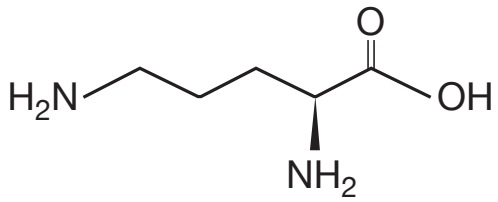
Monograph

L-Lysine



L-Lysine

Introduction

L-Lysine is classified as an essential amino acid; meaning the human body cannot synthesize lysine on its own and thus must rely on adequate dietary intake to function properly. Animal proteins, such as meats, poultry, and milk are rich sources of lysine; proteins from grains, such as wheat and corn, generally tend to be low in lysine. An exception is wheat germ, which contains high amounts of lysine.

Lysine made its initial appearance on the U.S. dietary supplement market in the mid-1950s. Historically, there was interest in fortifying bread and other grain-based foods with lysine to improve the protein value for populations with lysine-poor diets. However, this broad-scale application did not materialize in the United States, not for any safety concerns regarding lysine fortification, but because the U.S. Food and Drug Administration (FDA) would not change the Standards of Identity for white bread.[1] On the other hand, fortification of animal feeds with lysine has been a common practice since 1970, with current usage estimated at 800,000 tons/year globally.[1-3] Today, lysine is a common human dietary supplement as well, typically in the form of lysine hydrochloride.

Of the many biological functions requiring lysine, some notable applications include synthesis of connective tissues such as bone, skin, collagen, and elastin; synthesis of carnitine and resultant conversion of fatty acids to energy; support for healthy growth and development in children; and maintenance of healthy immune function, particularly with regard to antiviral activity. Concerning the latter, lysine is well known for its potential benefit in the management of *Herpes simplex* virus (HSV) infections.

An interesting note concerning lysine is that it is involved in the browning or carmelization reaction applied to foods such as pastries, cereals, and desserts. When heated, lysine links with a reducing sugar (such as fructose, glucose, or lactose), creating a carmelized substance that, although desirable from a culinary perspective, renders lysine nearly impossible for the body to absorb. Consequently, carmelized foods are low in usable lysine.

Biochemistry and Pharmacokinetics

Lysine, (S)-2,6,-diaminohexanoic acid, is a basic amino acid, positively charged at physiological pH, and highly water soluble. It has a molecular weight of 146.19 daltons.

Oral administration is the preferred route for lysine supplementation. Upon ingestion, it is absorbed from the lumen of the small intestine into the enterocytes via active transport and moves from the gut to the liver via the portal circulation. Once in the liver, lysine joins other amino acids to facilitate protein synthesis. Catabolism of lysine also occurs in the liver, where it undergoes condensation with ketoglutarate to form saccharopine. Saccharopine is converted to L-alpha-aminoadipic acid semialdehyde, which eventually becomes acetoacetyl-CoA.[1,4] Unlike other amino acids, lysine does not undergo transamination. Lysine is both glycogenic and ketogenic, and thus can aid in the formation of D-glucose, glycogen, lipids, and consequently energy production.

Human absorption studies have demonstrated lysine supplements have absorption rates similar to those from digestion of proteins, suggesting supplementation is an effective and efficient means of correcting a dietary lysine deficiency.[5]

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Lysine is rapidly transported into muscle tissue,[6] within 5-7 hours after ingestion,[7] and is more concentrated in the intracellular space of muscle tissue compared to other essential amino acids.[1] This suggests that muscle may serve as a reservoir for free lysine in the body.

Lysine is the most strongly conserved of the essential amino acids. In an experiment where adult rats were fed diets deficient in each essential amino acid for 14 weeks, rats lacking lysine exhibited the smallest amount of weight loss (30 g). By comparison, rats on a protein-free diet lost approximately 100 g in body weight during the same time period.[8] Assuming the human body's ability to conserve lysine is similar, one could endure a low-lysine diet for a period of time without experiencing a significant amount of body wasting compared to other essential amino acids (illustrated in this case by administering a protein-free diet).

Mechanisms of Action

Lysine is converted to acetyl CoA, a critical component in carbohydrate metabolism and the production of energy. Lysine is also the precursor of the amino acid carnitine, which aids in transporting long-chain fatty acids into the mitochondria for energy production and other metabolic functions. Once lysine is bound to a polypeptide structure, biosynthesis of carnitine is initiated by methylation of one of lysine's amine groups.[9] Transformation of this same amine group is also involved in the biosynthesis of collagen and elastin.

Lysine appears to have an antagonistic relationship with the amino acid arginine, which is required for the replication of HSV.[10] Lysine competes with arginine for absorption in the intestine, re-absorption in the renal tubules, and transport across the plasma membrane into cells.[11] *In vitro*, lysine inhibits the growth-promoting action of arginine on HSV.[10] Increasing overall lysine intake or influencing the lysine-to-arginine ratio is the basis for lysine's potential benefit in managing an HSV outbreak.

