Alpha Lipoic Acid

Overview

Alpha lipoic acid, or just lipoic acid (LA), is a unique and potent antioxidant. It can deliver antioxidant activity in both fat- and water-soluble mediums, and it is capable of having an antioxidant effect in both its oxidized (LA) and reduced (DHLA [dihydrolipoic acid]) forms (Goraca et al., 2011). This effectively allows LA to deliver its antioxidant effect to any cell or tissue type, as well as to any subcellular compartment, in the body (Packer et al., 1997; Rochette et al., 2013). It appears to be particularly effective in recharging enzymes in the mitochondria, the "energy centers" of the cells (Arivazhagan et al., 2001).

While vitamin C and glutathione are absolutely essential to good health, LA can be considered a master antioxidant ***orchestrator***, facilitating the optimal interactions among the other antioxidants. DHLA directly recharges vitamin C and indirectly recharges vitamin E. LA also increases intracellular glutathione levels (Kleinkauf-Rocha et al., 2013) and coenzyme Q10 levels. LA administration has been documented to increase intracellular glutathione levels by as much as 70%, and this bolstering of glutathione has been seen both *in vivo* and *in vitro* (Han et al., 1995). Reduced LA (DHLA) can regenerate glutathione from its oxidized counterpart, and LA can also help provide the cysteine needed for the synthesis of glutathione. Furthermore, LA administration increases vitamin C levels inside the cells (Shay et al., 2009)

In reviewing the medical literature, it is important to note the many different names ascribed to LA, so that it can be better realized all that LA has been documented to do. These synonyms include, but are still not completely limited to, thioctic acid, 6,8-thioctic acid, 6,8-dithioctane acid, 1,2-dithiol-3-valeric acid, lipoate, and α-lipoic acid. This article will only use the names LA for the oxidized form and DHLA for the reduced form.

Biochemical Properties

DHLA, the reduced form of LA, is capable of exerting an antioxidant effect directly by donating electrons to a pro-oxidant or an oxidized molecule. It can regenerate reduced vitamin C (ascorbic acid) from dehydroascorbic acid (oxidized ascorbic acid), and it can indirectly regenerate vitamin E back from its oxidized state (Scholich et al., 1989). As well, LA metabolites have been shown to have anti-inflammatory (antioxidant) effects (Kwiecien et al., 2013).

Uniquely, even LA, the oxidized form of DHLA, can exert an antioxidant effect. But this does not mean there is any donation of electrons by LA to an pro-oxidant or oxidized molecule, since there are none to give. However, it has been documented that LA can inactivate free radicals, which is a significant antioxidant effect (Packer et al., 2001). Also, the ability of LA to chelate metals can produce an antioxidant effect (Ghibu et al., 2009). And just like reduced vitamin C, DHLA can exert a pro-oxidant effect by donating its electrons for the reduction of iron, which can then break down peroxide to the pro-oxidant hydroxyl radical via the Fenton reaction (Packer et al., 1994). So, depending upon the microenvironment in which it is found, LA and its reduced partner, DHLA, can promote antioxidation or oxidation.

LA has been to show to effectively chelate toxic metals directly, and it also indirectly strongly supports the chelation of metals by its ability to increase glutathione levels inside the cells. Glutathione and its associated enzymes play important roles in the ability of the body to chelate and excrete a wide variety of toxins, toxic metals included. Metals known to form complexes directly with LA and DHLA include manganese, zinc, cadmium, lead, cobalt, nickel, iron, copper, cadmium, arsenic, and mercury.

The use of LA in the detoxification of individuals with high levels of mercury is not a straightforward situation clinically, however. Some evidence exists that LA can redistribute the heavy metals that it binds to other tissues under the right clinical circumstances. What these circumstances are is not always clear, and a long-term detoxification program containing LA should be monitored by a knowledgeable healthcare practitioner. Certainly, unlike many other antioxidant supplements, a good clinical response to a smaller dose of LA does not always mean that more is better.

