Amino acid breakdown

Amino acids comprise one of the three major energy sources for animals. They are an especially important energy source for carnivorous animals, and for all animals during early starvation (*i.e*. after glycogen has been depleted but before ketone body production has been induced). Herbivores tend to obtain most of their energy from carbohydrates, which are generally more abundant in plants than other energetic molecules.

Amino acids are of variable importance as an energy source for microorganisms: microorganisms will use any available energy source based entirely on availability. In contrast, plants use carbohydrates for energy; their breakdown of amino acids is performed as part of the biosynthesis of other molecules, and not for energy.

Free amino acids are not stored. Therefore, in all organisms, amino acid breakdown occurs whenever amino acid levels exceed requirements for synthetic processes.

Absorption

For animals dietary nitrogen is present primarily in the form of proteins. Free amino acids are normally not present; health food stores sell free amino acids, but free amino acids in bulk form are usually poorly absorbed.

Dietary proteins are degraded by digestive proteases, beginning in the stomach and continuing in the small intestine. The small peptides and free amino acids are then absorbed by the intestinal cells and transported in the blood to the tissues.

In humans, plant proteins may not be entirely adequate to support normal metabolism. This is because plants and humans require a different distribution of amino acids, and therefore many dietary plants are low in some essential amino acids (especially lysine and methionine). In addition, the cellulose content of plants frequently inhibits digestion and absorption of the plant protein.

Ammonium transport

Free ammonium is not transported in the blood. Instead, ammonium is transported in the form of amino acids and proteins, and for excretion, in the form of purines and urea. The most important amino acids used for ammonium transport are glutamate, glutamine, and alanine.

