



Lysine: biosynthesis, catabolism and roles

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Abstract

Amino acids are an essential building block of all life and are commonly incorporated into extending polypeptide chains to produce proteins. Lysine is one such amino acid and is classified as basic and positively charged at physiological pH due to the presence of an additional amino chemical group on the side chain. Lysine has two main biosynthetic pathways, namely the diaminopimelate and α -aminoadipate pathways, which employ different enzymes and substrates and are found in different organisms. Lysine catabolism occurs through one of several pathways, the most common of which is the saccharopine pathway. Lysine plays several roles in humans, most importantly proteinogenesis, but also in the crosslinking of collagen polypeptides, uptake of essential mineral nutrients, and in the production of carnitine, which is key in fatty acid metabolism. Furthermore, lysine is often involved in histone modifications, and thus, impacts the epigenome. Due to the importance of lysine in several biological processes, a lack of lysine can lead to several disease states including; defective connective tissues, impaired fatty acid metabolism, anaemia, and systemic protein-energy deficiency. In juxtaposition to this, an overabundance of lysine, caused by ineffective catabolism, can cause severe neurological issues.

Introduction

Lysine (abbreviated as Lys or K), is an α -amino acid used for protein biosynthesis (proteinogenesis). There are many different kinds of amino acids, but only twenty are used universally by all forms of life for protein synthesis (i.e., proteogenic amino acids). The process of translation is how proteins are synthesised and lysine is added at the codons AAA and AAG. Lysine is an essential amino acid to all animals, including

Plain language summary

Proteins are key biomolecules found in all life and are composed of smaller structural units called amino acids. There are twenty amino acids found in all domains of life that are incorporated into proteins. These amino acids are composed of three key features, namely a carboxyl group (-COOH), an amino group (-NH₂), and side chain (-R-group). One such amino acid, lysine, is classified as a basic and positively charged amino acid, due to the presence of an -NH₃⁺ located on the R-group. Lysine is considered essential in animals and, thus, must be obtained through dietary sources. Plants, bacteria, and fungi can biosynthesise their own lysine. There are two biosynthesis pathways that can generate lysine; the diaminopimelate and the α -aminoadipate pathways. Whilst animals lack the biosynthesis machinery necessary to produce lysine, all organisms are capable of breaking down lysine into alternative biomolecules. The most common pathway for the breakdown of lysine is the saccharopine pathway that yields molecules used in the tricarboxylic acid cycle, which is a key carbon metabolic pathway found in all organisms. Lysine also plays several roles in human health and disease and, thus, an adequate amount of lysine must be obtained from the diet, which is commonly exceeded in western culture. Lysine has a primary role as a building block for proteins, however it also plays other key roles including in the structural protein, collagen, in calcium homeostasis, and in fatty acid metabolism. In addition to this, lysine plays an important role in epigenetics, as lysine is commonly the site of histone modification by addition or removal of a chemical or protein group. There are several disease states associated with either a lack or overabundance of lysine. There needs to be a delicate balance of all metabolites in living organisms and lysine is no exception, with a lack of lysine leading to symptoms such as anaemia, impaired fatty acid metabolism, and altered connective tissue properties as well as systemic affects due to protein-energy malnutrition. Conversely, the overabundance of lysine in plasma can be asymptomatic or lead to several debilitating neurological disorders, including psychomotor impairment, epilepsy, and ataxia.

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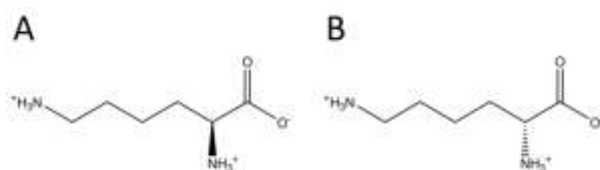


Figure 1 | Structure of lysine enantiomers at physiological pH. Lysine can exist as one of two enantiomers, namely (A) *L*-lysine and (B) *D*-lysine.

humans, and therefore must be obtained through dietary intake.^{[1][2]} Bacteria, archaea, fungi, some protista (euglenids), and plants, on the other hand, are able to synthesise lysine. The organisms that are able to synthesise lysine can be thought of as the primary producers, on which all animals are dependent for their nutritional lysine requirement.

