Lysine: Biosynthesis, Catabolism and Roles

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Lysine: Biosynthesis, Catabolism and Roles

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Abstract
Amino acids are an essential building block of all life, commonly they are incorporated into extending polypeptide chains to produce larger macromolecules, 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 2 main biosynthetic pathways, namely the diaminopimelate and α-aminoadipate pathways, which employ different enzymes and substrates and are found in different organisms. Lysine catabolism is accomplished 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. 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.

Plain Language Summary
Proteins are key biomolecules found in all life and are composed of smaller structural units called amino acids. There are 20 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 mammals and, thus, must be obtained through dietary sources. ~~However, plants~~Plants, bacteria, ~~and~~ fungi and protists can biosynthesise their own lysine. There are two biosynthesis pathways that can generate lysine; the diaminopimelate and α-aminoadipate pathways. Whilst ~~mammals~~ 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 of being 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. 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 retardation, epilepsy, and ataxia.

Key words: *Amino Acids, Lysine, Biosynthesis, Catabolism, Nutrition*

Introduction

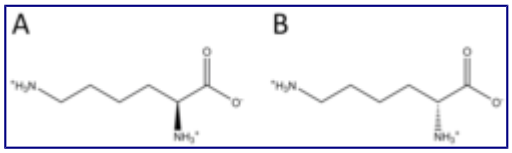

Figure 1 | Structure of lysine enantiomers at physiological pH. Lysine can exist as one of two enantiomers, namely (A) *L*-lysine and (B) *D*-lysine.

Lysine (abbreviated as Lys or K), ~~encoded by the codons~~ AAA and AAG, is an α-amino acid ~~involved in~~used for protein biosynthesis (proteinogenesis). There are many different kinds of amino acids, but only 20 are used universally by all of life for protein synthesis (proteogenic amino acids). The process of translation is how proteins are synthesized and lysine is added at the codons AAA and AAG. ~~It~~ Lysine is an essential amino acid to all animals, including humans, and therefore must be obtained through dietary intake.[1][2] Bacteria, archea, fungi, some protista (euglenids), and plants, on the other hand, are able to synthesize lysine. The organisms that are able to synthesize lysine can be thought of as the primary producers on which all animals are dependent for their nutritional lysine requirement.

~~Under~~ The free form ~~biological conditions,~~ of lysine kept at physiological pH contains a protonated α-amino group ($-NH_3^+$), a deprotonated α-carboxylic acid group ($-COO^-$), and a protonated ε-amino side chain ($-(CH_2)_4NH_3^+$) (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.[3][4] The reason for the greater abundance is that all living organisms selectively use the L-enantiomer form of all the proteogenic amino acids for protein synthesis.

Biosynthesis

Lysine is an essential amino acid in animals, but can be synthesised *de novo* in bacteria, lower eukaryotes, and plants.[5] Unlike the other naturally occurring amino acids, lysine is the only one known to have two distinct biosynthetic pathways.[6] 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 also involved in the synthesis of threonine, methionine and isoleucine.[5][7] Whereas the α-aminoadipate (AAA) pathway (Fig. 2B) is part of the glutamate biosynthetic family.[8][9]

The DAP pathway (Fig. 2A) is found in both prokaryotes and ~~eukaryotes~~ 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 (4*S*)-4-hydroxy-2,3,4,5-

tetrahydro-(2*S*)-dipicolinic acid (HTPA) (Fig. 2A).[10][11][12][13][14][15] The product is then reduced by dihydrodipicolinate reductase (DHDPR) (E.C 1.3.1.26), with NAD(P)H as a proton donor, to yield 2,3,4,5-tetrahydrodipicolinate (THDP) (Fig. 2A).[16] From this point on, there exist ~~pathway diverges into~~ four pathway variations found in different species~~sub pathways~~, namely the acetylase, aminotransferase, dehydrogenase, and succinylase pathways.[17][18] 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 [add reference http://jb.asm.org/content/190/9/3256.full]. These four ~~sub~~variant-pathways ~~converge~~ end with ~~for~~ the formation of the penultimate product, *meso*-diaminopimelate, which is subsequently enzymatically decarboxylated in an irreversible reaction catalyzed by diaminopimelate decarboxylase (DAPDC) (E.C 4.1.1.20) to produce *L*-lysine (Fig. 2A).[19][20] 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.[21][22] Lysine imparts a strong negative feedback loop on these enzymes and, subsequently, regulates the entire pathway.[21]