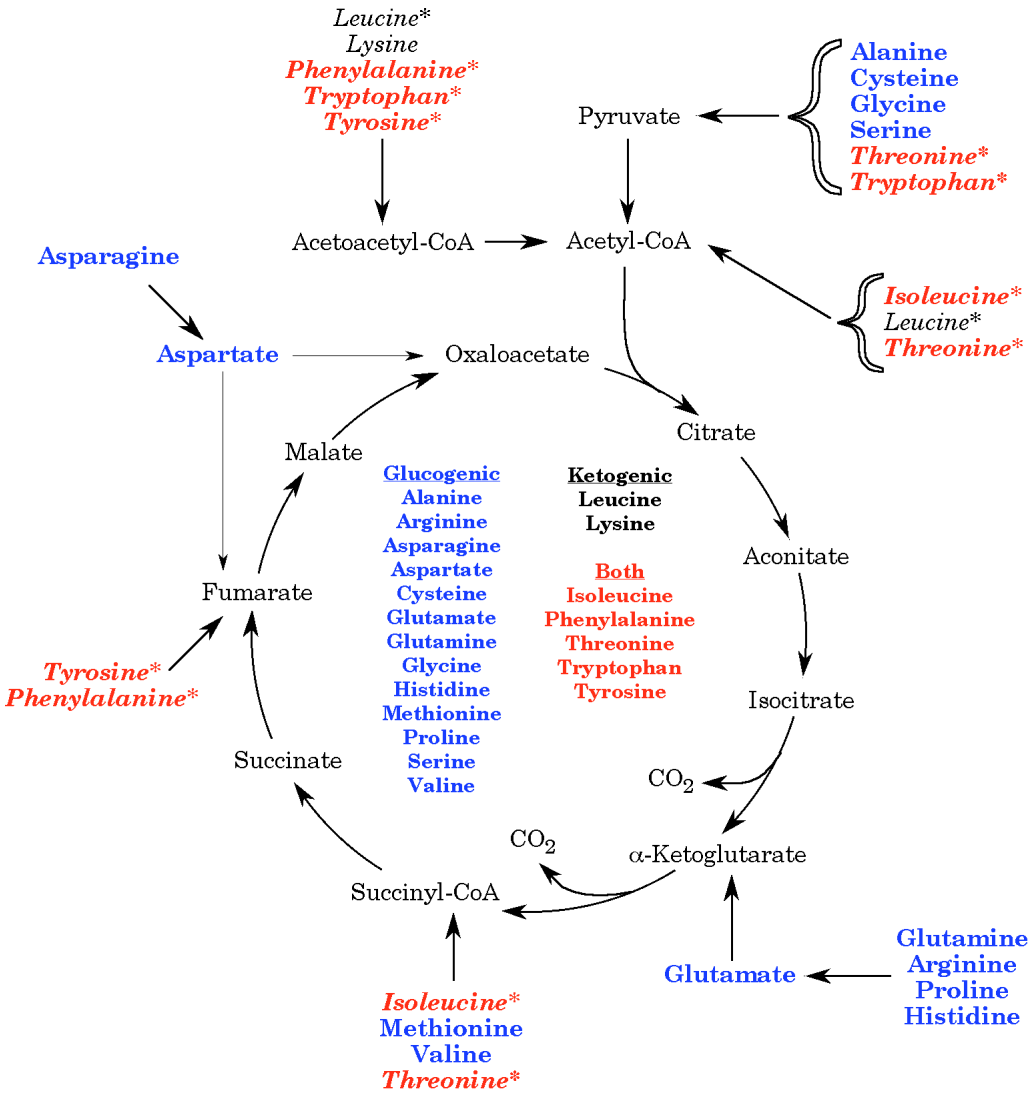
Amino acid breakdown for energy

Amino acid catabolism is critically important. There are two reasons for this: 1) amino acids are a potential source of energy, and especially during fasting, of glucose, and 2) incomplete metabolism of a number of amino acids results in accumulation of toxic amino acid breakdown intermediates.

When considering their degradation, amino acids are generally divided into two classes. The term **glucogenic** refers to amino acids with a carbon skeleton that can be converted to a gluconeogenic or TCA cycle intermediate. These amino acids can be used to synthesize glucose. The term **ketogenic** refers to amino acids with a

carbon skeleton that can only be converted to acetyl CoA, to acetoacetyl-CoA, or to acetoacetate. The ketogenic amino acids are a potential source of ketone bodies (hence the name "ketogenic"), but cannot be used to synthesize glucose. Some amino acids fall into both categories.

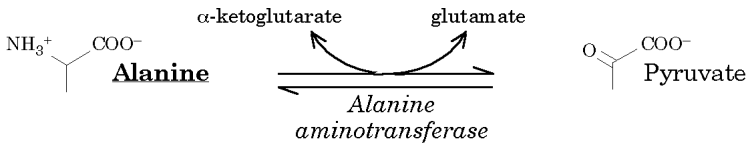
The diagram below summarizes the conversion of the twenty standard amino acids into compounds that can be used for energy. Note that some of the amino acids are converted into more than one metabolite; these amino acids are indicated by an asterisk in the figure.



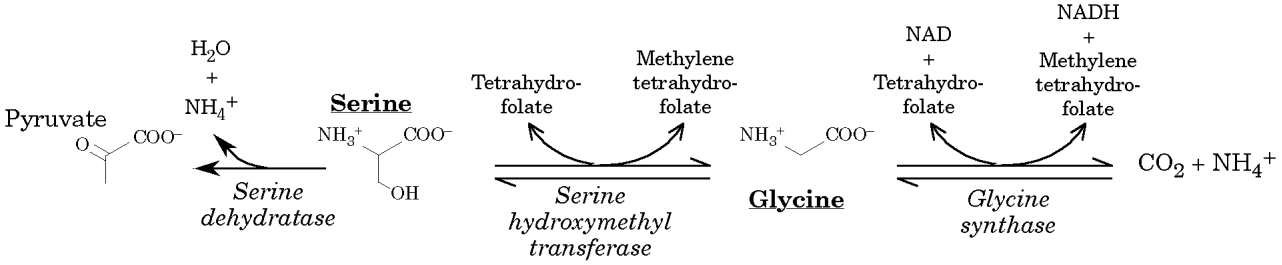
The amino acids are also frequently divided into families, based on the type of amino acid, or the final product formed from the amino acid.

C3 Family: amino acids convertible to pyruvate

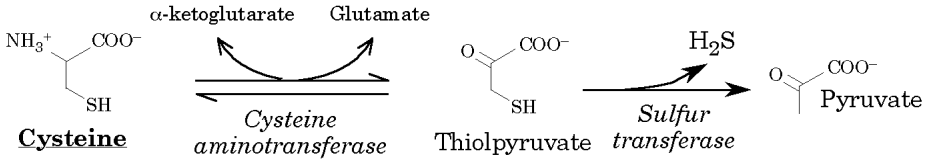
Alanine is converted directly to pyruvate by an aminotransferase reaction.



