interviews with nutritional experts

Lipoic Acid Basics

Interview With **Dr. Jim Clark**
Interviewed By **Richard A. Passwater Ph.D.**

In several recent articles, Dr. Lester Packer and I have discussed the merits of alpha-lipoic acid as an unique antioxidant that is critical to the antioxidant network involving vitamin C, vitamin E and glutathione. Last month we discussed how alpha-lipoic acid protects nuclear factor-kappa-B which has a role in gene expression and control. These articles have resulted in readers requesting more information about the basic properties of alpha-lipoic acid.

I have always found Dr. Jim Clark, Director of Technology Development of the Henkel Corporation to be an invaluable resource for information regarding the biochemistry of the antioxidant nutrients. Readers may remember the discussion on carotenoids with Dr. Clark and Lance Schlipalius in the September 1993 issue. In this issue, Dr. Clark and I will discuss some of the basic properties of this important antioxidant. Well, actually it is more than an antioxidant as Dr. Clark will explain.

Passwater: Let's start at the beginning for the benefit of those readers who have not heard very much about alpha-lipoic acid. What is alpha-lipoic acid and what does it do?

Clark: Alpha-lipoic acid is often referred to as the metabolic antioxidant. It really has two functions in the human body. First, it plays a role in the metabolism of the food that we eat to convert it into energy. The second role, and this is more recently discovered, is that of an antioxidant where it prevents oxidative damage to body components.

The chemical structure of alpha-lipoic acid gives it very unique capabilities. It consists of a relatively small, eight-carbon atom chain having two attached sulfur atoms, one attached to the sixth carbon atom and the other sulfur atom attached to the eighth carbon atom, with the sulfur atoms also linked to each other.

Passwater: The sulfur atoms are what make this unique compound so versatile, but let's talk some more about the benefits of alpha-lipoic acid before we discuss more about its structure. Do we make optimal amounts of alpha-lipoic acid in the body or is it "conditionally essential?"

Clark: That's difficult to answer because no one has determined the optimal level of alpha-lipoic acid. Certainly the optimal level will vary from individual to individual depending upon their lifestyle and especially how much exercise and oxidative stress they experience. There is no doubt at all but what the body does synthesize alpha-lipoic acid. There is a lot of evidence that the synthesized alpha-lipoic acid is only adequate for the metabolic function and that additional alpha-lipoic acid that is needed for the antioxidant function comes from dietary sources including supplements.

Passwater: Let's look at the converse of that. If it is such that the body makes barely enough for metabolic purposes if we are well-nourished and environmental factors and everything else is going right, and then we encounter oxidative stress due to free radicals or other reactive oxygen species, is some of the alpha-lipoic acid consumed in the battle against free radicals?

Clark: That is not well understood. It is certainly conceivable that severe oxidative stress could deplete the level of alpha-lipoic acid needed to fulfill its metabolic function. However, the control mechanisms for synthesis of alpha-lipoic acid aren't well enough understood yet so that we could unambiguously say that the body would or would not replenish the consumed alpha-lipoic acid.

Passwater: In essence, alpha-lipoic acid is converting food carbohydrates and fats into blood sugar (glucose) and fatty acids which then go through a process that leads to the extraction of energy. What is alpha-lipoic acid helping the body do?

Clark: The body needs to "burn" blood sugar to produce energy, but instead of using high temperatures like we have in fire, the body has special biological catalysts called enzymes which extract the energy from sugars and fatty acids at normal body temperatures.

Catalysts are atoms or molecules that facilitate reactions that either, as in the body, would not occur to any significant degree without their help, or in the case of chemical plant productions, need to be sped up to be commercially feasible. Catalysts are not consumed in these reactions, and a small amount can facilitate many reaction cycles.

Enzymes act as catalysts and are not consumed in the process. They are present to facilitate the process along the way. In essence, the multi-enzyme complex involving alpha-lipoic acid is breaking down the molecules produced in earlier metabolism, pyruvate, into a slightly smaller molecules called acetyl-coenzyme A. This results in molecules that can enter into a series of reactions called the citric acid cycle or Kreb's cycle which finishes the conversion of food into energy.

Sugars and fats are first partially oxidized in the body by other enzymes that combine them with oxygen that we have respired through our lungs. These products such as pyruvate, must then be acted upon by the alpha-lipoic enzyme complex in order for the process to continue into the citric acid cycle. A shortage of alpha-lipoic acid would be a critical bottleneck slowing down the energy-production process.