The free form of lysine kept at physiological pH contains a protonated α -amino group ($-\text{NH}_3^+$), a deprotonated α -carboxylic acid group ($-\text{COO}^-$), and a protonated ϵ -amino side chain ($-(\text{CH}_2)_4\text{NH}_3^+$) (Fig. 1). Since its side can accept a proton at physiological pH, lysine is classified as a basic amino acid akin to histidine and arginine.^[3] Lysine can exist as the *L*- (left handed) (Fig. 1A) or *D*- (right handed) (Fig. 1B) enantiomer due to its chiral α -carbon atom, with the *L*-enantiomer being more abundant in nature.^{[4][3]} The reason for the greater abundance is that all living organisms selectively use the *L*-enantiomer form of all proteogenic amino acids for protein synthesis.

Biosynthesis

Two different pathways have been identified in nature for the synthesis of lysine. The diaminopimelate (DAP) pathway (Fig. 2A) belongs to the aspartate derived biosynthetic family, which is also involved in the synthesis of threonine, methionine and isoleucine.^{[5][6]} Whereas the α -aminoadipate (AAA) pathway (Fig. 2B) is part of the glutamate biosynthetic family.^{[7][8]}

The DAP pathway (Fig. 2A) is found in both prokaryotes and plants and begins with the dihydrodipicolinate synthase (DHDPs) (E.C 4.2.1.52) catalysed condensation reaction between the aspartate derived, *L*-aspartate semialdehyde, and pyruvate to form (4S)-4-hydroxy-2,3,4,5-tetrahydro-(2S)-dipicolinic acid (HTPA) (Fig. 2A).^{[9][10][11][12][13]} The product is then reduced by dihydrodipicolinate reductase (DH DPR) (E.C 1.3.1.26), with NAD(P)H as a proton donor, to yield 2,3,4,5-tetrahydrodipicolinate (THDP) (Fig. 2A).^[14] From this point on, there are four pathway variations found in different

species, namely the acetylase, aminotransferase, dehydrogenase, and succinylase pathways.^{[5][15]} Both the acetylase and succinylase variant pathways use four enzyme catalysed steps, the aminotransferase pathway uses two enzymes, and the dehydrogenase pathway uses a single enzyme.^[16] These four variant pathways converge at the formation of the penultimate product, meso-diaminopimelate, which is subsequently enzymatically decarboxylated in an irreversible reaction catalysed by diaminopimelate decarboxylase (DAPDC) (E.C 4.1.1.20) to produce *L*-lysine (Fig. 2A).^{[17][18]} The DAP pathway is regulated at multiple levels, including upstream at the enzymes involved in aspartate processing as well as at the initial DHDPs catalysed condensation step.^{[18][19]} Lysine imparts a strong negative feedback loop on these enzymes and, subsequently, regulates the entire pathway.^[19]

The AAA pathway (Fig. 2B) involves the condensation of α -ketoglutarate and acetyl-CoA via the intermediate AAA for the synthesis of *L*-lysine. This pathway has been shown to be present in several yeast species, as well as protists and higher fungi.^{[8][20][21][22][23][24][25]} It has also been reported that an alternative variant of the AAA route has been found in *Thermus thermophilus* and