LA should always be taken in light of how one feels. While most individuals will respond very well right from the start, a supplementing individual who feels poorly after LA supplementation either needs to discontinue it or needs to consult with a practitioner experienced in detoxification protocols. There is no denying the long-term benefits of LA for most people (see list below), but everyone is not the same, and caution needs to be exerted when a positive clinical response is not seen at the outset of supplementation (Patrick, 2002).

While humans are capable of synthesizing LA from fatty acids and cysteine, the amounts are very small at best (Carreau, 1979). To realize the now well-established benefits of LA, enough must be taken in from outside sources (Packer, 1998). Although LA is present in both animal and plant sources, some form of supplementation needs be taken to reliably realize these benefits. It has been estimated that 200 to 600 mg LA supplements effectively deliver up to 1,000 times more LA that can be obtained from most diets (Singh and Jialal, 2008).

LA is rapidly absorbed after a single oral dose ranging between 50 and 600 mg. It is also very rapidly cleared, as its half-life in plasma is only 30 minutes (Breithaupt-Grogler et al., 1999). This rapid clearance reflects both transport into tissues as well as renal excretion (Harrison and McCormick, 1974). However, the absolute amount absorbed has been variable and incomplete, ranging between 20 and 40% in one study. Food also impaired the absorption of supplemented LA (Teichert et al., 1998). LA is primarily metabolized in the liver, an organ for which LA has been shown to lessen the negative effects of a variety of toxic agents (Saad et al., 2010; Tabassum et al., 2010).

Clinical and Laboratory Effects

LA has been documented to have positive effects on a wide variety of clinical conditions, which is completely consistent with its antioxidant, selective pro-oxidant, and metal/toxin chelation properties. Any condition with increased oxidative stress can be expected to respond favorably to LA administration (Harding et al., 2012). These effects and conditions include the following:

1. Anti-aging (McCarty et al., 2009; Bagh et al., 2011; Jiang et al., 2013)
2. Decreased oxidative stress (Li et al., 2013)
3. Improved memory (Stoll et al., 1993)
4. Depression (Silva et al., 2013)
5. Antitoxin (Ozturk et al., 2013; Sokolowska et al., 2013); toxic mushroom poisoning (Bustamante et al., 1998); prevention against lead toxicity (Flora et al., 2012); lessened cisplatin-induced toxicity (Hussein et al., 2012)
6. Alcoholism (Ledesma and Aragon, 2013; Peana et al., 2013)
7. Ulcerative colitis (Trivedi and Jena, 2013)
8. Cataract prevention (Ou et al., 1996; Li et al., 2013)
9. Diabetes and its complications (Bajaj and Khan, 2012; Nebbioso et al., 2013); suppression of hyperinsulinemia and insulin resistance (Ozdogan et al., 2012)
10. Anti-inflammatory (Kwiecien et al., 2013)
11. Anti-proliferative effects in cancers (Feuerecker et al., 2012; Kapoor, 2013; Michikoshi et al., 2013)
12. Prevention of malignant transformation (Kumar et al., 2013)
13. Decreased myocardial infarct size and myocardial protection (Deng et al., 2013)
14. Lessened bone loss in osteoporosis (Mainini et al., 2012; Polat et al., 2013)
15. Decreased ectopic calcification (Kim et al., 2013)
16. Glaucoma (Filina et al., 1995)