Alpha-Lipoic acid is involved in what is called a "decarboxylation" which simply means that it cleaves off carbon dioxide. In the process excess energy is liberated which the body captures as ATP (adenosine triphosphate) and then uses that to provide the energy for muscle contraction.

The carbon dioxide is then expired in our breath and the energy is used for body functions including everything from thinking to exercising. So we're converting food into carbon dioxide, water and energy.

Passwater: How does lipoic acid work as a coenzyme?

Clark: Alpha-lipoic acid is a co-factor in what is called a multi-enzyme complex that catalyzes what biochemists like to call "oxidative decarboxylation of alpha-keto acids" such as pyruvic acid. Forget the jargon and just remember that pyruvic acid is a product of a process called glycolysis, which is the first step in converting blood sugar (glucose) into energy that the body can use. The alpha-lipoic acid itself is bound to a very complex enzyme which is a high molecular weight protein and is not consumed when it is serving as a metabolic co-factor but it is continually regenerated.

Passwater: Does this process wherein alpha-lipoic acid facilitates the conversion of blood sugar into energy have an effect on blood sugar level?

Clark: Normally it doesn't, because this entire process is subject to other types of enzymatic control. However, there is strong evidence that very high intake of alpha-lipoic acid does influence glucose metabolism. It appears to increase the absorption of glucose into muscle tissue in non-insulin dependent diabetes ("Type II diabetes," also called "adult onset diabetes.")

Passwater: Very high intake -- this implies a level that the body normally doesn't produce. This would be an effect of either diet or supplementation. Is that correct?

Clark: That is correct. It would take consumption of let's say more than 1,500 milligrams per day before any effect would be seen on glucose metabolism.

Passwater: Do alpha-lipoic acid supplements reduce glycation?

Clark: Yes. Glycation is the process where proteins react with excess glucose. This sugar damage to protein is just as detrimental as oxygen damage to proteins. There is strong evidence that alpha-lipoic acid reduces glycation.

Passwater: That is important. You have explained how alpha-lipoic acid is critical to energy production and reduces glycation. How does lipoic acid work as an antioxidant?

Clark: It works in many different ways. The first thing that we have to realize is that when we talk about alpha-lipoic acid there are actually two molecules that we have to consider. The first is alpha-lipoic acid itself and the second is a reduced form called dihydrolipoic acid. In the reduced form, two atoms of hydrogen have been added to alpha-lipoic acid, one hydrogen attached to each of the sulfur atoms.

Passwater: What effect does having the sulfur-sulfur linkages split and hydrogen added to them have on the function of the molecule. Why does this change make the two molecules so different and what is the significance of this?

Clark: They are different because you now have different chemical functionalities and they can react in different ways with other materials. Compounds that supply hydrogen atoms or electrons in chemical reactions are called reducing agents. Oxidizing agents are compounds that receive hydrogen atoms or electrons. The primary difference is the fact that the reduced form --the dihydrolipoic acid-- is a much stronger reducing agent and it is capable of regenerating vitamin C and vitamin E from their oxidized forms. Both dihydrolipoic acid and alpha-lipoic acid can form strong chelates. These are complexes with transition metal ions such as iron and copper.

Passwater: The chelation role of alpha-lipoic acid is also very important, and I want to follow up on that point later. But let's continue with the transport and interconversion of alpha-lipoic acid and dihydrolipoic acid. Is there evidence that the alpha-lipoic acid is taken up into cells then?

Clark: Normally dihydrolipoic acid is formed in the cells. Cells tend to absorb the alpha-lipoic acid, reduce it and then secrete the dihydrolipoic acid back into the bloodstream.

Passwater: We have mentioned how lipoic acid gets into the cell. Is there an active transport mechanism through the membrane? Does it have receptors or is it a chemical process or diffusion?. Just how does it get into the cells?

Clark: No one knows that for sure. There is some indication that there may be a specific transporter for alpha-lipoic acid but it has not been pinned down yet.

Passwater: Alpha-lipoic acid can be converted into dihydrolipoic acid inside of cells. Can dihydrolipoic acid be converted back into alpha-lipoic acid in the cells?

