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Lipoic Acid

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Summary

- α-Lipoic acid (LA), also known as thioctic acid, is a naturally occurring compound that is synthesized in small amounts by humans. *(More information)*
- Endogenously synthesized LA is bound to protein and functions as a cofactor for several important mitochondrial enzymes. *(More information)*
- Supplementation with high doses of LA transiently increases plasma and cellular levels of free LA. *(More information)*
- Although LA is a potent antioxidant in the test tube, LA supplementation may affect health by stimulating glutathione synthesis, enhancing insulin signaling, and modulating the activity of other cell-signaling molecules and transcription factors. *(More information)*
- Overall, the available research indicates that treatment with 600 mg/day of intravenous LA for three weeks significantly reduces the symptoms of diabetic peripheral neuropathy. *(More information)*
- Compared with intravenous administration, the effect of long-term, oral LA supplementation for diabetic peripheral neuropathy is less clear, yet some studies show that oral supplementation with at least 600 mg/day of LA may be beneficial. *(More information)*
- It is not yet known whether LA supplementation is beneficial in the treatment of multiple sclerosis or neurodegenerative diseases like Alzheimer's disease. *(More information)*
- If you choose to take LA supplements, the Linus Pauling Institute recommends a daily dose of 200-400 mg/day of LA for generally healthy people.

Introduction

Factors

> L-Carnitine

> Coenzyme Q10

> Lipoic Acid

> Phytochemicals

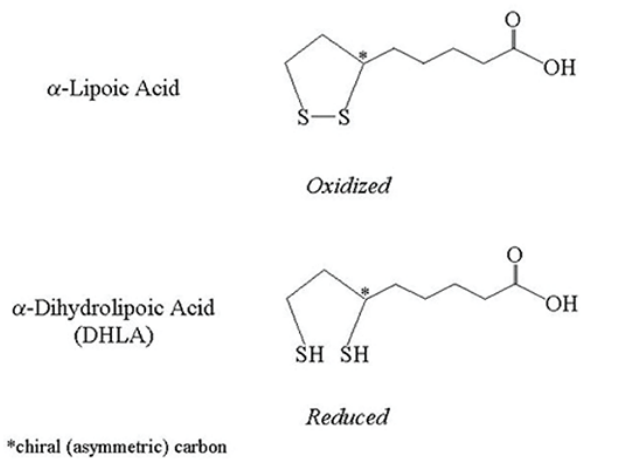
Food and Beverages

Life Stages

Health and Disease

α-Lipoic acid (LA), also known as thioctic acid, is a naturally occurring compound that is synthesized in small amounts by plants and animals, including humans (1, 2). Endogenously synthesized LA is covalently bound to specific proteins, which function as cofactors for several important mitochondrial enzyme complexes (see Biological Activities). In addition to the physiological functions of protein-bound LA, there is increasing scientific and medical interest in potential therapeutic uses of pharmacological doses of free LA (3). LA contains two thiol (sulfur) groups, which may be oxidized or reduced (**Figure 1**). The reduced form is known as dihydrolipoic acid (DHLA), while the oxidized form is known as LA (4). LA also contains an asymmetric carbon, meaning there are two possible optical isomers that are mirror images of each other (*R*-LA and *S*-LA). Only the *R*- isomer is endogenously synthesized and bound to protein: *R*-LA occurs natural in foods (see Food sources). Free LA supplements may contain either *R*-LA or a 50/50 (racemic) mixture of *R*-LA and *S*-LA (see Supplements).

Figure 1. Chemical Structure of Lipoic Acid



*Lipoic has a chiral center, which means it can be found in two mirror image forms (S- and R-α-lipoic acid) that cannot be superimposed on each other.

