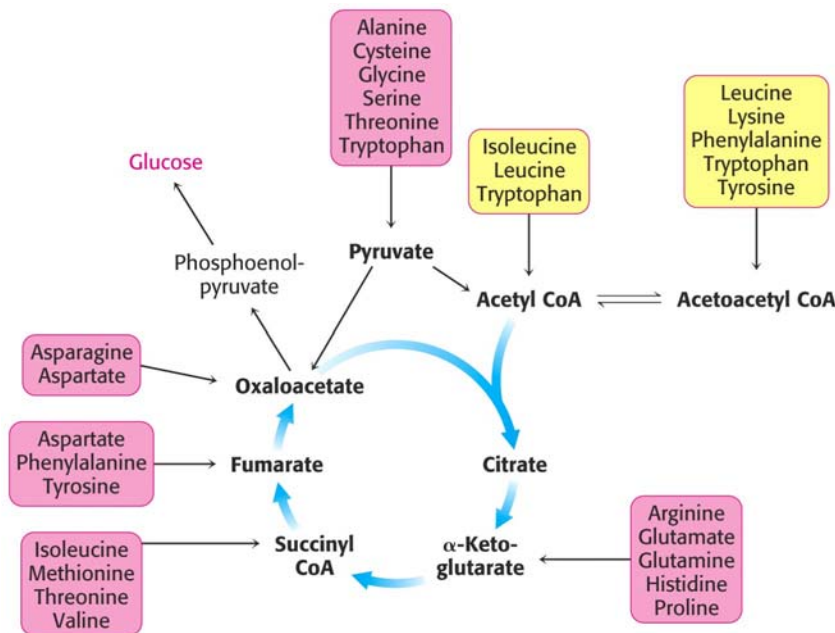


Amino Acid Degradation

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The carbon skeletons of amino acids are broken down into metabolites that can either be oxidized into CO_2 and H_2O to generate ATP, or can be used for gluconeogenesis. The catabolism of amino acids accounts for 10 to 15% of the human body's energy production. Each of the 20 amino acids has a separate catabolic pathway, yet all 20 pathways converge into 5 intermediates, all of which can enter the citric acid cycle. From the citric acid cycle the carbon skeletons can be completely oxidized into CO_2 or diverted into gluconeogenesis or ketogenesis.

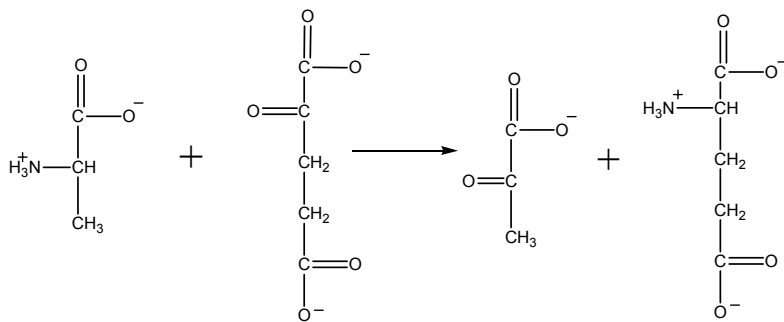


Glucogenic amino acids are broken down into one of the following metabolites: pyruvate, α -ketoglutarate, succinyl CoA, fumarate or oxaloacetate. Ketogenic amino acids are broken down into acetoacetate or acetyl-CoA. Larger amino acids, tryptophan, phenylalanine, tyrosine, isoleucine and threonine are both glucogenic and ketogenic. Only 2 amino acids are purely ketogenic they are lysine and leucine. If 2 of the amino acids are purely ketogenic and 5 amino acids are both ketogenic and glucogenic, than that leaves 13 amino acids that are purely glucogenic: Arg, Glu, Gln, His, Pro, Val, Met, Asp, Asn, Ala, Ser, Cys, and Gly.

