

## **The Role of Alpha Lipoic Acid in Glucose Homeostasis and Human Health**

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**A**lpha lipoic acid (ALA) is an organic sulfur derivative that is formed in de novo synthesis from octanoic acid (Cicchillo, et al., 2004). The body typically produces what is needed for metabolic purposes while food intake provides a slight addition to this. The primary role of endogenously produced ALA in the body is that of an antioxidant and cofactor in numerous enzyme complexes within the mitochondria such as: pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, branched chain ketoacid dehydrogenase, and the glycine cleavage system (Shay, Moreau, Smith, Smith, & Hagen, 2009). Interestingly, one of the key factors that sparked the idea of supplementing ALA was that many patients with chronic diseases typically possessed lower tissue concentrations of the compound (Shay, et al., 2009).

The richest food sources of ALA are typically meats or animal organs, but vegetables such as spinach and broccoli also contain lesser amounts (Higdon J., 2002). In foods, ALA is bound to the amino acid lysine, while supplemental ALA is free (Higdon J., 2002). As it is unlikely that adequate amounts of ALA can be attained through diet to produce measureable effects, supplemental ALA is typically used. In supplements all isomers of ALA are usually present (R-,S-, and d,l-) this is also the mixture that has been used in most human data though R-ALA appears to be the most biologically active isomer (Higdon J., 2002). It is also solely the R isomer that is produced endogenously (Higdon J., 2002).

### **Pharmacologic Applications**

Diabetes/Glucose Disposal

The primary pharmacologic application of ALA is through its role treating or improving diabetes or diabetes related complications. It mainly acts through its insulin mimetic properties though it may possess various other roles which will be discussed in this section. In regards to glucose disposal, ALA activates numerous intracellular kinases and phosphatases such as p38 MAPK, PI3 kinase, and Akt (Shay, et al., 2009). Most of its actions are indirect through the mediation of redox status which causes conformational changes to molecules. An exception to this may be the insulin receptor substrate 1 (IRS1) which ALA has shown to directly increase the expression of (Shay, et al., 2009). Much like muscular contraction, these signals lead to the downstream activation of AMP- activated protein kinase (AMPK) which increase GLUT-4 translocation to the plasma membrane (or sarcolemma in muscle). Unlike insulin which is quite fast acting and has a maximal effect on glucose uptake within thirty minutes, ALA takes roughly double the amount of time to exert its effects (Shay, et al., 2009). This is of interest because an oral dose of ALA results in a rapid and transient rise of plasma and tissue levels before being quickly broken down and cleared from the body (Shay, et al., 2009). This again highlights the indirect action of ALA. In comparing the R- and S- isomers on glucose metabolism in rats, both resulted in improved glucose disposal but S- was half as effective as R-. Furthermore, only R-ALA increased glycogen synthesis and glucose oxidation while S-ALA actually decreased GLUT-4 to a small degree (Shay, et al., 2009). In animal exercise models, ALA has also been shown to have a beneficial effect on GLUT-4 translocation in addition to that stimulated by the exercise itself (Shay, et al., 2009). The maximal effective dosage for ALA in regards to glucose utilization is currently suggested to be 600mg/day (Higdon J., 2002).

### Vascular Disease

Supplementation of ALA has also been proposed to be of benefit in the prevention or progression of vascular disease through its antioxidant properties. In the vascular endothelium nitric oxide is a primary regulator of blood vessel diameter through its potent

vasodilatory properties. The enzyme endothelial nitric oxide synthase (eNOS) produces and releases this gas within the blood vessel walls upon phosphorylation but it can be negatively regulated by excessive oxidative stress. This leads to reduced vasodilatation and an increased risk of clotting. Through increasing the redox potential of the blood it is believed that ALA can preserve proper eNOS functioning but it also plays a more direct role in relation to this enzyme (C.M. Sena, 2007). It has been shown that activation of the PI3K pathway also plays an important role in the activation of eNOS (Montagnani, Ravichandran, Chen, Esposito, & Quon, 2002). In vivo data in rats, animals, and small human studies have confirmed this belief with doses as low as 150-300 mg/day exhibiting a positive effect upon vasodilation (Sola, et al., 2005).