Metabolism and Bioavailability

Endogenous biosynthesis

LA is synthesized *de novo* from an 8-carbon fatty acid (octanoic acid) in mitochondria, where protein-bound LA functions as an enzyme cofactor. Evidence suggests that

LA can be synthesized "on site" from octanoic acid that is already covalently bound to LA-dependent enzymes (5, 6). The final step in LA synthesis is the insertion of two sulfur atoms into octanoic acid. This reaction is catalyzed by lipoyl synthase, an enzyme that contains iron-sulfur clusters, which are thought to act as sulfur donors to LA (7, 8). The gene for lipoyl synthase has been cloned, and research is under way to learn more about its regulation (9).

Dietary and supplemental α-lipoic acid

Exogenous LA from the diet can be activated with ATP or GTP by lipoate-activating enzyme, and transferred to LA-dependent enzymes by lipoyltransferase (10, 11). Consumption of LA from food has not yet been found to result in detectable increases of free LA in human plasma or cells (3, 12). In contrast, high oral doses of free LA (≥50 mg) result in significant but transient increases in free LA in plasma and cells. Pharmacokinetic studies in humans have found that about 30%-40% of an oral dose of LA (a 50/50 mixture of *R*-LA and *S*-LA) is absorbed (12, 13). Oral LA supplements are better absorbed on an empty stomach than with food: taking LA with food decreased peak plasma LA concentrations by about 30% and total plasma LA concentrations by about 20% compared to fasting (14). Additionally, the sodium salt of *R*-LA may be better absorbed than free LA, presumably because of its higher aqueous solubility (15).

There may also be differences in bioavailability of the two isomers of LA. After oral dosing with LA, peak plasma concentrations of *R*-LA were found to be 40%-50% higher than *S*-LA, suggesting that *R*-LA is better absorbed than *S*-LA (12, 14, 16). Following oral administration, both isomers are rapidly metabolized and excreted. Plasma LA concentrations generally peak in one hour or less and decline rapidly (12, 13, 16, 17). In cells, LA is quickly reduced to DHLA, and studies *in vitro* studies indicate that DHLA is rapidly exported from cells (3).

Biological Activities

Protein-bound α-lipoic acid

Enzyme cofactor

R-LA is an essential cofactor for several mitochondrial enzyme complexes that catalyze critical reactions related to energy production and the catabolism (breakdown) of α-keto acids and amino acids (18). In each case, *R*-LA is covalently bound to a specific lysine residue in one of the proteins of the enzyme complex. The pyruvate dehydrogenase complex catalyzes the conversion of pyruvate to acetyl-coenzyme A (CoA), an important substrate for energy production via the citric acid cycle. The α-ketoglutarate dehydrogenase complex catalyzes the conversion of α-ketoglutarate to succinyl CoA, another important intermediate of the citric acid cycle. The activity of the branched-chain α-ketoacid dehydrogenase complex results in the catabolism of the branched-chain amino acids: leucine, isoleucine, and valine (19). The glycine cleavage system is a multi-enzyme complex that catalyzes the oxidation of glycine to form 5,10-methylene tetrahydrofolate, an important cofactor in the synthesis of nucleic acids (20).

Free α-lipoic acid

When considering the biological activities of supplemental free LA, it is important to keep in mind the limited and transient nature of the increases in plasma and tissue LA (see Metabolism and Bioavailability) (3).

Antioxidant activities

Scavenging reactive oxygen and nitrogen species: Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are highly reactive compounds with the potential to damage DNA, proteins, and lipids (fats) in cell membranes. Both LA and DHLA can directly scavenge (neutralize) physiologically relevant ROS and RNS in the test tube (reviewed in 3). However, it is not clear whether LA acts directly to scavenge ROS and RNS

in vivo. The highest tissue concentrations of free LA likely to be achieved through oral supplementation are at least 10 times lower than those of other intracellular antioxidants, such as vitamin C and glutathione. Moreover, free LA is rapidly eliminated from cells, so any increases in direct radical scavenging activity are unlikely to be sustained.