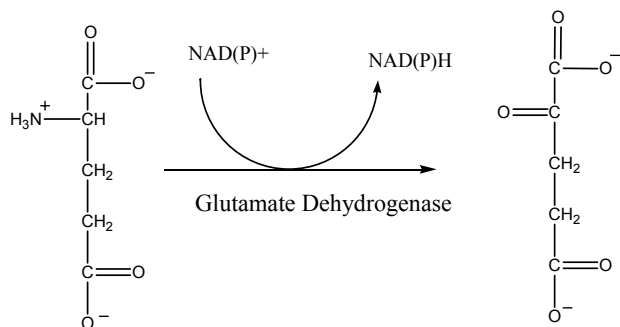
I. Amino Acids that are Catabolized into Pyruvate.

Pyruvate is the entry point for amino acids that contain 3 carbons, alanine, serine and cysteine.

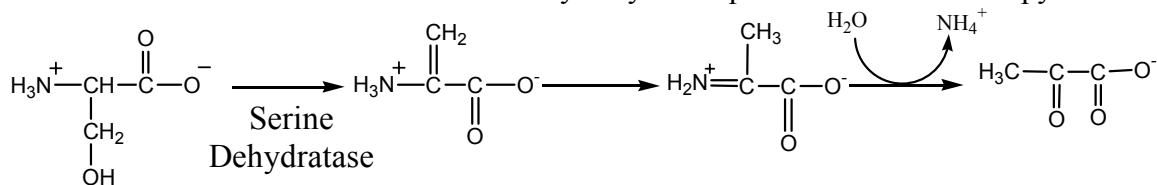
Alanine transaminase reversibly transfers the amino group from alanine to α -ketoglutarate to form pyruvate and glutamate. Note that enzyme requires a pyridoxal phosphate cofactor. The α -ketoglutarate is regenerated by glutamate dehydrogenase.



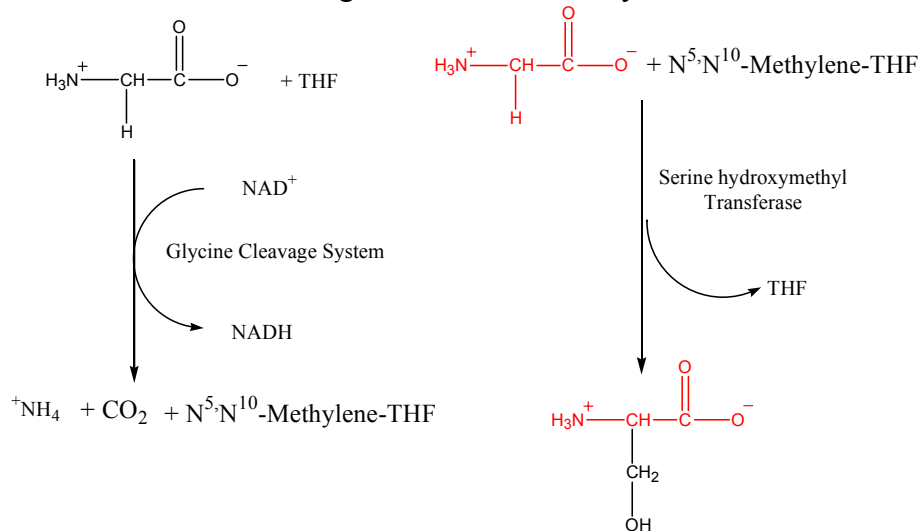
Alanine Transaminase



Serine dehydratase is another enzyme that requires a pyridoxal phosphate cofactor. This enzyme catalyzes the β -elimination of the hydroxyl group of serine to form an amino acrylate intermediate which tautomerizes into the imine which is then hydrolyzed to produce ammonia and pyruvate.