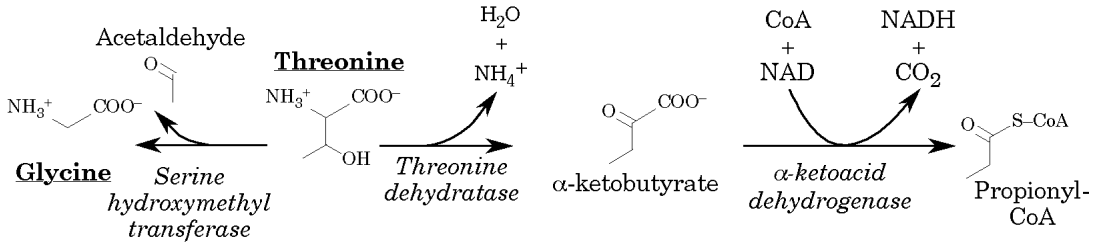
Serine can be converted to pyruvate by **serine dehydratase**; this reaction is common in some animals, but is a relatively minor pathway in humans. In humans the main pathway for metabolism of both **serine** and **glycine** is the conversion of serine to glycine by **serine hydroxymethyltransferase**, and glycine to carbon dioxide and ammonium by **glycine synthase**. These reactions both generate methylene tetrahydrofolate, which can then be used for other biosynthetic processes. This pathway therefore requires free tetrahydrofolate. Both reactions are reversible; if methylene tetrahydrofolate is available, serine levels tend to increase, and serine may be converted to pyruvate.



Cysteine can be metabolized by more than one pathway, generally producing pyruvate as the end product. These pathways begin with an aminotransferase reaction that removes the ammonium. The next steps vary depending on the organism and on conditions. The best-characterized pathway releases the toxic hydrogen sulfide (as shown below); other, less well-understood pathways appear to release sulfate.



Threonine can be converted to **glycine** by **serine hydroxymethyltransferase** (the same enzyme that converts serine to glycine; in both reactions, this pyridoxal phosphate-dependent enzyme catalyzes the cleavage of the bond between the α- and β-carbons); in this case, the reaction involves the loss of acetaldehyde, which can be converted to acetyl CoA. The enzymes mentioned above then metabolize the glycine formed. This means that threonine can be used as a source of either glycine or serine. The reverse, however, is not true; humans cannot synthesize threonine.



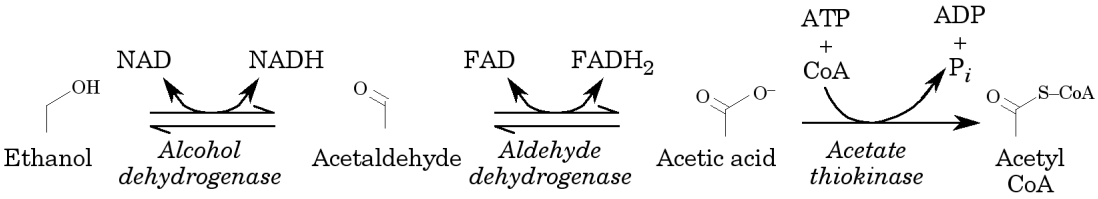
Threonine can also be converted to α-ketobutyrate by **threonine dehydratase**; the four-carbon α-ketobutyrate is converted to the three-carbon propionyl-CoA by α-ketoacid dehydrogenase, an enzyme complex similar to pyruvate dehydrogenase. The α-ketoacid dehydrogenase reaction is driven by the loss of carbon dioxide.

Threonine can therefore be both glucogenic and ketogenic: breakdown of threonine results in either synthesis of the ketogenic acetyl CoA and the potentially glucogenic glycine, or in the production of the glucogenic propionyl-CoA.

Side Note: Ethanol and Acetaldehyde

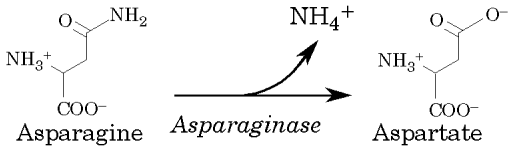
Acetaldehyde is produced by the action of serine hydroxymethyltransferase on threonine. It is also produced from ethanol by alcohol dehydrogenase. Acetaldehyde is mildly toxic. In addition, the reduction of NAD to NADH by alcohol dehydrogenase can inhibit gluconeogenesis by inhibiting the conversion of lactate to pyruvate, resulting in lactate accumulation, and decreased plasma pH. These and other factors can result in liver damage following chronic ethanol ingestion.

The liver has more than one pathway for metabolism of ethanol. One major pathway for the conversion of ethanol or acetaldehyde to acetyl-CoA is shown below.



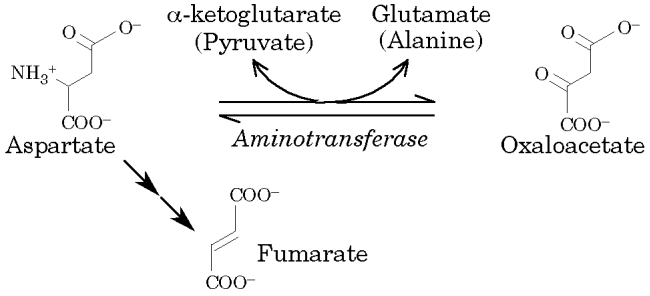
C4 Family: amino acids convertible to oxaloacetate

Asparagine is converted to **aspartate** by release of free ammonium in a reaction catalyzed by **asparaginase**.