Regeneration of other antioxidants: When an antioxidant scavenges a free radical, it becomes oxidized itself and is not able to scavenge additional ROS or RNS until it has been reduced. DHLA is a potent reducing agent with the capacity to reduce the oxidized forms of several important antioxidants, including vitamin C and glutathione (21). DHLA may also reduce the oxidized form of α-tocopherol (the α-tocopheroxyl radical), directly or indirectly, by reducing the oxidized form of vitamin C (dehydroascorbate), which is able to reduce the α-tocopheroxyl radical (22). Coenzyme Q_{10}, an important component of the mitochondrial electron transport chain, also has antioxidant activity. DHLA can reduce oxidized forms of coenzyme Q_{10} (23), which may reduce the α-tocopheroxyl radical (24). Although DHLA has been found to regenerate oxidized antioxidants in the test tube, it is not known whether DHLA effectively regenerates other antioxidants under physiological conditions (3).

Metal chelation: Redox-active metal ions, such as free iron and copper, can induce oxidative damage by catalyzing reactions that generate highly reactive free radicals (25). Compounds that chelate (bind) free metal ions in a way that prevents them from generating free radicals offer promise in the treatment of neurodegenerative diseases and other chronic diseases in which metal-induced oxidative damage may play a pathogenic role (26). Both LA and DHLA have been found to inhibit copper- and iron-mediated oxidative damage in the test tube (27, 28) and to inhibit excess iron and copper accumulation in animal models (29, 30).

Induction of glutathione synthesis: Glutathione is an important intracellular antioxidant that also plays a role in the detoxification and elimination of potential carcinogens and toxins. Studies in rodents have found that glutathione synthesis and tissue glutathione levels are significantly lower in aged animals compared to younger animals, leading to decreased ability of aged animals to respond to oxidative stress or toxin exposure (31). LA has been found to increase glutathione levels in cultured cells and in the tissues of aged animals fed LA (32, 33). Research suggests that LA may increase glutathione synthesis in aged rats by increasing the expression of γ-glutamylcysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis (34) and by increasing cellular uptake of cysteine, an amino acid required for glutathione synthesis (35).

Modulation of signal transduction

Insulin signaling: The binding of insulin to the insulin receptor (IR) triggers the autophosphorylation of several tyrosine residues on the IR. Activation of the IR in this manner stimulates a cascade of protein phosphorylations, resulting in the translocation of glucose transporters (GLUT4) to the cell membrane and thus increased cellular glucose uptake (3, 36). LA has been found to activate the insulin signaling cascade in cultured cells (3, 36, 37), increase GLUT4 translocation to cell membranes, and increase glucose uptake in cultured adipose (fat) and muscle cells (38, 39). A computer modeling study showed that LA binds to the tyrosine kinase domain of the IR and may stabilize the active form of the enzyme (37).

PKB/Akt-dependent signaling: In addition to insulin signaling, phosphorylation and dephosphorylation of other cell-signaling molecules affect a variety of cellular processes, including metabolism, stress responses, proliferation, and survival (3). One such molecule is protein kinase B, also known as Akt (PKB/Akt). LA has been found to activate PKB/Akt-dependent signaling *in vitro* (37, 40-42) and *in vivo* (42), inhibit apoptosis in

cultured hepatocytes (37), and increase survival of cultured neurons (40). LA has also been shown to improve nitric oxide-dependent vasodilation in aged rats by increasing PKB/Akt-dependent phosphorylation of endothelial nitric oxide synthase (eNOS), which increases eNOS-catalyzed production of nitric oxide (43).

Redox-sensitive transcription factors: Transcription factors are proteins that bind to specific sequences of DNA and promote or repress the transcription of selected genes. Some transcription factors are sequestered outside the nucleus until some sort of signal induces their translocation to the nucleus. Oxidative stress or changes in the balance between oxidation and reduction (redox status) in a cell can trigger the translocation of redox-sensitive transcription factors to the nucleus. One such redox-sensitive transcription factor, known as nuclear factor-kappa B (NF-κB), regulates a number of genes related to inflammation and cell cycle control, which are involved in the pathology of diabetes, atherosclerosis, and cancer (20). Physiologically relevant concentrations of LA added to cultured cells have been found to inhibit NF-κB nuclear translocation (44). Another redox-sensitive transcription factor known as Nrf2 enhances the transcription of genes that contain specific DNA sequences known as antioxidant response elements (AREs). LA has been found to enhance the nuclear translocation of Nrf2 and the transcription of genes containing AREs *in vivo*, including genes for GCL, the rate-limiting enzyme in glutathione synthesis (34).