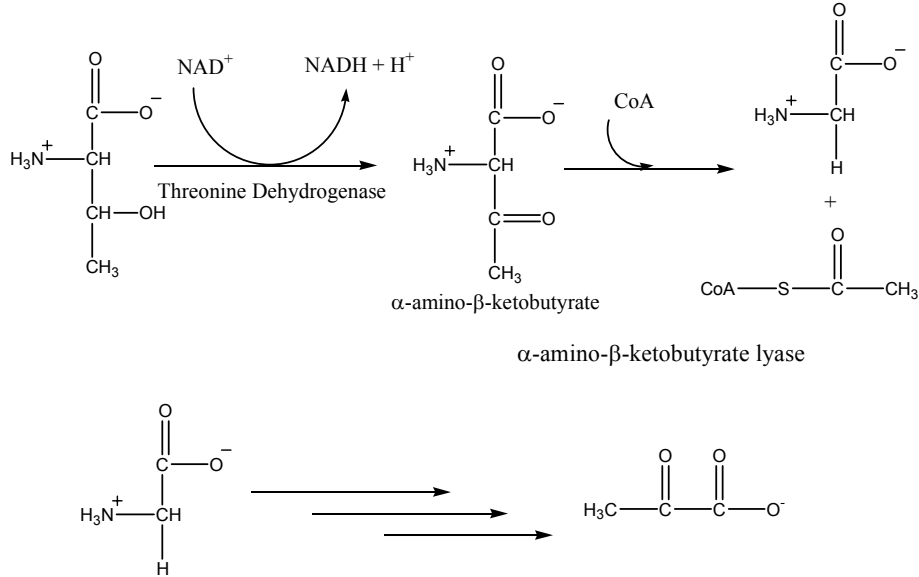


Glycine is converted into pyruvate via conversion of glycine to serine by serine hydroxymethyl transferase which is an incredibly interesting enzyme. It contains a pyridoxal phosphate cofactor and a N^5, N^{10} -methylene-tetrahydrofolate which is a cofactor we have not encountered yet. The N^5, N^{10} -methylene-tetrahydrofolate is produced by the glycine cleavage system which transfers a methylene group from glycine to THF. The THF cofactor is a one carbon acceptor and donor. We will discuss this cofactor further when we get to amino acid biosynthesis.



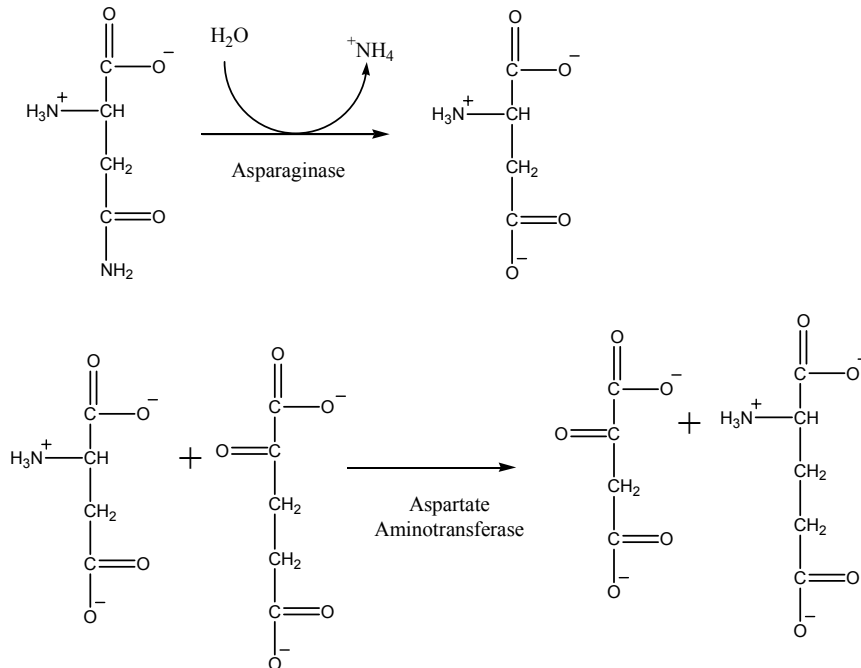
They are several pathways by which cysteine is converted into pyruvate. The three alkyl carbons of tryptophan are converted into alanine which is then converted by alanine transaminase into pyruvate.

Threonine is both glucogenic and ketogenic. There are a couple of routes for the degradation of threonine. The major route is shown below. Threonine is converted into acetyl CoA and glycine. Glycine is then converted into serine by serine hydroxymethyl transferase, and serine is then converted into pyruvate by serine dehydratase.