Deficiency States and Symptoms

Signs and symptoms of lysine deficiency include fatigue, nausea, dizziness, anorexia, irritability, slow growth, anemia, and reproductive disorders. Incidence of marked lysine deficiency in the diet is rare in developed countries like the United States. However, certain individuals, such as vegetarians following a strict macrobiotic diet or athletes undergoing frequent vigorous exercise, are at risk for lysine deficiency. Legumes are a good source of lysine for vegetarians.[12]

Clinical Indications

Herpes

A multicentered trial observed 45 patients with frequently recurring HSV infections taking 312-1200 mg lysine daily for two months to three years; foods with high arginine content were restricted. The study revealed a dramatic reduction in recurrence of infection while subjects were on the treatment; when lysine was discontinued lesions recurred within 1-4 weeks.[13]

Similar results were observed in a small trial of nine HSV patients receiving 500 mg lysine daily in conjunction with a low-arginine diet. Reductions in recurrence, severity, and duration were observed.[11]

In a double-blind, placebo-controlled trial, 27 patients given 1,000 mg lysine three times daily for six months experienced fewer herpes outbreaks ($p<0.05$), a substantial reduction in severity of symptoms ($p<0.05$), and shortened healing time ($p<0.05$) compared to the placebo group.[14]

In a survey of 1,543 individuals suffering from either cold sores or genital herpes, 88 percent reported supplemental lysine to be an effective form of treatment.[15]

In a double-blind, placebo-controlled, crossover trial, 41 subjects with recurrent HSV infections were given lysine (500 or 1,000 mg daily) or placebo for 24 weeks, and then the alternate treatment for an additional 24 weeks. All study participants were prescribed a high-lysine and low-arginine diet. Individuals receiving high-dose lysine experienced significantly fewer recurrences during the lysine period than during the placebo period. Those receiving the lower dose of lysine experienced no significant change compared to placebo.[16]

Similarly, 65 patients with recurrent HSV infections received lysine (500 mg twice daily) or placebo for 12 weeks and then the alternate treatment for an additional 12 weeks. Significantly more patients experienced a reduction in recurrence during lysine treatment than during placebo treatment (27.7% versus 12.3%; $p<0.05$). Although not statistically significant, the total number of recurrences was 12.5 percent lower in the lysine group compared to the placebo group.[17]

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Twenty patients with frequently recurring oral or genital HSV outbreaks were randomly assigned to receive 400 mg lysine three times daily or placebo for 4-5 months, and number of lesion-free days were assessed. There was no statistical significance between the lysine group, which experienced lesions on 41 percent of the study days, compared to the placebo group, which experienced lesions on 46 percent of the study days.[18]

In summary, these studies suggest lysine supplementation may be helpful in reducing the rate of recurrence for HSV infections, especially when accompanied by a high-lysine, low-arginine diet.

Osteoporosis

Two clinical studies were conducted by the same researchers to determine the effect of lysine on calcium absorption. In the first study, 10 women with osteoporosis were given 3 g calcium (as $CaCl_2$) and 400 mg lysine. The control group consisted of 10 women, age-matched, but without osteoporosis/osteopenia, who were given 3 g calcium (as $CaCl_2$) and placebo. Blood and urine samples were collected pre-treatment and every hour for three hours following treatment. As expected, both groups demonstrated increased serum calcium levels and increased urine excretion of calcium after treatment. Although all subjects experienced an increase in urinary excretion of calcium, the amount excreted in healthy subjects taking lysine was significantly less than the other groups, suggesting lysine may suppress calcium excretion in healthy individuals.[19]

In the second study, 45 women with osteoporosis were randomly assigned a blinded 800-mg oral preparation of L-lysine, L-valine, or L-tryptophan to be taken daily for three days to determine the effect on intestinal calcium absorption. Calcium absorption was significantly increased in the lysine group compared to the other amino acid groups whose values remained unchanged.[19]

Although somewhat small in sample size, these trials demonstrate that lysine supplementation can decrease urinary excretion of calcium after an oral calcium load and may facilitate intestinal calcium absorption.

Angina Pectoris

Dr. Linus Pauling reported on several cases of angina pectoris relieved by lysine.[20-22] In the first case, a 71-year-old male with advanced coronary artery disease, suffering from effort angina not controlled by medication, experienced a dramatic amelioration of symptoms by taking a daily combination of 6 g ascorbic acid and 6 g lysine in divided doses. The patient, who was on several prescription medications and an extensive dietary supplement regimen including the 6 g ascorbic acid, did not experience marked angina amelioration until addition of the lysine. Similar results were observed in two other cases.[21,22]

Although the actual mechanism is unclear, Pauling hypothesized supplemental lysine may bind with and remove lipoprotein(a) from plaque deposits, thereby reducing thickening of the artery and increasing blood flow.[20] In addition, lysine may act as an intracellular cation, exerting vasodilation similar to potassium.[23,24]

Side Effects and Toxicity

In general, lysine supplementation is very safe. The estimated dietary lysine requirement for a 70-kg human is in the range of 800-3,000 mg/day.[25,26] Doses up to 3 g daily are typically well-tolerated. Very high doses (>10-15 g daily) may cause gastrointestinal upset, including nausea, abdominal cramps, and diarrhea.[4]

L-lysine supplementation is contraindicated in individuals with hyperlysinemia/hyperlysinuria, a rare genetic disorder. Because much of lysine catabolism occurs in the liver, individuals with a history of hepatic or renal failure should consult with a healthcare practitioner before using supplemental lysine.