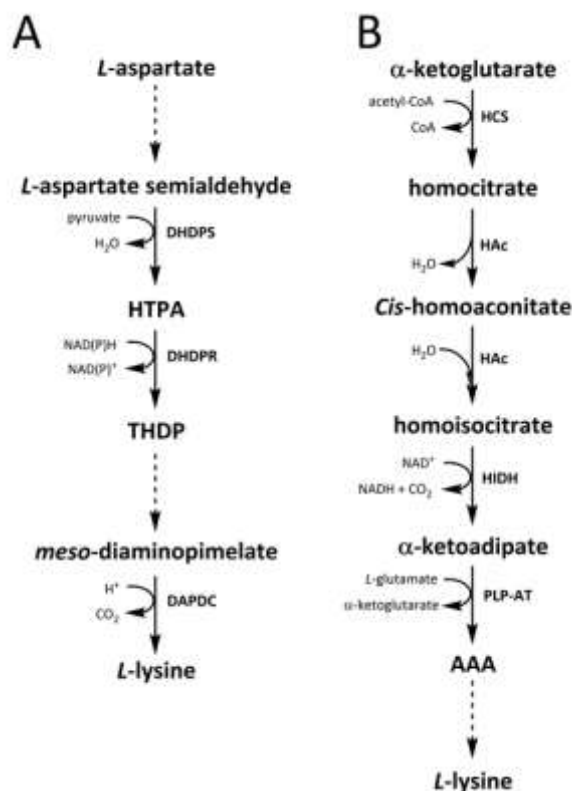


Figure 2 | Lysine biosynthesis pathways. Two pathways are responsible for the *de novo* biosynthesis of *L*-lysine, namely the (A) diaminopimelate pathway and (B) α -aminoadipate pathway.



Pyrococcus horikoshii, which could indicate that this pathway is more widely spread in prokaryotes than originally proposed.^{[26][27][28]} The first and **rate-limiting step** in the AAA pathway is the condensation reaction between acetyl-CoA and α -ketoglutarate catalysed by **homocitrate-synthase (HCS)** (E.C 2.3.3.14) to give the intermediate homocitryl-CoA, which is **hydrolysed** by the same enzyme to produce **homocitrate** (Fig. 2B).^[29] Homocitrate is enzymatically **dehydrated** by **homoaconitase (HAC)** (E.C 4.2.1.36) to yield **cis-homoaconitate**.^[30] HAC then catalyses a second reaction in which **cis-homoaconitate** undergoes **rehydration** to produce **homoisocitrate** (Fig. 2B).^[8] The resulting product undergoes an **oxidative decarboxylation** by **homoisocitrate dehydrogenase (HIDH)** (E.C 1.1.1.87) to yield α -keto adipate.^[8] AAA is then formed via a **pyridoxal 5'-phosphate (PLP)-dependent aminotransferase (PLP-AT)** (E.C 2.6.1.39), using glutamate as the amino donor (Fig. 2B).^[29] From this point on, the AAA pathway differs depending on the kingdom. In fungi, AAA is reduced to α -amino adipate-semialdehyde via AAA reductase (E.C 1.2.1.95) in a unique process involving both **adenylation** and reduction that is activated by a **phosphopantetheinyl transferase** (E.C 2.7.8.7).^[8] Once the semialdehyde is formed, **saccharopine reductase** (E.C 1.5.1.10) catalyses a condensation reaction with glutamate and NAD(P)H, as a proton donor, and the **imine** is reduced to produce the penultimate product, saccharopine.^[28] The final step of the pathway in fungi involves the **saccharopine dehydrogenase (SDH)** (E.C 1.5.1.8) catalysed oxidative **deamination** of saccharopine, resulting in *L*-lysine.^[8] In a variant AAA pathway found in some prokaryotes, AAA is first converted to *N*-acetyl- α -amino adipate, which is **phosphorylated** and then reductively **dephosphorylated** to the ϵ -aldehyde.^{[28][29]} The aldehyde is then **transaminated** to *N*-acetyl-lysine, which is deacetylated to give *L*-lysine.^{[28][29]} However, the enzymes involved in this variant pathway need further validation.