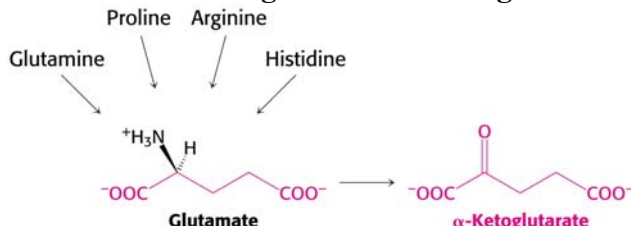


II. Amino Acids Degradated to Oxaloacetate

Aspartate and asparagines are both degraded into oxaloacetate. Asparagine is hydrolyzed into aspartate and ammonia by asparaginase. Aspartate is converted into oxaloacetate by aspartate amino transferase which is a PLP enzyme that transfers an amino group from aspartate to α -ketoglutarate to form glutamate and oxaloacetate.

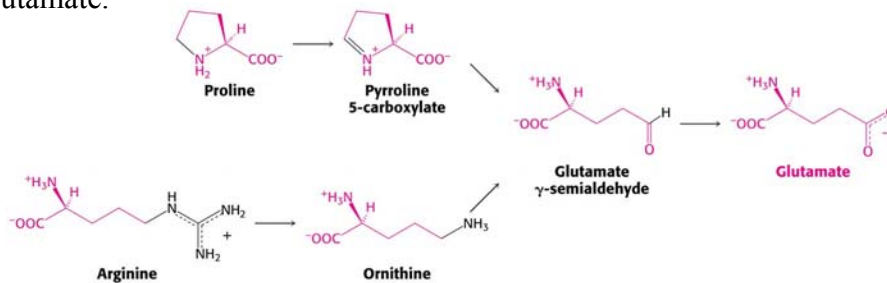


III. Amino Acids Degraded to α -Ketoglutarate.



Glutamine, proline, arginine and histidine are converted into glutamate which is then deaminated by a transaminase to form α -ketoglutarate.

Glutamine is converted into glutamate by glutaminase. Proline is oxidized by proline oxidase to form pyrroline 5-carboxylate which spontaneously hydrolyzes to form glutamate γ -semialdehyde. From the urea cycle we know that arginase converts arginine into ornithine and urea. Ornithine δ -aminotransferase transfers the δ -amino group of ornithine to α -ketoglutarate to form glutamate γ -semialdehyde and glutamate.



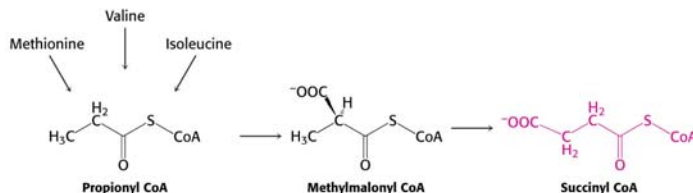
Glutamate γ -semialdehyde is oxidized to form glutamate by glutamate -5-semialdehyde dehydrogenase.

Histidine is deaminated by histidine ammonia lyase which forms urocanate. Urocanate hydratase adds water to form 4-Imidazolone-5-propionate which is hydrolyzed by imidazolone propionase to form N-formiminoglutamate. Glutamate formiminotransferase transfers the formimino group to tetrahydrofolate to generate glutamate and N⁵-formimino-THF.



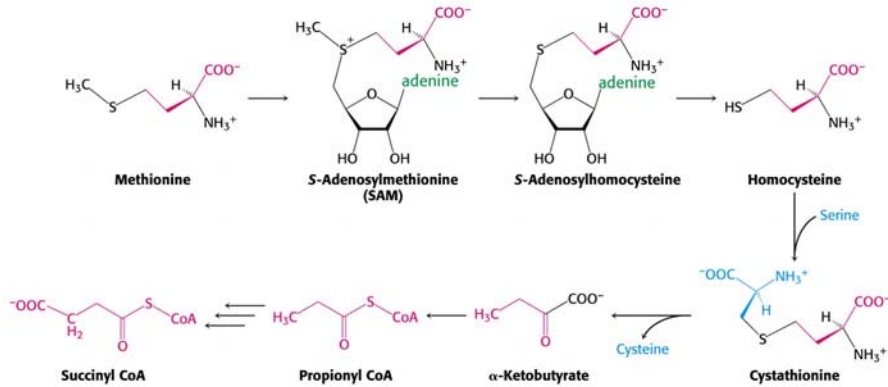
IV. Amino Acids that are Broken Down in Succinyl-CoA.