### Hypertension

ALA has direct effects upon the major intracellular antioxidant glutathione, increasing the expression of its rate limiting enzyme, gamma-glutamylcysteine ligase (Higdon J., 2002). Glutathione is an endogenous antioxidant that typically declines in performance with age, leading to increased oxidative stress. This situation relates to hypertension because increased oxidative stress leads to the alteration of membrane calcium channels and ultimately increased cytosolic calcium as well as blood pressure (Vasdev, Ann Ford, Parai, Longerich, & Gadag, 2000). ALA also limits overproduction of an endothelial vasoconstrictor called endothelin-1. This coupled with the previously discussed preservation of eNOS leads to improved levels of vasodilation thus less vascular tension (Shay, et al., 2009). At the current time human studies are conflicting but this may possibly be due to inadequate dosing (most studies are using 300mg/day in overweight subjects).

### Inflammatory Diseases

Chronic inflammatory states often coincide with high levels of oxidative stress. In light of previously described mechanisms it should come as no surprise that ALA can have a positive

therapeutic effect here as well. Studies in humans are few to date but those that have been undertaken have produced favorable results. One particular trial in which subjects were given 300mg/day for 4 weeks resulted in a 15% decrease in interleukin-6, a major marker of inflammation (Sola, et al., 2005). More research is currently needed in this area to develop a greater perspective on the role of ALA in chronic inflammation.

### **Disease Prevention**

Similar to its pharmacological role, ALA maintains many of its preventative benefits through its role as an antioxidant, preserving DNA and cellular integrity. Unlike many other antioxidants, ALA possesses the ability to neutralize free radicals without becoming one itself as both the oxidized (ALA) and reduced (dihydrolipoic acid; DHLA) forms possess antioxidant activity (Shay, et al., 2009). Specifically, DHLA has been shown to regenerate other known antioxidants (Shay, et al., 2009) such as vitamins c, e, glutathione, etc... The oxidized and reduced versions of lipoic acid also form chelates with metal ions (more so DHLA) which has implications in various diseases such as cardiovascular disease and alzheimer's (Higdon J., 2002; Shay, et al., 2009). By chelating these ions it prevents them from starting metal catalyzed free radical reactions in tissues such as the brain or vasculature. It is important to note that the antioxidative capability of ALA is likely a greater function of its ability to maintain the reduced status of other endogenous antioxidants rather than a direct action itself. This is again highlighted by the fact that ALA is quickly catabolized in the body. For healthy people the typical recommended dosage is roughly 300 mg/day R-ALA (Higdon J., 2002).

### **Ergogenic Aid**

Insulin is a very powerful anabolic hormone that increases tissue uptake of numerous compounds important to the athlete such as amino acids, glucose, and creatine. For this reason the insulinogenic effect of ALA is of particular interest to athletes, especially in the

postworkout period. The addition of 1 gram of ALA to a postworkout drink containing creatine monohydrate and carbohydrate has been proven to increase muscle phosphocreatine to a significant degree greater than the ingestion of creatine alone or creatine + carbohydrate (Burke DG, 2003). To a lesser degree, ALA may also enhance long duration aerobic performance through its glutathione sparing effects (Sen & Packer, 2000). The literature currently suggests an intake of 300-600mg/day of ALA in general for athletes taken post workout. Strength/power athletes looking to maximize phosphocreatine storage should aim towards the higher end of this recommendation (Lockwood, 2008).

### **Safety**

There is not currently an upper limit established on ALA intake by the USDA however animal studies have been undertaken to establish LD<sub>50</sub> values. In canines 400-500 mg/kg bodyweight has been established (Packer, Witt, & Tritschler, 1995) and rats who have a much higher tolerance to the compound have an LD<sub>50</sub> of >2 g/kg bodyweight (Cremer, Rabeler, Roberts, & Lynch, 2006). Clinical trials have taken humans up to doses as high as 2.4 grams/day without reported adverse effects (Ziegler, et al., 1999) and sustained doses of 1.8 g/day have been given for six months without significant problems noted (Ziegler, et al., 1999). The most commonly reported side effects are hives, rashes, and itchiness of the skin, GI distress/diarrhea, and malodorous urine (Higdon J., 2002). It should be noted that all of these side effects seem to appear at doses that are roughly double what the current literature suggests to be the maximally effective amount (600 mg/day) (Higdon J., 2002).