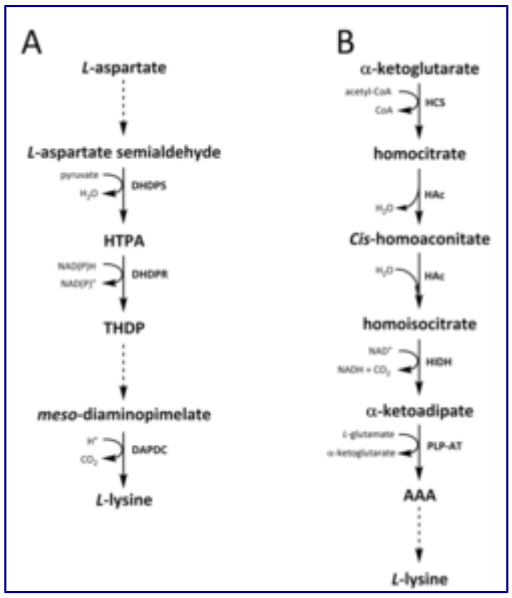

Figure 2 | Lysine biosynthesis pathways. Two pathways are responsible for the *de novo* biosynthesis of *L*-lysine, namely the (A) diaminopimelate pathway and (B) α-aminoadipate pathway.

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 and mould species, as well as protists (euglenoids) and higher fungi.[9][23][24][25][26][27][28][29] It has also been reported that an alternative variant of the AAA route has been found in *Thermus thermophilus* and *Pyrococcus horikoshii*, which could indicate that this pathway is more widely spread in prokaryotes than originally proposed[30][31][32] 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).[33] Homocitrate is enzymatically dehydrated by homoaconitase (HAc) (E.C 4.2.1.36) to yield *cis*-homoaconitate.[34] HAc then catalyses a second reaction in which *cis*-homoaconitate undergoes rehydration to produce homoisocitrate (Fig. 2B).[9] The resulting product undergoes an oxidative

decarboxylation by homoisocitrate dehydrogenase (HIDH) (E.C 1.1.1.87) to yield α-ketoadipate.[9] 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).[33] From this point on, the AAA pathway differs depending on the kingdom. In fungi, AAA is reduced to α-aminoadipate-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).[9] 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.[9] 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.[9] In a variant AAA pathway found in some prokaryotes, AAA is first converted to *N*-acetyl-α-aminoadipate, which is phosphorylated and then reductively dephosphorylated to the ε-aldehyde.[32] The aldehyde is then transaminated to *N*-acetyl-lysine, which is deacetylated to give *L*-lysine.[32][33] However, this sub-pathway needs further validation of the enzymes involved.

Catabolism

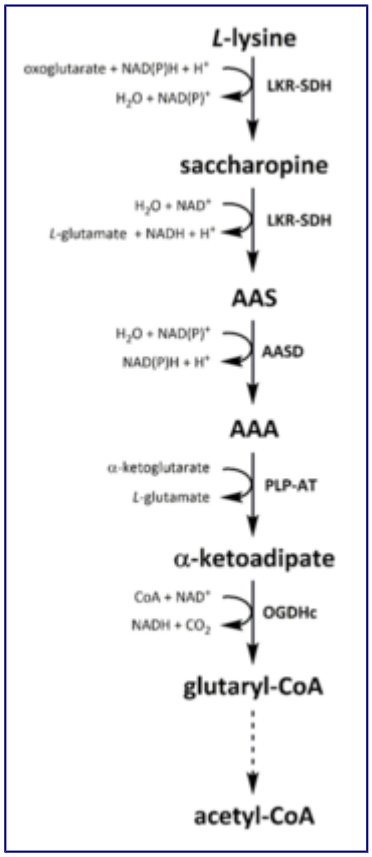

Figure 3 | Saccharopine lysine catabolism pathway. The saccharopine pathway is the most prominent pathway for the catabolism of lysine.