Catabolism

Like all amino acids, **catabolism** of lysine is initiated from the uptake of dietary lysine or from the breakdown of **intracellular** protein. Catabolism is also used as a means to control the intracellular concentration of free lysine and maintain a **steady-state** to prevent the toxic effects of excessive free lysine.^[31] There are several pathways involved in lysine catabolism but the most commonly used is the saccharopine pathway (Fig. 3), which primarily takes place in the **liver** (and equivalent organs) in animals, specifically within the **mitochondria**.^{[2][31][32][33]} Interestingly, this is the reverse of

the previously described AAA pathway (Fig. 2B).^{[2][34]} In animals and plants, the first two steps of the saccharopine pathway are catalysed by the bifunctional enzyme, **α -amino adipate semialdehyde synthase (AASS)**, which possess both lysine-ketoglutarate reductase (LKR) (E.C 1.5.1.8) and SDH activities, whereas in other organisms, such as bacteria and fungi, both of these enzymes are encoded by separate **genes**.^{[35][36]} The first step involves the LKR catalysed reduction of *L*-lysine in the presence of α -ketoglutarate to produce saccharopine, with NAD(P)H acting as a proton donor (Fig. 3).^[37] Saccharopine then undergoes a dehydration reaction, catalysed by SDH in the presence of **NAD⁺**, to produce AAS and glutamate.^[38] **AAS dehydrogenase (AASD)** (E.C 1.2.1.31) then further dehydrates the molecule into AAA (Fig. 3).^[37] Subsequently, PLP-AT catalyses the reverse reaction to that of the AAA biosynthesis pathway, resulting in AAA being converted to α -keto adipate. The

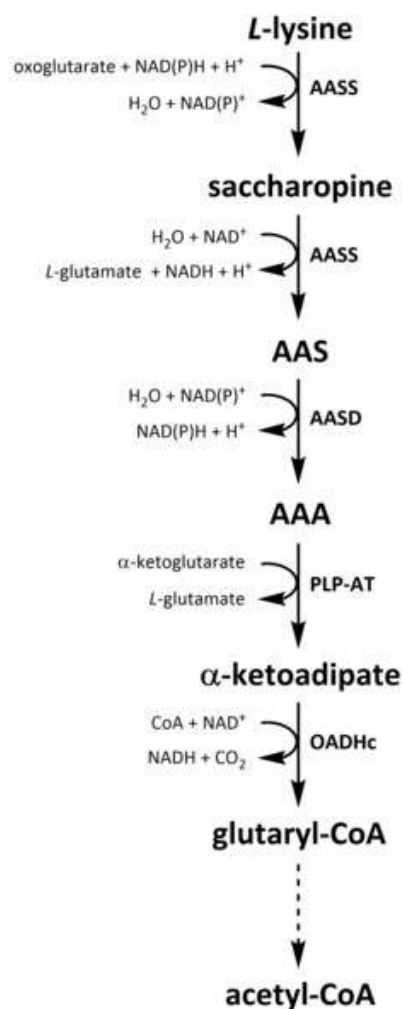


Figure 3 | Saccharopine lysine catabolism pathway. The saccharopine pathway is the most prominent pathway for the catabolism of lysine.



product, α -ketoacid, is decarboxylated in the presence of NAD^+ and coenzyme A to yield glutaryl-CoA, however the enzyme involved in this is yet to be fully elucidated (Fig. 3).^{[39][40]} Some evidence suggests that the 2-oxoadipate dehydrogenase complex (OADHc), which is structurally homologous to the E1 subunit of the oxoglutarate dehydrogenase complex (OGDHc) (E.C 1.2.4.2), is responsible for the decarboxylation reaction.^{[39][41]} Finally, glutaryl-CoA is oxidatively decarboxylated to crotonyl-CoA by glutaryl-CoA dehydrogenase (E.C 1.3.8.6), which goes on to be further processed through multiple enzymatic steps to yield acetyl-CoA; an essential carbon metabolite involved in the tricarboxylic acid cycle (TCA).^{[37][42][43][44]}