Clark: Definitely. Most of that evidence comes from animal studies and from cell culture studies . But it is quite clear that under those conditions alpha-lipoic acid is taken up by cells and of course the metabolic function of alpha-lipoic acid occurs inside cells. The processes that it catalyzes actually occur in the mitochondria. Mitochondria are sometimes called the "powerhouse" of the cell where food is converted into energy.

Passwater: What is "redox cycling" and what is the advantage of a compound that undergoes redox cycling?

Clark: Redox cycling is simply the interconversion of an oxidized form of the material to a reduced form and back again. In some materials, the oxidation or reduction is irreversible. But the reduction and oxidation of alpha-lipoic acid is quite reversible. So since it is quite reversible, it can sit there and switch from one to the other. This is a real advantage because it allows it to act as a carrier, as a transfer agent for electrons from one compound to another.

One of the earlier discoveries concerning alpha-lipoic acid was that it could prevent the symptoms of scurvy and also vitamin E deficiency in animals. It appears to be very clear that what it is doing is regenerating vitamin E and vitamin C from their oxidized form back to their active reduced forms.

Passwater: So we have evidence that lipoic acid is carried from the bloodstream through the cell membrane into the cell interior, the cytosol, and then we also know it can go from the cell interior through another membrane that surrounds mitochondria. Do we know if it goes through any other of the cellular structures components?

Clark: Since mitochondria are reconstructed every ten days, alpha-lipoic acid must get into them. It probably penetrates other cellular components also. The remaining question is: Is there a specific alpha-lipoic acid transporter? Unfortunately, we don't have an answer for that question yet.

Passwater: Now we have discussed the fact that it's transported very well into cell and critical cell components like the mitochondria, that as dihydrolipoic acid, it regenerates vitamin C which in turn can regenerate vitamin E. It's a pretty universal antioxidant. Can it get into various compartments of the body, both lipid-based areas and water-based areas?

Clark: Yes, that is one of the reasons why it is sometimes referred to as a universal antioxidant, as well as the metabolic antioxidant. Not only does it react with many different free radicals and oxidizing species including singlet oxygen, but it also, because of the size and functionality of the molecule is soluble in both water-based and fat-based areas of tissues. It is not as water-soluble as vitamin C, but it is much more water-soluble than vitamin E. This degree of water-solubility and fat-solubility will allow alpha-lipoic acid into all body systems. The main reason for this dual solubility is the size of the molecule. It is larger than ascorbic acid but it is much smaller than vitamin E.

The other factor is the functionality of the molecule. It does contain a carboxylic acid end-group, and that has a tendency to make it more soluble in water than vitamin E. At the same time it has more carbon atoms than vitamin C and that makes it more soluble in lipid compartments.

Passwater: Already it is apparent that alpha-lipoic acid is a versatile antioxidant. However, there is still more to its antioxidant protective actions. Let's discuss the ability of dihydrolipoic acid to chelate transition metals. If iron and copper are present in excess as free, unbound ions, they can be oxidants. Any compound that would chelate free ions of iron and copper would thus indirectly reduce oxidation and be considered an antioxidant.

Clark: In most cases in the body, iron and copper are complexed with other proteins so the concentration of free metal ions is quite low, but under some conditions of trauma, you can have these metal ions released and under those conditions, the ability to complex is very important because that prevents these ions catalyzing oxidative processes. There is experimental evidence that both alpha-lipoic acid and dihydrolipoic acid can form chelation complexes, but dihydrolipoic acid is probably more effective in this role.

Passwater: Would lipoic acid be of use for someone with iron overload disease?

Clark: Alpha-lipoic acid has been used to treat individuals with heavy metal poisoning.

Passwater: Is the ability to chelate due to the presence of both sulfhydryl and carboxylic groups in the molecule?

Clark: The chelation ability is due to both sulfur atoms and the carboxyl functionality with mixed results. This property still needs investigation.

Passwater: Are there other roles for the sulfur atoms in the ring? Here we have a simple molecule having a "backbone" of eight carbon atoms and nature, instead of adding a hydroxyl group to form a monophenol nutrient like vitamin E, or adding several hydroxyl groups similar to bioflavonoids, adds two sulfur atoms and links them together. What do the sulfur atoms have to do with alpha-lipoic acid's function as a coenzyme in the bonding of this multi-enzyme complex system?