Methionine, valanine and isoleucine are broken down into propionyl CoA. By studying β -oxidation of odd chain fatty acids we know that propionyl CoA is converted into D-methylmalonyl CoA by propionyl CoA carboxylase. D-methylmalonyl CoA is racemized into L-methylmalonyl CoA by methylmalonyl CoA racemase. Methylmalonyl mutase produces succinyl CoA.



The degradation of methionine requires 9 steps. One of which involves the synthesis of S-adenosylmethionine (SAM). The methyl group of SAM is highly reactive making it an important methylating reagent. SAM is a common methyl-group donor in the cell. The degradation of methionine is shown on the next page.

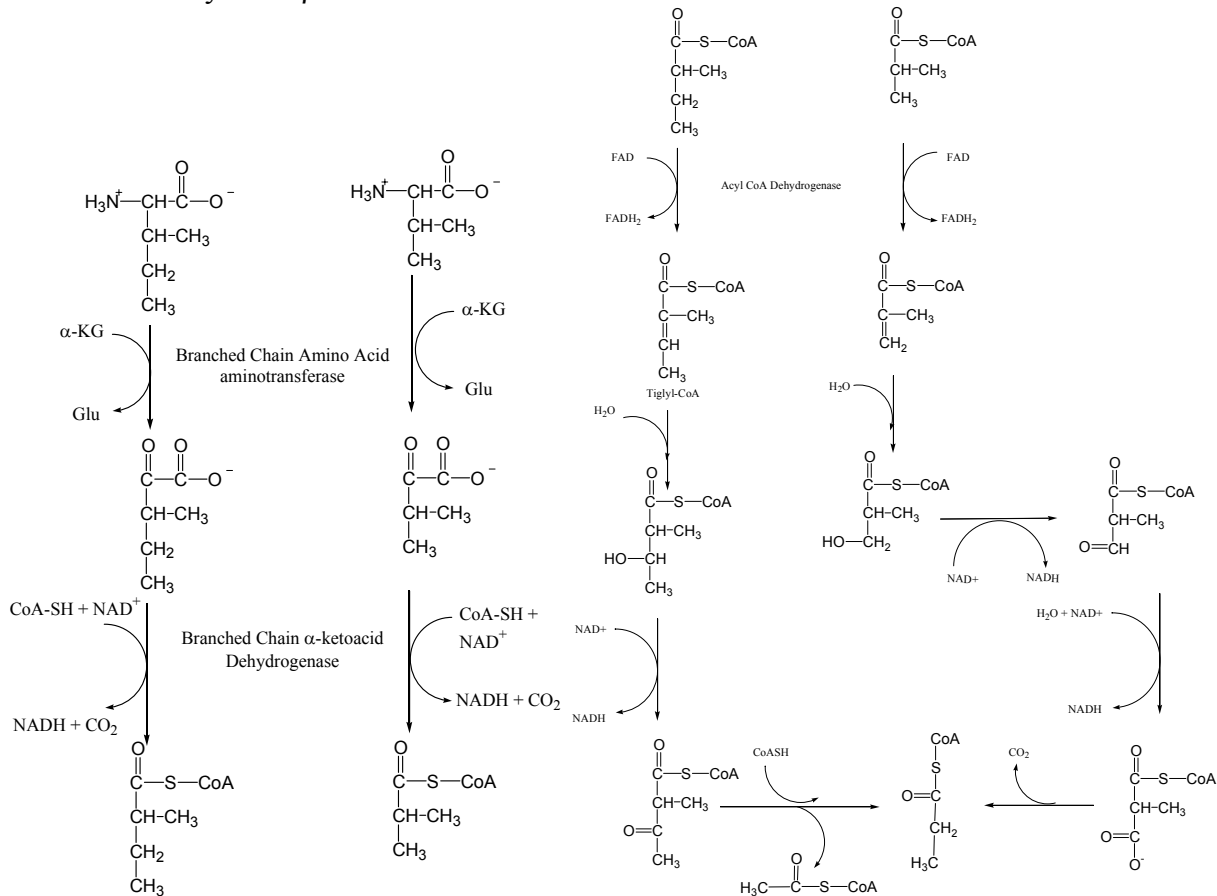
The first step is catalyzed by methionine adenosyl transferase which transfers the adenosyl group of ATP to the sulfur of methionine to form SAM. Sam methylase transfers the activated methyl group to an acceptor to form S-adenosylhomocysteine which is hydrolyzed by adenosylhomocysteinase to form homocysteine. Cystathionine β -synthase is a PLP dependent enzyme that catalyzes the condensation of a serine residue with homocysteine to form cystathionine.