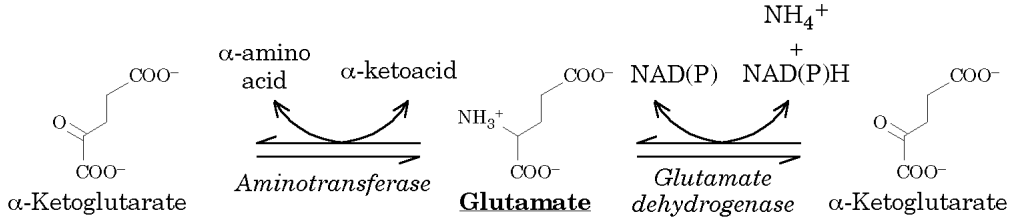
Aspartate is converted to oxaloacetate by a variety of aminotransferases. However, aspartate can also be converted to fumarate as part of the urea cycle, and in the

adenylosuccinate lyase reaction of the adenosine biosynthesis pathway.

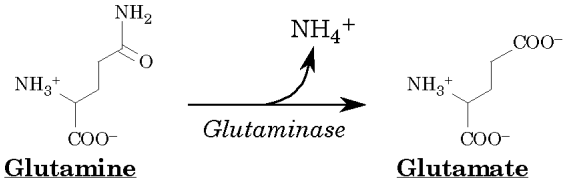


C5 Family: amino acids convertible to α-ketoglutarate

Glutamate can be converted to α-ketoglutarate, either by release of free ammonium in the **glutamate dehydrogenase** reaction, or by transamination reactions catalyzed by any of a large number of aminotransferases. These reactions are key steps in metabolism of nearly all of the amino acids, and are critical in nitrogen metabolism. Glutamate is also an intermediate in the breakdown of all of the other C5 family amino acids.



Glutamine is converted to glutamate by **glutaminase**. Glutaminase and glutamate dehydrogenase are the two most important enzymes used for releasing free ammonium from amino acids.