Dosage

Optimal lysine dosage for HSV prophylaxis is not yet definitive, with doses ranging between 500-3,000 mg daily. A reasonable recommendation is between 500-1,000 mg daily for prophylaxis, reserving higher dosages of 3,000 mg daily for active outbreaks and only for a limited time until the current episode subsides.

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References

1. Flodin NW. The metabolic roles, pharmacology, and toxicology of lysine. *J Am Coll Nutr* 1997;16:7-21.
2. Toride Y. Lysine and other amino acids for feed: production and contribution to protein utilization in animal feeding. Protein Sources for the Animal Feed Industry; FAO Corporate Document Repository. http://www.fao.org/docrep/007/y5019e/y5019e0a.htm [Accessed 04/24/2007]
3. Ajinomoto Co, Inc. http://www.ajinomoto.com/press/g2002_01_30_01.html. Accessed 04/24/2007.
4. PDRhealth. http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/lly_0166.shtml [Accessed 03/01/2007]
5. Flodin NW. Lysine supplementation of cereal foods: a retrospective. *J Am Coll Nutr* 1993;12:486-500.
6. Longenecker JB, Hause NL. Relationship between plasma amino acids and composition of the ingested protein. *Arch Biochem Biophys* 1959;84:46-59.
7. Uhe AM, Collier GR, O'Dea K. A comparison of the effects of beef, chicken and fish protein on satiety and amino acid profiles in lean male subjects. *J Nutr* 1992;122:467-472.
8. Gahl MJ, Finke MD, Crenshaw TD, Benevenga NJ. Use of a four-parameter logistic equation to evaluate the response of growing rats to ten levels of each indispensable amino acid. *J Nutr* 1991;121:1720-1729.
9. Broquist HP. Carnitine biosynthesis and function. Introductory remarks. *Fed Proc* 1982;41:2840-2842.
10. Griffith RS, DeLong DC, Nelson JD. Relation of arginine-lysine antagonism to *Herpes simplex* growth in tissue culture. *Chemotherapy* 1981;27:209-213.
11. Miller CS, Foulke CN. Use of lysine in treating recurrent oral *Herpes simplex* infections. *Gen Dent* 1984;32:490-493.
12. University of Maryland Medical Center. http://www.umm.edu/altmed/ConsSupplements/Print/Lysinecs.html [Accessed 02/22/2007]
13. Griffith RS, Norins AL, Kagan C. A multicentered study of lysine therapy in *Herpes simplex* infection. *Dermatologica* 1978;156:257-267.
14. Griffith RS, Walsh DE, Myrmel KH, et al. Success of L-lysine therapy in frequently recurrent *Herpes simplex* infection. Treatment and prophylaxis. *Dermatologica* 1987;175:183-190.
15. Walsh DE, Griffith RS, Behforooz A. Subjective response to lysine in the therapy of *Herpes simplex*. *J Antimicrob Chemother* 1983;12:489-496.
16. McCune MA, Perry HO, Muller SA, O'Fallon WM. Treatment of recurrent *Herpes simplex* infections with L-lysine monohydrochloride. *Cutis* 1984;34:366-373.
17. Milman N, Scheibel J, Jessen O. Lysine prophylaxis in recurrent *Herpes simplex* labialis: a double-blind, controlled crossover study. *Acta Derm Venereol* 1980;60:85-87.
18. DiGiovanna JJ, Blank H. Failure of lysine in frequently recurrent *Herpes simplex* infection. Treatment and prophylaxis. *Arch Dermatol* 1984;120:48-51.
19. Civitelli R, Villareal DT, Agnusdei D, et al. Dietary L-lysine and calcium metabolism in humans. *Nutrition* 1992;8:400-405.
20. Pauling L. Case report: lysine/ascorbate-related amelioration of angina pectoris. *J Orthomolecular Med* 1991;6:144-146.
21. McBeath M, Pauling L. A case history: lysine/ascorbate-related amelioration of angina pectoris. *J Orthomolecular Med* 1993;8:77-78.
22. Pauling L. Third case report on lysine-ascorbate amelioration of angina pectoris. *J Orthomolecular Med* 1993;8:137-138.
23. Overbeck HW, Clark DW. Vasodilator responses to K+ in genetic hypertensive and in renal hypertensive rats. *J Lab Clin Med* 1975;86:973-983.
24. Lowe RD, Thompson JW. The effect of intra-arterial potassium chloride infusion upon forearm blood flow in man. *J Physiol* 1962;162:69P-70P.
25. Meredith CN, Wen ZM, Bier DM, et al. Lysine kinetics at graded lysine intakes in young men. *Am J Clin Nutr* 1986;43:787-794.
26. Duncan AM, Ball RO, Pencharz PB. Lysine requirement of adult males is not affected by decreasing dietary protein. *Am J Clin Nutr* 1996;64:718-725.

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