Cystathionine γ -lyase cleaves cystathionine into cysteine and α -ketobutyrate. α -ketobutyrate is converted into propionyl CoA by α -ketobutyrate dehydrogenase which catalyzes a reaction that is analogous to pyruvate dehydrogenase and α -ketoglutarate dehydrogenase.

Branched Chain Amino Acids

The degradation of branched chain amino acids uses some of the enzymes we have already encountered in the citric acid cycle or β -oxidation.



Most amino acid catabolism occurs in the liver. The branched chain amino acids are not catabolized in the liver. Branched chain amino acids are catabolized mainly in the muscle, adipose, kidney and the brain. The liver does not contain the branched amino acid aminotransferase enzyme which these other tissues contain.

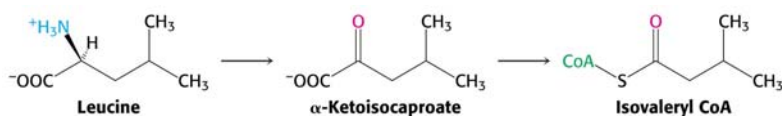
Branched chain α -ketoacid dehydrogenase is a huge multienzyme complex homologous to pyruvate dehydrogenase and α -ketoglutarate dehydrogenase. This enzyme contains a thiamine pyrophosphate cofactor, a lipoamide cofactor, a FAD prosthetic group. The chemistry, mechanism and structure of these enzymes is very similar.

Branched chain α -ketoacid dehydrogenase is phosphorylated by a kinase which inactivates the enzyme in a similar manner that pyruvate dehydrogenase is phosphorylated and inactivated. The intake of dietary branched amino acids activates a phosphatase which activates this enzyme.

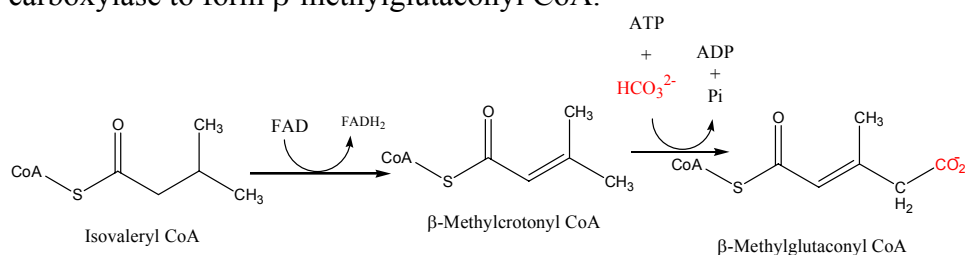
A genetic deficiency in the branched chain α -ketoacid dehydrogenase enzyme is called maple syrup urine disease. The deficiency causes an excessive buildup of branched α -ketoacids in the blood and the urine. The urine of these patients has the odor of maple syrup and hence the name of the disease. Maple syrup disease usually leads to mental retardation unless the patient is placed on diet that is low in valine, isoleucine and leucine early in life.