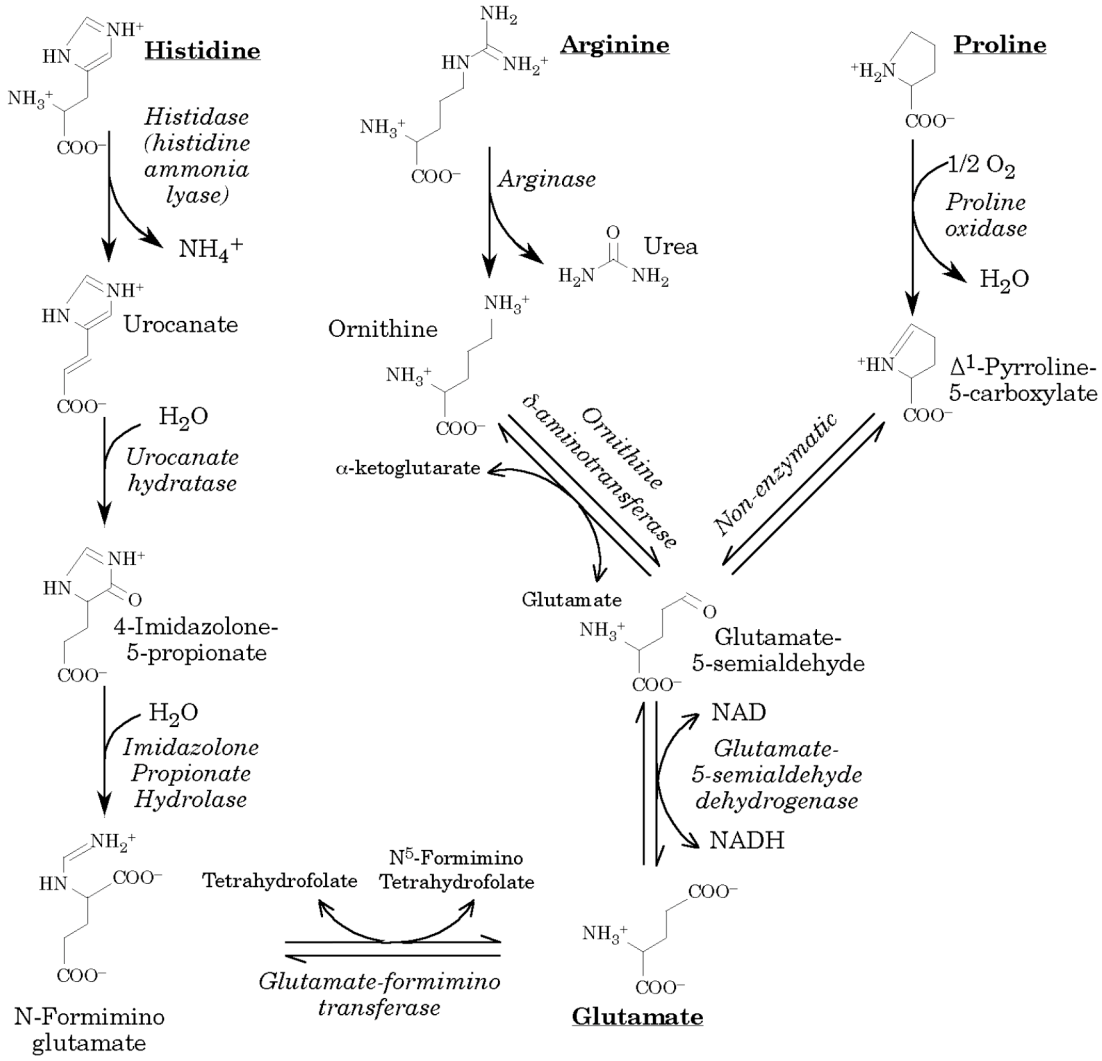


Arginine is converted to ornithine in the urea cycle. Because the urea cycle is a cycle, net breakdown of arginine by the urea cycle requires net breakdown of ornithine. Ornithine can be converted to glutamate-5-semialdehyde by **ornithine δ-aminotransferase**, an unusual type of aminotransferase that transfers the δ-amino group of ornithine to the δ-carbon of α-ketoglutarate. Glutamate-5-semialdehyde is then converted to glutamate by **glutamate-5-semialdehyde dehydrogenase**.