Deficiency

LA deficiency has not been described, suggesting that humans are able to synthesize enough to meet their needs for enzyme cofactors (45).

Disease Treatment

Diabetes mellitus

Chronically elevated blood glucose levels are the hallmark of diabetes mellitus (DM). In type 1 DM, insulin production is insufficient due to autoimmune destruction of the insulin-producing β-cells of the pancreas. Type 1 DM is also known as insulin-dependent DM because exogenous insulin is required to maintain normal blood glucose levels. In contrast, impaired cellular glucose uptake in response to insulin (insulin resistance) plays a key role in the development of type 2 DM (46). Although individuals with type 2 DM may eventually require insulin, type 2 DM is also known as noninsulin-dependent DM because interventions that enhance insulin sensitivity may be used to maintain normal blood glucose levels.

Glucose utilization

There is limited evidence that high doses of LA can improve glucose utilization in individuals with type 2 DM. A small clinical trial in 13 patients with type 2 DM found that a single intravenous infusion of 1,000 mg of LA improved insulin-stimulated glucose disposal (insulin sensitivity) by 50% compared to a placebo infusion (47). In an uncontrolled pilot study of 20 patients with type 2 DM, intravenous infusion of 500 mg/day of LA for 10 days also improved insulin sensitivity when measured 24 hours after the last infusion (48). A placebo-controlled study of 72 patients with type 2 DM found that oral administration of LA at doses of 600 mg/day, 1,200 mg/day or 1,800 mg/day improved insulin sensitivity by 25% after four weeks of treatment (49). There were no significant differences among the three doses of LA, suggesting that 600 mg/day may be the maximum effective dose (46). Data from animal studies suggest that the *R*-isomer of LA may be more effective in improving insulin sensitivity than the *S*-isomer (39, 50), but this possibility has not been tested in any published human trials.

The effect of LA supplementation on long-term blood glucose (glycemic) control has not been well studied. In an uncontrolled pilot study of a controlled-release form

of oral LA, 15 patients with type 2 DM took 900 mg/day for six weeks and 1,200 mg/day for another six weeks, in addition to their current medications (17). At the end of 12 weeks, plasma fructosamine concentrations decreased by about 10% from baseline, but glycated hemoglobin (HbA1c) levels did not change. Plasma fructosamine levels reflect blood glucose control over the past 2-3 weeks, while HbA1c values reflect blood glucose control over the past 2-4 months. At present, it is not clear whether oral or intravenous LA therapy improves long-term glycemic control in individuals with type 2 DM.

Vascular disease

The inner lining of blood vessels, known as the endothelium, plays an important role in vascular disease. Endothelial function is often impaired in diabetic patients, who are at high risk for vascular disease (51). Intra-arterial infusion of LA improved endothelium dependent vasodilation in 39 diabetic patients but not in 11 healthy controls (52). In addition, a randomized, double-blind, placebo-controlled study in 30 patients with type 2 diabetes found that intravenous infusion of 600 mg of LA improved the response to the endothelium-dependent vasodilator acetylcholine, but not to the endothelium-independent vasodilator, glycerol trinitrate (53). Endothelial function can be assessed noninvasively by using ultrasound to measure flow-mediated vasodilation, which is endothelium-dependent (54). Using ultrasound, intravenous LA has also been shown to improve endothelial function in patients with impaired fasting glucose (55) or impaired glucose tolerance (56), which are prediabetic conditions.