V. Amino Acids that are degraded into Acetyl CoA and Acetoacetate.

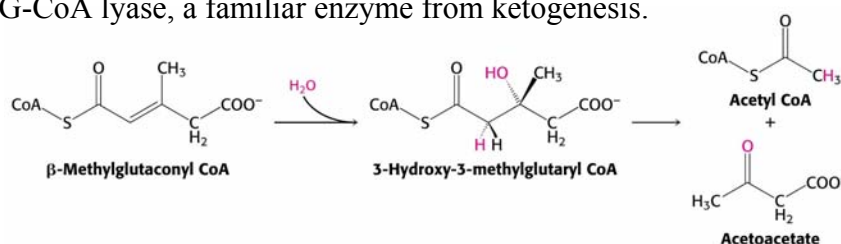
There are only two amino acids that are purely ketogenic, lysine and leucine. Leucine catabolism is similar to the branched amino acids valine and isoleucine.



First leucine is transaminated by branched amino acid aminotransferase to form α -ketoisocaproate which is then oxidatively decarboxylated to form isovaleryl CoA by the branched chain α -ketoacid dehydrogenase complex we just discussed. In the next step isovaleryl CoA is dehydrogenated to form β -methylcrotonyl CoA. The enzyme that catalyzes this dehydrogenation is isovaleryl CoA dehydrogenase. β -methylcrotonyl CoA is then carboxylated by a biotin containing enzyme called methylcrotonyl CoA carboxylase to form β -methylglutaconyl CoA.

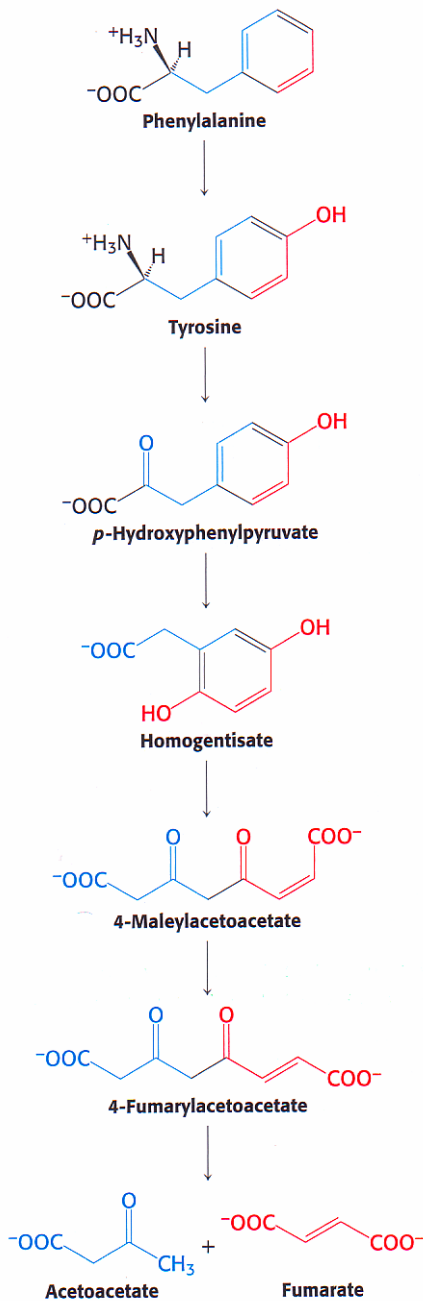


β -methylglutaconyl CoA is then hydrated by β -methylglutaconyl CoA hydratase to form β -hydroxy- β -methylglutaryl CoA which is then cleaved into acetyl CoA and acetoacetate. The enzyme that catalyzes the last step is HMG-CoA lyase, a familiar enzyme from ketogenesis.



If you are curious the pathway for the catabolism of lysine is shown in the text on page 630. The carbons of lysine end as acetyl CoA and acetoacetate.