Proline is converted to glutamate by two enzymes that essentially reverse the synthesis pathway. The first enzyme, proline oxidase uses molecular oxygen to

create the Schiff base, which allows the opening of the ring in a non-enzymatic process to form glutamate-5-semialdehyde.

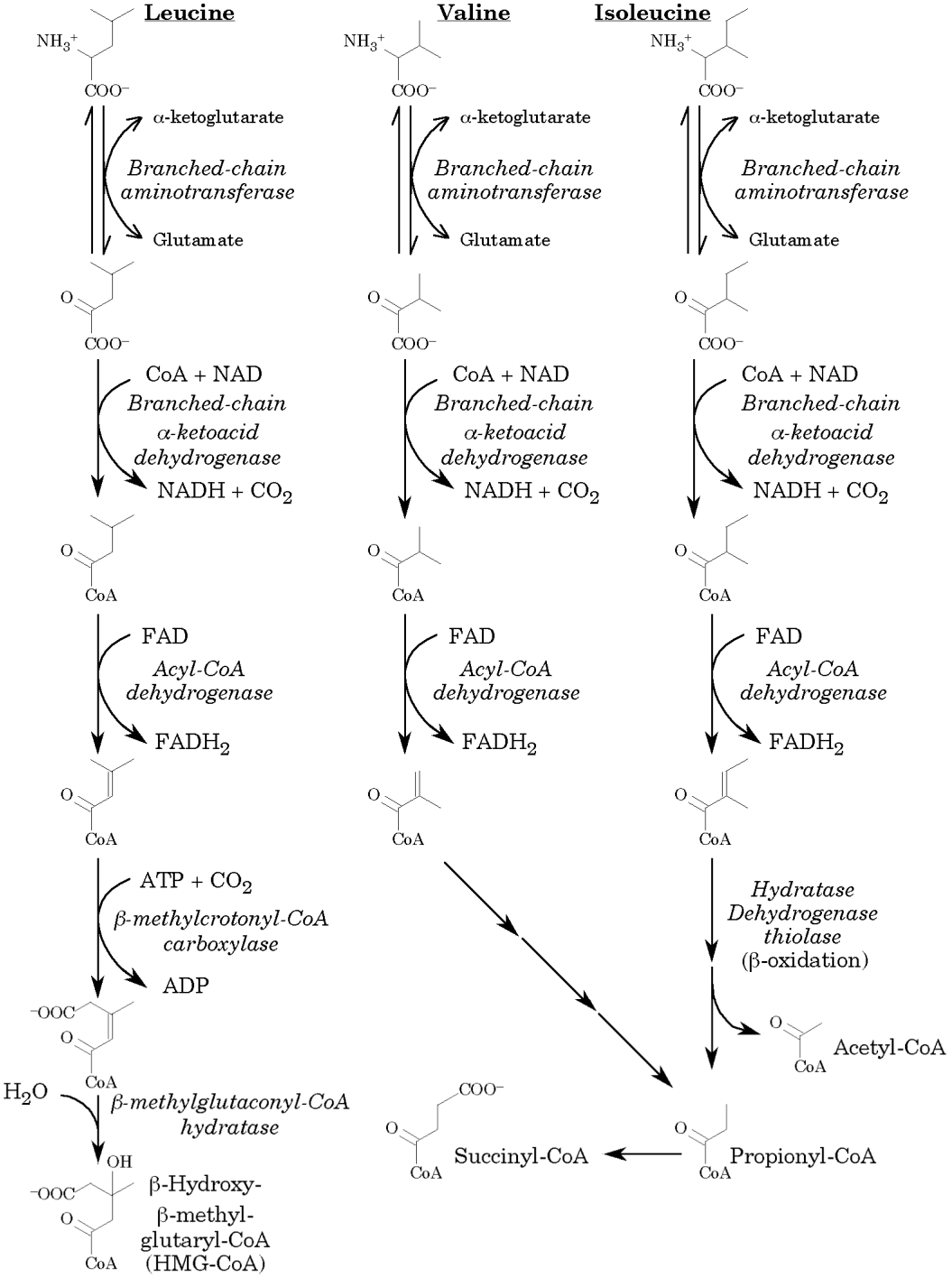
Histidine breakdown is more complex, and involves a significant rearrangement; the α-carboxylate group of histidine becomes the α-carboxylate of the glutamate product of the pathway. The final step in the production of glutamate results in formation of N^5-formimino tetrahydrofolate, another tetrahydrofolate derivative used for some biosynthetic reactions.