17. Interruption of HIV replication (Baur et al., 1991; Fuchs et al., 1993; Patrick, 2000)
18. Hypertension [high blood pressure] (Vasdev et al., 2011)
19. Neuroprotection (Ji et al., 2013; Sayin et al., 2013)
20. Erectile dysfunction (Mitkov et al., 2013)
21. Low back pain (Battisti et al., 2013)
22. Lessened weight gain and obesity (Prieto-Hontoria et al., 2009; Seo et al., 2012)
23. Neuropathic pain (Mijnhout et al., 2010)
24. Prevention of fatty liver disease (Jung et al., 2012; Kaya-Dagistanli et al., 2013)
25. Prevention of damage to DNA (Unal et al., 2013)
26. Protection against NSAID-induced gastric damage (Kaplan et al., 2012)
27. Lessened evolution of diabetic cardiomyopathy (Lee et al., 2012)
28. Synergistically increases the tumor-killing effects of vitamin C in the treatment of cancer (Casciari et al., 2001)
29. Effective treatment in advanced cancer in humans (Berkson et al., 2009)
30. Effective monotherapy for cancer in mice (Al Abdan, 2012)
31. Protection against radiation damage in a palladium complex (Ramachandran et al., 2010)

Safety

No defined toxic level or upper limit for consumption has been established for LA in humans. However, unlike an antioxidant like vitamin C, LA does reliably show toxicity in animals at very high levels of intake. As discussed above, the multiple potential effects of LA in the body, including the binding and possible redistribution of toxic metals, makes individualized dosing and clinical follow-up a reasonable approach. The stored toxin profile and its response to a regular intake of LA will always be a factor that differs from one person to the next.

In rats, an LD_{50} of 2,000 mg/kg of body weight was observed. This means at this dosage level, 50% of the rats died. In humans, such a dose would range from about 100,000 mg for a small woman to about 200,000 mg for a large man, even though such toxicity cannot be reliably extrapolated from the animal study. Supplemental dosing and intravenous dosing of LA have never remotely approached these levels. Clinical trials in humans have given daily doses of 1,800 and 2,400 mg daily for extended periods with no evidence of adverse effects (Goraca et al., 2011).

Liposome-Encapsulated Lipoic Acid

When the regular form of LA is supplemented, the absorption is rapid but incomplete, and the half-life in the plasma is very short, as noted above. As with other liposome-encapsulated preparations, liposome-encapsulated lipoic acid (LELA) will have the additional characteristics of this delivery system. Absorption will be virtually complete, no loss of payload will result from gastrointestinal acid or digestive enzymes, and no energy consumption should occur while it is assimilated, ultimately into the cytoplasm of cells throughout the body. Regular LA utilizes an energy-dependent transport across intestinal cells (Takaishi et al., 2007). LA also appears to use a Na^+-dependent multivitamin transporter to go from the blood plasma into tissues (Shay et al., 2009; Ohkura et al., 2010; de Carvalho and Quick, 2011).

While there is a sizeable body of evidence on liposomes in general, and there is a growing body of evidence on the especially striking benefits of a nutrient such as vitamin C in a liposome-encapsulated form, there does not yet exist an accumulated body of evidence on the benefits of LELA. The lack of energy consumption by the liposome delivery system in LELA is always desirable. Also, the ability of liposomes to penetrate into subcellular compartments should make LELA an especially useful supplement, as it is the mitochondria inside the cells that concentrate and use the most LA. A possible additional benefit of LELA is that it effectively makes the contained LE a “sustained-release” formulation. Regular LE gets cleared rapidly from the plasma, a significant amount of which is excreted into the urine. LELA would be expected to get substantially more of the ingested LE inside the cells throughout the body.

Multiple older studies have asserted that regular LE has no problem crossing the blood-brain barrier. A recent study now asserts that LA does not cross the blood-brain barrier readily, even though the brain does end up receiving significant antioxidant benefit from any administered LA (Chng et al., 2009). The unique bioavailability of LELA might prove to be especially useful in brain and neurological disorders.

A final note would be to re-emphasize that LE has many different effects inside the body, most of them extraordinarily positive, as the list of LE effects above demonstrates. However, LA is a powerful detoxifier, and anyone who experiences undesirable symptoms after taking LELA or regular LA should not continue it without the guidance of a healthcare practitioner experienced in dealing with patients on detoxification regimens.

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