In conclusion, ALA looks to be a promising compound for just about every population. It is generally well tolerated with few side effects. Future research should focus on compiling more human data to clearly elucidate ALA activity in vivo as well as more concrete evidence of optimal dosing protocols. Furthermore, ALA's association with disease states, specifically Alzheimer's and cardiovascular disease requires further investigation.

**Brief Author Biography**

Ben Esgro is a Certified Sports Nutritionist through the International Society of Sports Nutrition, he also holds a B.S in Nutrition with a minor in exercise science from West Chester University. Ben is pursuing a Master's in Sports Nutrition at Marywood University. Ben is also a competitive Natural Bodybuilder. He can be contacted at [besgro@gmail.com](mailto:besgro@gmail.com).

**References**

- Burke DG, C. P., Parise G, Tarnopolsky MA, Candow DG. (2003). Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. *Int J Sport Nutr Exerc Metab.*, 13(3), 294-302.
- C.M. Sena, E. N., T. Louro, T. Proenca, R. Fernandes, M.R. Boarder, R.M. Seica. (2007). Effects of alpha-lipoic acid on endothelial function in aged diabetic and high-fat fed rats. *British Journal of Pharmacology*, 153(5).
- Cicchillo, R. M., Iwig, D. F., Jones, A. D., Nesbitt, N. M., Baleanu-Gogonea, C., Souder, M. G., et al. (2004). Lipoyl Synthase Requires Two Equivalent of S-Adenosyl-l-methionine To Synthesize One Equivalent of Lipoic Acid†. [doi: 10.1021/bi049528x]. *Biochemistry*, 43(21), 6378-6386.
- Cremer, D. R., Rabeler, R., Roberts, A., & Lynch, B. (2006). Safety evaluation of [alpha]-lipoic acid (ALA). [doi: DOI: 10.1016/j.yrtph.2006.06.004]. *Regulatory Toxicology and Pharmacology*, 46(1), 29-41.
- Higdon J. (2002). Lipoic Acid. Retrieved 04/05/2010, 2010, from <http://lpi.oregonstate.edu/infocenter/othernuts/la/#intro>
- Lockwood, C. (2008). An Overview of Sports Supplements. In K. D. Antonio J., Stout J., Greenwood M., Willoughby D., Haff G. (Ed.), *Essentials of Sports Nutrition and Supplements* (pp. 465). Totowa, NJ: Humana Press.
- Montagnani, M., Ravichandran, L. V., Chen, H., Esposito, D. L., & Quon, M. J. (2002). Insulin Receptor Substrate-1 and Phosphoinositide-Dependent Kinase-1 Are Required

- for Insulin-Stimulated Production of Nitric Oxide in Endothelial Cells. *Mol Endocrinol*, 16(8), 1931-1942.
- Packer, L., Witt, E. H., & Tritschler, H. J. (1995). Alpha-lipoic acid as a biological antioxidant. [doi: DOI: 10.1016/0891-5849(95)00017-R]. *Free Radical Biology and Medicine*, 19(2), 227-250.
- Sen, C. K., & Packer, L. (2000). Thiol homeostasis and supplements in physical exercise. *Am J Clin Nutr*, 72(2), 653S-669.
- Shay, K. P., Moreau, R. F., Smith, E. J., Smith, A. R., & Hagen, T. M. (2009). Alpha-lipoic acid as a dietary supplement: Molecular mechanisms and therapeutic potential. [doi: DOI: 10.1016/j.bbagen.2009.07.026]. *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1790(10), 1149-1160.
- Sola, S., Mir, M. Q. S., Cheema, F. A., Khan-Merchant, N., Menon, R. G., Parthasarathy, S., et al. (2005). Irbesartan and Lipoic Acid Improve Endothelial Function and Reduce Markers of Inflammation in the Metabolic Syndrome: Results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) Study. *Circulation*, 111(3), 343-348.
- Vasdev, S., Ann Ford, C., Parai, S., Longerich, L., & Gadag, V. (2000). Dietary [alpha]-lipoic acid supplementation lowers blood pressure in spontaneously hypertensive rats. *Journal of Hypertension*, 18(5), 567-573.
- Ziegler, D., Hanefeld, M., Ruhnau, K. J., Hasche, H., Lobisch, M., Schütte, K., et al. (1999). Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care*, 22(8), 1296-1301.