Branched-chain amino acids

The branched-chain amino acids **valine**, **isoleucine**, **leucine** are metabolized by similar pathways. (Note: threonine also contains a β-branch, but it is broken down in other pathways.) The first step is a reversible transamination reaction catalyzed by **branched-chain aminotransferase**. The second step is catalyzed by an enzyme complex similar to the pyruvate dehydrogenase complex, and results in branched-chain coenzyme A derivatives, with the α-carboxylate lost as carbon dioxide. The third step is a dehydrogenase reaction similar to the first step in fatty acid β-oxidation.

Because the same enzymes catalyze these initial steps, a defect in one enzyme results in elevated levels of partial breakdown products from all three amino acids. A deficiency in branched-chain □-ketoacid dehydrogenase complex results in severe neurological problems and death unless treated. The urine of affected individuals smells like maple syrup, hence the name Maple Syrup Urine Disease.

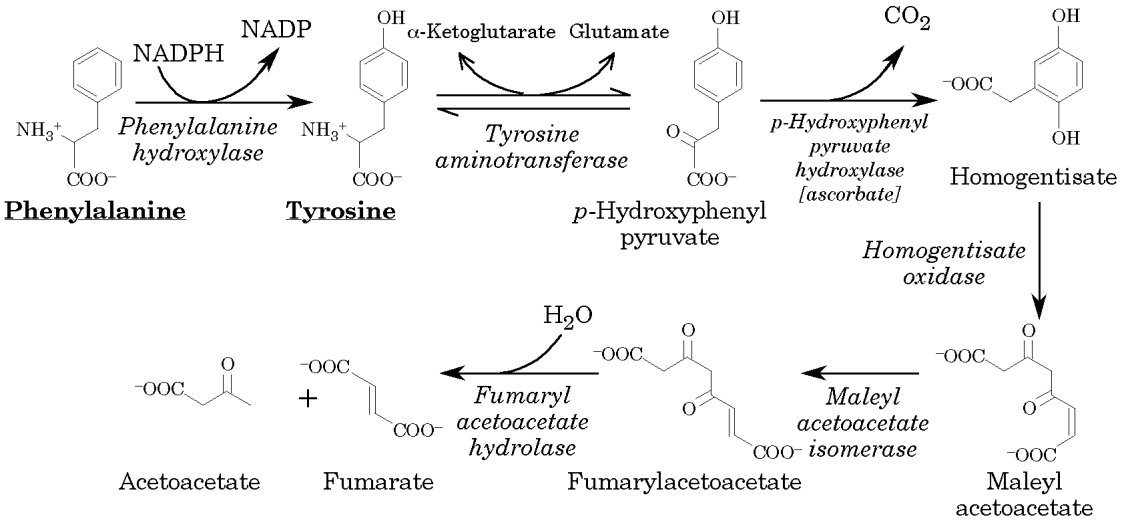


The later steps vary depending on the structure of the amino acid. **Isoleucine** is metabolized by reactions identical to those in a β-oxidation spiral, yielding an acetyl-CoA and a propionyl-CoA. The metabolism of **valine** is slightly more complex, but the pathway also results in propionyl-CoA. Propionyl-CoA is converted to the TCA cycle intermediate succinyl-CoA; these amino acids can therefore be used to synthesize glucose. Isoleucine is both glucogenic and ketogenic, because it also results in acetyl-CoA formation.

Leucine is converted to HMG-CoA (the ketone body precursor), and is then metabolized by cellular pathways that use HMG-CoA as an intermediate; **leucine is thus a purely ketogenic** amino acid. One of the enzymes in the leucine breakdown pathway, **β-methylcrotonyl-CoA carboxylase**, is the fourth **biotin-dependent** enzyme in humans. Biotin is thus critical for branched-chain amino acid metabolism; both conversion of propionyl-CoA to succinyl-CoA and conversion of leucine to HMG-CoA require biotin-dependent enzymes.

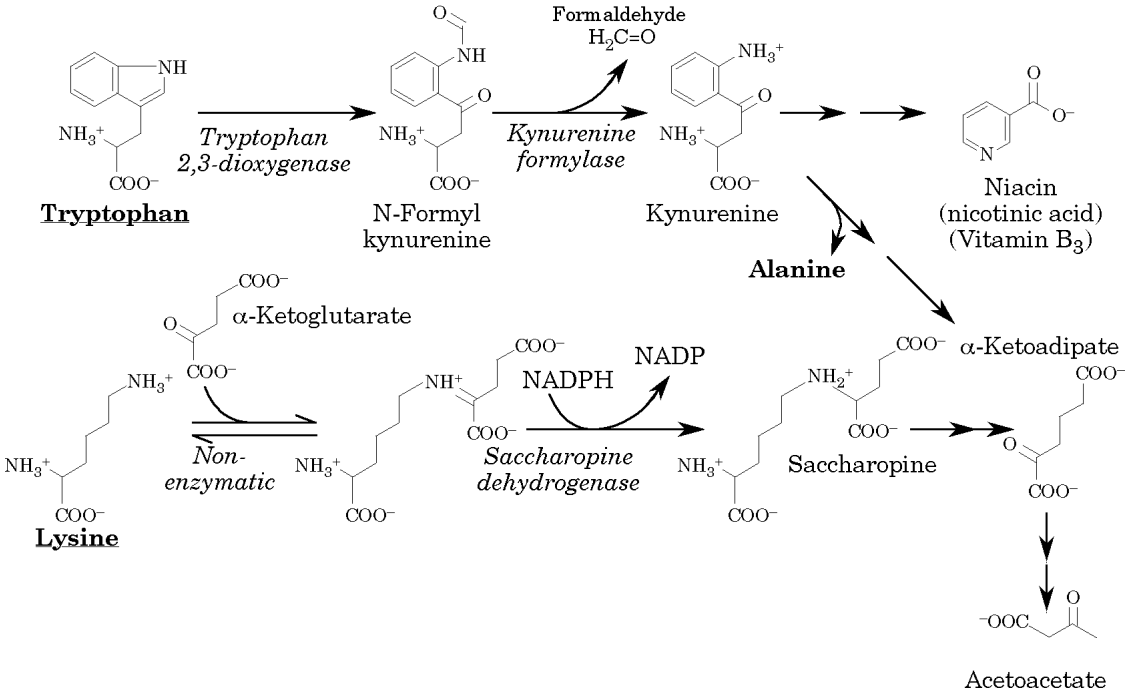
Aromatic amino acids and Lysine

Phenylalanine is converted to tyrosine by **phenylalanine hydroxylase**. This step is essential both in the production of tyrosine from phenylalanine, and in the breakdown of phenylalanine. A genetic deficiency in phenylalanine hydroxylase causes **phenylketonuria**, a moderately rare disorder (~1 in 10,000 live births) in which phenylketones such as phenylpyruvate accumulate to the point that they become detectable in the urine. Phenylketones interfere with brain development; untreated individuals with phenylketonuria experience irreversible abnormalities in brain functioning. Treatment involves a diet with strict limitations on phenylalanine levels. After the age of about ten, the brain development is essentially complete, and dietary restrictions are less critical. Because phenylketones are readily detectable, and because the effects of untreated phenylketonuria are so severe, in the United States screening for phenylketonuria is routinely performed at birth. The disorder phenylketonuria illustrates the fact that the ascorbate-dependent enzyme ***p*-Hydroxyphenyl pyruvate hydroxylase** requires the hydroxyl on the aromatic ring for activity.