Nutritional value

Lysine is one of the nine essential amino acids in humans.^[4] The human nutritional requirements varies from $\sim 60 \text{ mg}\cdot\text{kg}^{-1}$ in infancy to $\sim 30 \text{ mg}\cdot\text{kg}^{-1}$ in adults.^[2] This requirement is commonly met in a western society with the intake of lysine from meat and vegetable sources well in excess of the recommended requirement.^[2] In vegetarian diets, the intake of lysine is less due to the limiting quantity of lysine in cereal crops compared to meat sources.^[2] Given the limiting concentration of lysine in cereal crops, it has long been speculated that the content of lysine can be increased through genetic modification practices.^{[1][45]} Often these practices have involved the intentional dysregulation of the DAP pathway by means of introducing lysine feedback-insensitive orthologues of the DHDPs enzyme.^{[1][45]} These methods have met limited success likely due to the toxic side effects of increased free lysine and indirect effects on the TCA cycle.^[46] Plants accumulate lysine and other amino acids in the form of seed storage proteins, found within the seeds of the plant, and this represents the edible component of cereal crops.^[47] This highlights the need to not only increase free lysine, but also direct lysine towards the synthesis of stable seed storage proteins, and subsequently, increase the nutritional value of the consumable component of crops.^{[48][49]} Whilst genetic modification practices have met limited success, more traditional selective breeding techniques have allowed for the isolation of 'Quality Protein Maize', which has significantly increased levels of lysine (and tryptophan). This increase in lysine content is attributed to an opaque-2 mutation that reduced the transcription of lysine lacking zein related seed storage proteins and, as a result, increased the abundance of other proteins that are rich in lysine.^{[49][50]} Commonly, to overcome the limiting abundance of lysine in livestock feed, industrially

produced lysine is added.^{[51][52]} The industrial process includes the fermentative culturing of *Corynebacterium glutamicum* and the subsequent purification of lysine.^[51]

Biological roles

The most common role for lysine is proteinogenesis. Lysine frequently plays an important role in protein structure. Since its side chain contains a positively charged group on one end and a long hydrophobic carbon tail close to the backbone, lysine is considered somewhat amphipathic (Fig. 1). For this reason, lysine can be found buried as well as more commonly in solvent channels and on the exterior of proteins, where it can interact with the aqueous environment.^[53] Lysine can also contribute to protein stability as its ϵ -amino group often participates in hydrogen bonding, salt bridges and covalent interactions to form a Schiff base.^{[53][54][55][56]}

A second major role of lysine is in epigenetic regulation by means of histone modification.^{[57][58]} There are several types of covalent histone modifications, which commonly involve lysine residues found in the protruding tail of histones. Modifications often include the addition or removal of an acetyl ($-\text{CH}_3\text{CO}$), up to three methyl ($-\text{CH}_3$), ubiquitin or a sumo protein group.^{[57][59][60][61][62]} The various modifications have downstream effects on gene regulation, in which genes can be activated or repressed.

Lysine has also been implicated to play a key role in other biological processes including; structural proteins of connective tissues, calcium homeostasis, and fatty acid metabolism.^{[63][64][65]} Lysine has been shown to be involved in the crosslinking between the three helical polypeptides in collagen, resulting in its stability and tensile strength.^{[63][66]} This mechanism is akin to the role of lysine in bacterial cell walls, in which lysine (and meso-diaminopimelate) are critical to the formation of crosslinks, and therefore, stability of the cell wall.^[67] This concept has previously been explored as a means to circumvent the unwanted release of potentially pathogenic genetically modified bacteria. It was proposed that an auxotrophic strain of *Escherichia coli* (x1776) could be used for all genetic modification practices, as the strain is unable to survive without the supplementation of DAP, and thus, cannot live outside of a laboratory environment.^[68] Lysine has also been proposed to be involved in calcium intestinal absorption and renal retention, and thus, may play a role in calcium homeostasis.^[64] Finally, lysine has been shown to be a precursor for carnitine, which transports fatty acids to the mitochondria, where they can be oxidised for the release



of energy.^{[65][69]} Carnitine is synthesised from trimethyllysine, which is a product of the degradation of certain proteins, as such lysine must first be incorporated into proteins and be methylated prior to being converted to carnitine.^[65] It must be noted however, that in mammals the primary source of carnitine is through dietary sources, rather than through lysine conversion.^[65]