VI. Catabolism of Aromatic Amino acids.

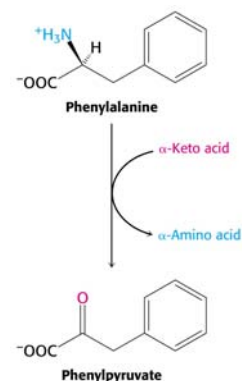


- The degradation of aromatic amino acids requires molecular oxygen to break down the aromatic rings.
- The degradation of phenylalanine begins with a monooxygenase, phenylalanine hydroxylase which adds a hydroxyl group to phenylalanine to form tyrosine.
- Tyrosine aminotransferase deaminates tyrosine to form p-hydroxyphenylpyruvate.
- p-hydroxyphenylpyruvate dioxygenase catalyzes the formation of homogentisate.
- Homogentisate 1,2-dioxygenase catalyzes the formation of maleylacetoacetate.
- Maleylacetoacetate isomerase produces fumarylacetoacetate.
- Fumarylacetoacetase produces fumarate and acetoacetate.

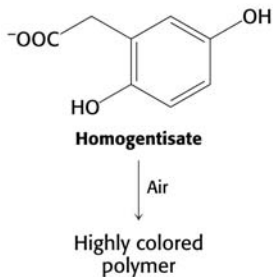
Many genetic defects of phenylalanine catabolism in humans has been identified.

A deficiency in phenylalanine hydroxylase is responsible for the disease phenylketonuria (PKU) which is caused by elevated concentrations of phenylalanine.

Individuals with a deficiency in phenylalanine hydroxylase rely on a secondary catabolic pathway which in normal individuals is not used. In this pathway phenylalanine is converted into phenylpyruvate by a transaminase which transfers the amino group to pyruvate to form alanine. Phenylalanine and phenylpyruvate accumulate in the blood and excreted in the urine hence the term phenylketonuria. Some of the phenylpyruvate is decarboxylated to form phenylacetate. Some of the phenylpyruvate is reduced to phenyllactate. Phenyllactate gives the urine a distinctive odor used for diagnosis.

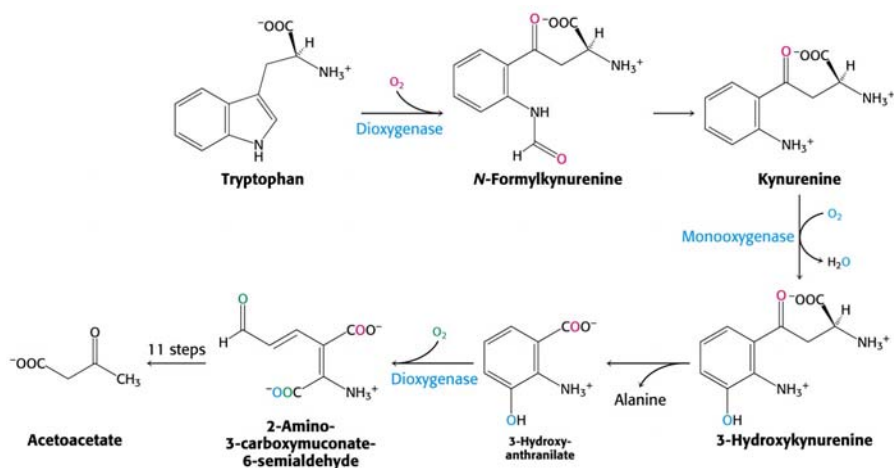


The high concentration of phenylalanine in the blood limits the transport of amino acids across the blood-brain barrier resulting in impairment of normal brain development, causing severe mental retardation. This can be avoided by early detection and rigid dietary control. The diet must only provide enough phenylalanine and tyrosine to meet the needs of protein synthesis.



Alkaptonuria is another inheritable disease of phenylalanine catabolism. In this case the defective enzyme is homogentisate dioxygenase. This disease is less severe than PKU. Large amounts of homogentisate are excreted in the urine. The oxidation of homogentisate turns the urine black. Individuals who have this disease develop arthritis at an early age.

Tryptophan catabolism is shown below:



Like phenylalanine catabolism, dioxygenases are required to catabolize the aromatic rings.