Like all amino acids, catabolism of lysine is initiated from the uptake of dietary lysine or from the breakdown of intracellular protein. There are several pathways for lysine catabolism but the most commonly used is the saccharopine pathway (Fig. 3), which in humans takes place in the liver.[35][36][37][38][39][40][41][42][43][44] Interestingly, this is the reverse of the previously described

AAA pathway (Fig. 2B).[2][45][46] In animals and plants, the first two steps of the saccharopine pathway are catalysed by a bifunctional enzyme with 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.[47][48] 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 donator (Fig. 3).[49] Saccharopine then undergoes a dehydration reaction, catalysed by SDH in the presence of NAD^+, to produce AAS and glutamate.[50] AAS dehydrogenase (AASD) (E.C 1.2.1.31) then further dehydrates the molecule into AAA (Fig. 3).[49] Subsequently, PLP-AT catalyses the reverse reaction to that of the AAA biosynthesis pathway, resulting in AAA being converted to α-ketoadipate. Finally, α-ketoadipate is decarboxylated by the oxoglutarate dehydrogenase complex (OGDHc) (E.C 1.2.4.2) in the presence of NAD^+ and coenzyme A to produce glutaryl-CoA (Fig. 3).[42][51] Glutaryl-CoA goes on to be further processed through multiple enzymatic steps to yield acetyl-CoA, which is an essential carbon metabolite involved in the tricarboxylic acid cycle.[49][52][53]

Nutritional Value

Lysine is one of the nine essential amino acids in humans (Nelson & Cox, 2013). The human nutritional requirements varies from ~60 $mg \cdot kg^{-1}$ in infancy to ~30 $mg \cdot kg^{-1}$ 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 as 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.[54] 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][54] Thus far, these methods have met limited success. Commonly, lysine has been added to animal stock feed to improve nutritional value.[55][56]

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.[57] 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.[57][58][59][60]

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.[61][62][63] Lysine has been shown to be involved in the crosslinking between the three helical polypeptides in collagen, resulting in its stability and tensile strength.[62][64] 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.[65] Lysine has been proposed to be

involved in calcium intestinal absorption and renal retention and, thus, may play a role in calcium homeostasis.[61] 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.[63][66]

Disputed Roles

There has been a long discussion that lysine, when administered intravenously or orally, can significantly increase the release of growth hormones.[67] 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.[67][68] 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.[69][70] This claim has long been disputed, with studies concluding that lysine has no efficacy as a prophylactic or in the treatment of HSV.[71][72][73]

Disease States Related to Lysine

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.[74] As carnitine is a key lysine-derived metabolite involved in fatty acid metabolism, a lack of lysine leads to decreased carnitine levels, which can have significant cascading effects on an individual's health.[66][75] 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.[76] However, the exact mechanism of action is yet to be elucidated.[76] 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.[77][78] There is also a hereditary genetic disease that involves mutations in the enzymes responsible for lysine catabolism, namely the bifunctional LKR-SDH enzyme of the saccharopine pathway (Fig. 3).[79] (Houten et al., 2013). Due to the 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 retardation.[79][80]

Concluding Remarks

Lysine is a basic positively charged amino acid involved in several biological processes, including proteinogenesis, crosslinking, mineral uptake, and metabolite production. Lysine is an essential amino acid as it cannot be synthesised *de novo* in ~~mammals~~ animals and must be obtained through dietary intake of organisms that possess the biosynthetic pathways. 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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