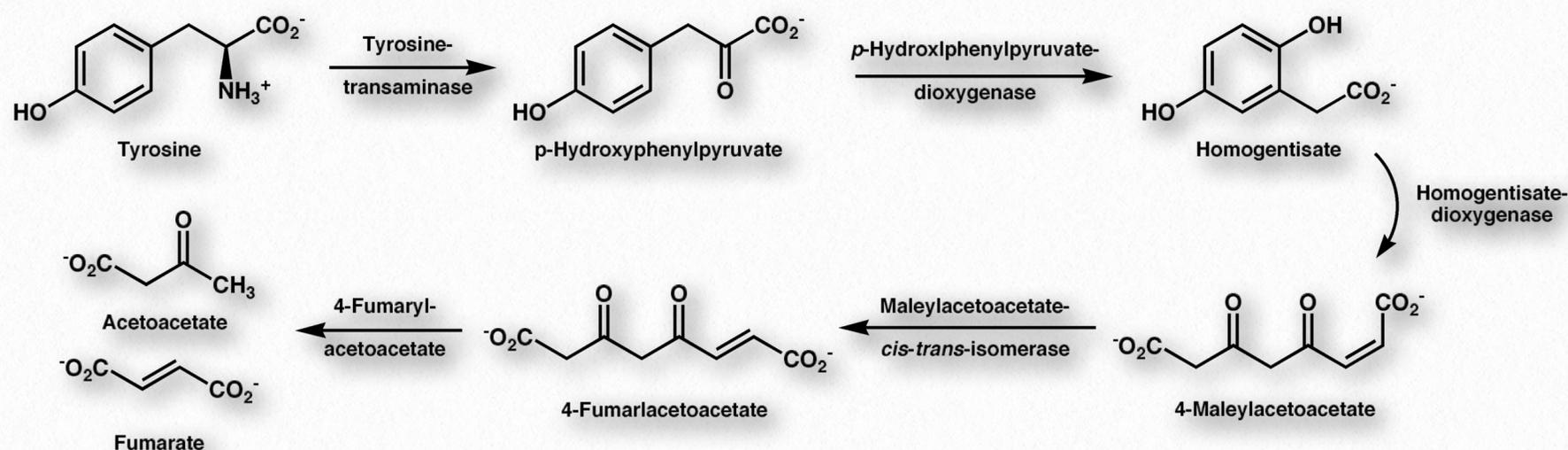


Figure 6.169 - Catabolism of tyrosine to fumarate and acetoacetate.

and isoleucine) rely on Branched Chain AminoTransferase (BCAT) followed by Branched Chain α -ketoacid dehydrogenase (BCKD) for catabolism.

Breakdown of isoleucine yields intermediates that are both ketogenic and gluco-genic. These include acetyl-CoA and propionyl-CoA.

Breakdown of valine is a multi-step process ultimately yielding propionyl-CoA.

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They Call The Stuff Urea

To the tune of "They Call The Wind Mariah"

Metabolic Melodies Website [HERE](#)

Get ATPs, bicarbonate,
Ammonia catalyzing
To make carba-mo-yl phosphate
And then start the synthesizing
When joined up with an ornithine
In THE mi-TOE-chon-DREE-a
It turns into a citrulline
When cycling to urea

Urea!

Urea!

They call the stuff urea!

On exit to the cytosol
There's bonding aspartat-ic
The argininosuccinate
Is produced in this schematic

Bid farewell to a fumarate
Amino panacea
Arises when the arginine
Gets lysed to form urea

Urea!

Urea!

You've just made some urea!

The body handles many things
Requiring its attention
Like balancing aminos for
Uremia prevention

So if there's excess nitrogen
It is a good idea

To rid yourself of surplus by
Producing some urea

Urea!

Urea!

Go out and take a pee, yeah!

Urea!

Urea!

Have yourself a pee, yeah!

T

Recorded by David Simmons
Lyrics by Kevin Ahern

I Studied So Hard Last Night

To the tune of "I Saw Her Again Last Night"

Metabolic Melodies Website [HERE](#)

I studied so hard last night
But you know that I couldn't
Get all the reactions down right
Oh my brain simply wouldn't

I made lots of tries
To memorize
But it seemed the more I read the book
I never learned

'Twas much too complex in my head
And so truly confusing
Like most of the things Ahern said
Awfully tough but amusing

I got so upset
That I would forget
Oh I had to find another way
Or I'd never learn

Bridge

Metabolic Melodies
The pathways I could sing in time
They all put my mind at ease
Using just the power of rhyme
My grades began to climb

I studied so hard last night
Now I'll never forget it
The Melodies helped get it right
Just the way Kevin said it

I won't get it wrong
If I sing along
And it makes me feel so good to know
I've truly learned

Lyrics by Kevin Ahern
No Recording Yet For This Song