A few studies have investigated whether oral administration of LA might improve vascular function in patients with diabetes or metabolic syndrome. A randomized controlled trial assessed the effect of oral LA supplementation on flow-mediated vasodilation in 58 patients diagnosed with metabolic syndrome, a condition characterized by abnormal glucose and lipid

(fat) metabolism (57). Oral supplementation with 300 mg/day of LA for four weeks improved flow-mediated vasodilation by 44% compared to placebo. Diabetic patients are also at high risk for microvascular disease, which may contribute to diabetic neuropathy (46). In an uncontrolled study, oral supplementation with 1,200 mg/day of LA for six weeks improved a measure of capillary perfusion in the fingers of eight diabetic patients with peripheral neuropathy (58). While these results are encouraging, long-term randomized controlled trials are needed to determine whether LA supplementation can reduce the risk of vascular complications in individuals with diabetes.

Diabetic neuropathy

More than 20% of diabetic patients develop peripheral neuropathy, a type of nerve damage that may result in pain, loss of sensation, and weakness, particularly in the lower extremities (46). Peripheral neuropathy is also a leading cause of lower limb amputation in diabetic patients (59). Chronic hyperglycemia has been linked to peripheral nerve damage; several mechanisms have been proposed to explain the glucose-induced nerve damage, such as intracellular accumulation of sorbitol, glycation reactions, and oxidative and nitrosative stress (reviewed in 60). The results of several large randomized controlled trials indicate that maintaining blood glucose at near normal levels is the most important step in decreasing the risk of diabetic neuropathy (61, 62). However, such intensive blood glucose control may not be achievable in all diabetic patients.

Intravenous and oral LA are approved for the treatment of diabetic neuropathy in Germany (4). A meta-analysis that combined the results of four randomized controlled trials, including 1,258 diabetic patients, found that treatment with 600 mg/day of intravenous LA for three weeks significantly reduced the symptoms of diabetic neuropathy to a clinically meaningful degree (63).

The efficacy of oral LA in the treatment of diabetic neuropathy is less clear. A short-term study of 24 patients with type 2 diabetes mellitus (DM) found that the symptoms of peripheral neuropathy were improved in those who took 1,800 mg/day of oral LA for three weeks compared to those who took a placebo (64). More recently, a randomized, double-blind, placebo-controlled trial in 181 patients with diabetic neuropathy found that oral supplementation with 600 mg/day, 1,200 mg/day, or 1,800 mg/day of LA for five weeks significantly improved neuropathic symptoms (65). In this study, the 600 mg/day dose was as effective as the higher doses. A much larger clinical trial randomly assigned more than 500 patients with type 2 DM and symptomatic peripheral neuropathy to one of the following treatments: (1) 600 mg/day of intravenous LA for 3 weeks followed by 1,800 mg/day of oral LA for six months, (2) 600 mg/day of intravenous LA for three weeks followed by oral placebo for six months, or (3) intravenous placebo for three weeks followed by oral placebo for six months (66). Although symptom scores did not differ significantly from baseline in any of the groups, assessments of sensory and motor deficits by physicians improved significantly after three weeks of intravenous LA therapy. Motor and sensory deficits were also somewhat improved at the end of six months of oral LA therapy, but the trend did not reach statistical significance. In another trial of oral LA therapy, 299 patients with diabetic peripheral neuropathy were randomly assigned to treatment with 1,200 mg/day of LA, 600 mg/day of LA, or a placebo (67). However, after two years of treatment, only 65 of the original participants were included in the final analysis. In that subgroup, those who took either 1,200 mg/day or 600 mg/day of LA showed significant improvement in electrophysiological tests of nerve conduction compared to those who took the placebo. In the longest clinical trial of oral LA therapy, 421 diabetic patients with distal symmetric sensorimotor polyneuropathy took either 600 mg/day of LA or a placebo for four years (68). No difference between the two groups was seen for the

primary endpoint, a composite score that assessed neuropathic impairment of the lower limbs and nerve conduction; however, some measures of neuropathic impairment improved with LA supplementation.