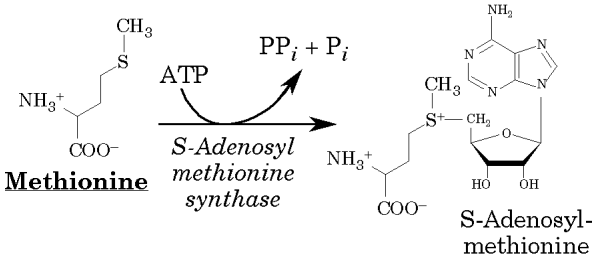
Tyrosine, like **phenylalanine,** is converted to the TCA cycle intermediate fumarate and the ketone body acetoacetate. After the phenylalanine hydroxylase step the pathways for tyrosine and phenylalanine breakdown are identical.

Tryptophan is degraded via a complicated pathway. The indole ring (*i.e.* the fused nitrogen-containing ring of tryptophan) can be converted to niacin or to acetoacetate (via α-ketoadipate). Conversion to niacin is inefficient, with only small amounts of this compound being formed; niacin is a vitamin because tryptophan breakdown levels are generally too low to support sufficient niacin synthesis. The carbon backbone of tryptophan is converted to alanine (and then to pyruvate). All three **aromatic amino acids are therefore both glucogenic and ketogenic**.



Lysine is converted to acetoacetate, and is thus **ketogenic**. The first step in the pathway is a non-enzymatic formation of a Schiff base to the ketone of α-ketoglutarate. This part of the molecule is later released as glutamate; in effect the pathway uses a transamination to remove the α-amino group of lysine, although the process requires multiple reactions. The α-amino group is also given to α-ketoglutarate in an aminotransferase reaction. The remainder of the pathway converges with the indole degradation pathway at the intermediate α-ketoadipate. The double arrow from α-ketoadipate to acetoacetate represents a series of seven different reactions. (Note: some evidence suggests that lysine is broken down by other pathways to glucogenic compounds; however, the major pathway for lysine breakdown results in the ketone body acetoacetate.)

Methionine is metabolized by conversion to S-adenosylmethionine. The S-adenosylmethionine is then used for either methyl donor functions or as part of polyamine synthesis (a process which uses essentially the entire carbon skeleton of methionine). The homocysteine produced from S-adenosylmethionine is used to produce cysteine. If the goal is amino acid breakdown, the sulfur is metabolized using cysteine as an intermediate. The remainder of the methionine carbon skeleton is converted to propionyl-CoA.



Summary

Amino acids are a major energy source, especially during conditions in which glucose availability is limited. Most of the amino acids can be used as substrates for gluconeogenesis, and are termed glucogenic. In contrast leucine and lysine are converted to ketone bodies or to acetyl-CoA, and are therefore termed ketogenic. The three aromatic amino acids, threonine, and isoleucine are converted into both gluconeogenic compounds and ketogenic compounds, therefore are both glucogenic and ketogenic.

The amino acids are grouped into families. The **C3 family** (alanine, serine, glycine, threonine, and cysteine) can all be converted to the 3-carbon □-ketoacid pyruvate, although some are converted to other molecules under appropriate conditions.

The **C4 family** (aspartate and asparagine) are converted to the 4-carbon compounds oxaloacetate or fumarate.

The branched-chain amino acids (leucine, isoleucine, and valine) are broken down by a series of common enzymes into coenzyme A derivatives. These are then metabolized by separate pathways depending on the structure of the original compound. Leucine is converted into HMG-CoA, the substrate for ketone body production, and is exclusively ketogenic. Valine is converted to propionyl-CoA and is exclusively glucogenic. Isoleucine is converted to acetyl-CoA and propionyl-CoA, and is therefore both ketogenic and glucogenic.

The **C5 family** (glutamate, glutamine, histidine, proline, and arginine) are all converted to glutamate, and then to □-ketoglutarate.

The aromatic amino acids phenylalanine and tyrosine result in formation of acetoacetate and fumarate, while tryptophan results in formation of acetoacetate and (via alanine) pyruvate. Each of these compounds is therefore both ketogenic and glucogenic.

Lysine is broken down by a pathway that is related to that for the tryptophan indole ring, and forms acetoacetate.

Methionine is used to produce a variety of biosynthetic intermediates; it can be converted into propionyl-CoA, and is therefore glucogenic.