Disputed roles

There has been a long discussion that lysine, when administered intravenously or orally, can significantly increase the release of [growth hormones](#).^[70] This has led to athletes using lysine as a means of promoting muscle growth while training, however, no significant evidence to support this application of lysine has been found to date.^{[70][71]} Another topic of discussion is the applicability of lysine as a treatment for the [herpes simplex virus \(HSV\)](#) due to a correlation between high levels of lysine and decreased symptoms and healing time of infected individuals.^{[72][73]} This claim has long been disputed, with studies concluding that lysine has no efficacy as a [prophylactic](#) or in the treatment of HSV.^{[74][75][76]}

Roles in disease

Diseases related to lysine are a result of the downstream processing of lysine, i.e. the incorporation into proteins or modification into alternative biomolecules. The role of lysine in collagen has been outlined above, however, a lack of lysine and [hydroxylysine](#) involved in the crosslinking of collagen peptides has been linked to a disease state of the connective tissue.^[77] As carnitine is a key lysine-derived metabolite involved in fatty acid metabolism, a substandard diet lacking sufficient carnitine and lysine can lead to decreased carnitine levels, which can have significant cascading effects on an individual's health.^{[69][78]} Lysine has also been shown to play a role in [anaemia](#), as lysine is suspected to have an effect on the uptake of [iron](#) and, subsequently, the concentration of [ferritin](#) in [blood plasma](#).^[79] However, the exact mechanism of action is yet to be elucidated.^[79] Most commonly, lysine deficiency is seen in non-western societies and manifests as [protein-energy malnutrition](#), which has profound and systemic effects on the health of the individual.^{[80][81]} There is also a [hereditary](#) genetic disease that involves [mutations](#) in the enzymes responsible for lysine catabolism, namely the bifunctional AASS enzyme of the saccharopine pathway (Fig. 3).^[82] Due to a lack of lysine catabolism, the amino acid accumulates in plasma and patients develop [hyperlysinaemia](#), which can present as asymptomatic to severe [neurological disabilities](#), including [epilepsy](#), [ataxia](#), [spasticity](#), and [psychomotor impairment](#).^{[82][83]} It must

be noted however, that the clinical significance of hyperlysinaemia is the subject of debate in the field with some studies finding no correlation between physical or mental disabilities and hyperlysinaemia.^[84] In addition to this, mutations in genes related to lysine metabolism have been implicated in several disease states, including [pyridoxine-dependent epilepsy \(ALDH7A1 gene\)](#), [\$\alpha\$ -ketoacidic and \$\alpha\$ -aminoacidic aciduria \(DHTKD1 gene\)](#), and [glutaric aciduria type 1 \(GCDH gene\)](#).^{[39][85][86][87][88]}

Concluding remarks

Lysine is a basic positively charged amino acid involved in several biological processes, including proteinogenesis, epigenetic regulation, crosslinking, mineral uptake, and metabolite production. Lysine is an essential amino acid as it cannot be synthesised *de novo* in animals and must be obtained through dietary intake of organisms that possess the biosynthetic pathways. Organisms that are capable of synthesising lysine do so using one of two major pathways, namely the DAP or the AAA pathway. The catabolism of lysine can vary significantly with several pathways involved in the breakdown of lysine into different metabolites. The most commonly used catabolic pathway is the saccharopine pathway, which results in the breakdown of lysine into the essential precursor involved in carbon flux, glutaryl-CoA. Lysine deficiency, arising from an inadequate diet, can lead to several disease states, thus highlighting the need for a balanced diet with sufficient intake of essential amino acids. In contrast to this, an excessive concentration of free lysine, due to stunted catabolism, can cause various neurological disorders. It must be noted that in highly complex organisms, such as humans, metabolites including lysine can be implicated in many different processes and this review has addressed some of these roles.

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