Another neuropathic complication of diabetes is cardiovascular autonomic neuropathy (CAN), which occurs in as many as 25% of diabetic patients (46). CAN is characterized by reduced heart rate variability (HRV; variability in the time interval between heartbeats) and is associated with increased risk of mortality in diabetic patients. In a randomized controlled trial of 72 patients with type 2 DM and reduced HRV, oral supplementation with 800 mg/day of LA for four months resulted in significant improvement in 2 out of 4 measures of heart rate variability compared to placebo (69).

Overall, the available research suggests that treatment with 600 mg/day of intravenous LA for three weeks significantly reduces the symptoms of diabetic peripheral neuropathy. Although the benefit of long-term oral LA supplementation is less clear, there is some evidence to suggest that oral LA may be beneficial in the treatment of diabetic peripheral neuropathy (600-1,800 mg/day) and cardiovascular autonomic neuropathy (800 mg/day).

Multiple sclerosis

Feeding high doses of LA to mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS), has been found to slow disease progression (70, 71). LA treatment through subcutaneous injection also reduced clinical signs of the disease in a rat model of MS (72). LA treatment has been shown to inhibit the migration of leukocytes (inflammatory T cells, monocytes, and macrophages) into the brain and spinal cord, possibly by decreasing endothelial expression of cell adhesion molecules, inhibiting enzymes called matrix metalloproteinases (MMP), and reducing the permeability of the blood-brain barrier (70, 72-74). More recently, LA has been found to reduce the production of proinflammatory cytokines (75)

and stimulate the production of cyclic AMP and cell signaling in certain immune cells (75, 76), which may also modulate the effects of LA in MS.

Although results of animal studies are promising, human research is needed to determine whether oral LA supplementation might be efficacious in MS. A small pilot study designed to evaluate the safety of LA in 30 people with relapsing or progressive MS found that treatment with 1,200-2,400 mg/day of oral LA for two weeks was generally well tolerated (see Safety), and that higher peak serum levels of LA were associated with greater decreases in serum MMP-9 levels (77). A pharmacokinetic study showed that an oral dose of 1,200 mg of LA can result in similar serum levels in MS patients as those found to be therapeutic in mice (78). However, large-scale, long-term clinical trials are needed to assess the safety and efficacy of LA in the treatment of MS (79).

Cognitive decline and dementia

LA, alone or in combination with other antioxidants or L-carnitine, has been found to improve measures of memory in aged animals or in animal models of age-associated cognitive decline, including rats (80, 81), mice (82-85) and dogs (86). Memory assessments were done at the end of LA treatment period, and it is not known whether LA treatment might have lasting memory effects in these animal models. It is not clear whether oral LA supplementation can slow cognitive decline related to aging or pathological conditions in humans. An uncontrolled, open-label trial in nine patients with probable Alzheimer's disease and related dementias, who were also taking acetylcholinesterase inhibitors, reported that oral supplementation with 600 mg/day of LA appeared to stabilize cognitive function over a one-year period (87). This study was subsequently extended to include 43 patients with probable Alzheimer's disease, who were followed up to four years. Patients with mild dementia or moderate-early dementia who took 600 mg/day of LA, in addition to acetylcholinesterase inhibitors, experienced slower

cognitive decline compared to the typical cognitive decline of Alzheimer's patients as reported in the literature (88). However, the significance of these findings is difficult to assess without a control group for comparison. A randomized controlled trial found that oral supplementation with 1,200 mg/day of LA for 10 weeks was of no benefit in treating HIV-associated cognitive impairment (89). Although studies in animals suggest that LA may be helpful in slowing age-related cognitive decline, randomized controlled trials are needed to determine whether LA supplementation is effective in preventing or slowing cognitive decline associated with age or neurodegenerative diseases.

Sources

Endogenous biosynthesis

R-LA is synthesized endogenously by humans and bound to proteins (see Metabolism and Bioavailability).

Food sources

R-LA occurs naturally in foods covalently bound to lysine in proteins (lipoyllysine). Although LA is found in a wide variety of foods from plant and animal sources, quantitative information on the LA or lipoyllysine content of food is limited and published databases are lacking. Animal tissues that are rich in lipoyllysine (~1-3 µg/g dry wt) include kidney, heart, and liver, while vegetables that are rich in lipoyllysine include spinach and broccoli (90). Somewhat lower amounts of lipoyllysine (~0.5 µg/g dry wt) have been measured in tomatoes, peas, and Brussels sprouts.

Supplements

Unlike LA in foods, LA in supplements is free, meaning it is not bound to protein. Moreover, the amounts of LA available in dietary supplements (200-600 mg) are likely as much as 1,000 times greater than the amounts that could be obtained in the diet. In Germany, LA is approved for the treatment of diabetic neuropathies and is available by prescription (45). LA is available as a

dietary supplement without a prescription in the US (91). Most LA supplements contain a (50/50) mixture of *R*-LA and *S*-LA (*d,l*-LA). Supplements that claim to contain only *R*-LA are usually more expensive, and information regarding their purity is not currently available (92). Since taking LA with a meal decreases its bioavailability, it is generally recommended that LA be taken on an empty stomach (one hour before or two hours after eating).

Racemic vs. R-LA supplements

R-LA is the isomer that is synthesized by plants and animals and functions as a cofactor for mitochondrial enzymes in its protein-bound form (see Biological Activities). Direct comparisons of the bioavailability of oral LA and *R*-LA supplements have not been published. After oral dosing with LA, peak plasma concentrations of *R*-LA were found to be 40%-50% higher than *S*-LA, suggesting *R*-LA is better absorbed than *S*-LA, but both isomers are rapidly metabolized and eliminated (12, 14, 16). In rats, *R*-LA was more effective than *S*-LA in enhancing insulin-stimulated glucose transport and metabolism in skeletal muscle (50), and *R*-LA was more effective than LA and *S*-LA in preventing cataracts (93). However, virtually all of the published studies of LA supplementation in humans have used racemic LA. At present, it is not clear whether *R*-LA supplements are more effective than LA supplements in humans.

Safety

Adverse effects

In general, LA supplementation at moderate doses has been found to have few serious side effects. When used to treat diabetic peripheral neuropathy, intravenous administration of LA at doses of 600 mg/day for three weeks (63) and oral LA at doses as high as 1,800 mg/day for six months (67) and 1,200 mg/day for two years (66) did not result in serious adverse effects when used to treat diabetic peripheral neuropathy. Two mild anaphylactoid reactions and one severe anaphylactic

reaction, including laryngospasm, were reported after intravenous LA administration (46). The most frequently reported side effects of oral LA supplementation are allergic reactions affecting the skin, including rashes, hives, and itching. Abdominal pain, nausea, vomiting, diarrhea, and vertigo have also been reported, and one trial found that the incidence of nausea, vomiting, and vertigo was dose-dependent (65). Further, malodorous urine has been noted by people taking 1,200 mg/day of LA orally (77).

Pregnancy and lactation

The safety of LA supplements in pregnant and lactating women has not been established (94).

Drug interactions

Because there is some evidence that LA supplementation improves insulin-mediated glucose utilization (49), it is possible that LA supplementation could increase the risk of hypoglycemia in diabetic patients using insulin or oral antidiabetic agents. Consequently, blood glucose levels should be monitored closely when LA supplementation is added to diabetes treatment regimens. Co-administration of a single oral dose of LA (600 mg) and the oral antidiabetic agents, glyburide or acarbose, did not result in any significant drug interactions in one study in 24 healthy volunteers (95).

Nutrient interactions

Biotin

The chemical structure of biotin is similar to that of LA, and there is some evidence that high concentrations of LA can compete with biotin for transport across cell membranes (96, 97). The administration of high doses of LA by injection to rats decreased the activity of two biotin-dependent enzymes by about 30%-35% (98), but it is not known whether oral or intravenous LA supplementation substantially increases the requirement for biotin in humans (99).

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