Clark: It gets rather complex, but when alpha-lipoic acid is in its role of a metabolic coenzyme, the carboxylic acid end-group anchors it to the enzyme through formation of a chemical bond called an "amide linkage" or a "peptide linkage." The sulfur groups on the other end of the alpha-lipoic acid molecule then actually undergo chemical reactions and bond to the carbonyl group on the keto acid which is undergoing the oxidative decarboxylation.

Also the sulfur atoms are essential for the antioxidant activity and for the chelation properties. The oxidation potential between the sulfur-sulfur bond and the sulfur-hydrogen bond is such that it allows easy interconversion under physiological conditions. Consequently, the tissues can quite easily convert alpha-lipoic acid which has a sulfur-sulfur bond to dihydrolipoic acid which has cleaved that sulfur-sulfur bond and replaced it with two sulfur- hydrogen bonds.

Passwater: That helps explains why alpha-lipoic acid is such a powerful and versatile antioxidant. How does the body make alpha-lipoic acid and what are the limiting factors for its biosynthesis?

Clark: We believe it is synthesized from an eight-carbon carboxylic acid called octanoic acid. It is also believed that the sulfur comes from cysteine, a sulfur-containing amino acid, but the exact chemical mechanism and the factors that control the synthesis are not known yet.

Passwater: Are there are any dietary conditions or disease conditions that you can think of that might limit one's production of lipoic acid?

Clark: I suppose if you had a deficiency of sulfur-containing amino acids. Certainly cysteine is an essential amino acid and if your dietary consumption of that were inadequate, then you would not have one of the building blocks for alpha-lipoic acid.

Passwater: Since dietary lipoic acid is so important to so many people, what are some good dietary sources?

Clark: Again this is an area where science doesn't fully understand. If you look in the literature, you don't find very much about the lipoic acid content of various foods. What does seem clear is that is present in mitochondria. So you would think foods that are rich in mitochondria should be good sources. Of course the most common foods rich in mitochondria would be red meat because they are some of the richest mitochondria sources. Also, alpha-lipoic acid is present in chloroplasts which are the "mitochondria" of plants.

Passwater: But we have a problem today where people today are de-emphasizing red meat in their diet and other sources in the scientific literature mentioned are yeast, which is not a staple of a typical American diet. Do you think that our emphasis on controlling dietary factors like the amount of fat are also possibly inadvertently putting a limiting factor on the amount of the dietary alpha-lipoic acid and its precursors like the sulfur-containing amino acid cysteine. Could you foresee this as a problem?

Clark: It certainly could be, particularly individuals who don't eat red meat could well benefit from supplementation of lipoic acid.

Passwater: How well is alpha-lipoic acid absorbed and is it absorbed intact?

Clark: There is a lot of evidence from animal studies that it is absorbed intact and absorption appears to be pretty efficient as you would expect for something that is fairly water soluble. I have seen figures as high as 80% for animal studies, but no one has really quantitated that with human trials.

Passwater: Once it is absorbed from the diet, can the body transport this in a form that can be utilized or is it degraded or somehow not made available to the body?

Clark: It is quite clear that cells do take up alpha-lipoic acid and some is retained, some is secreted. Some is secreted as dihydrolipoic acid. There is also metabolism of alpha-lipoic acid in the liver.

Passwater: What research has been conducted into possible therapeutic uses for alpha-lipoic acid in relation to its role in metabolism? It must be of value to diabetic patients who have oxidative stress as well as glycation problems. This seems like a nutrient that would have an influence on both, reducing oxidative stress and reducing glycation.

Clark: It certainly does. This is one of the earliest areas that has been explored with alpha-lipoic acid. In Europe it is actually used as a pharmacological agent to prevent some of the side effects of diabetes and oxidative stress. Large clinical trials have shown a clinically meaningful reduction in diabetic polyneuropathy, one of the complications of diabetes.

Passwater: How about other long-term uses such as detoxification. You mentioned earlier that it chelates transition metals. Has this been used for purposes such as this?

Clark: It has been used for detoxification of heavy metal poisoning in Europe. This is taking advantage of its ability as a chelator instead of its antioxidant function, but there is fairly decent evidence showing its beneficial effects against cadmium and mercury poisoning.

Passwater: What are some of the latest areas of research interest in lipoic acid?

Clark: Alpha-lipoic acid is being looked at in many of the areas where oxidative stress is believed to be a causative agent. One of these is cataracts. The interior of the eye is a very aqueous environment and many of the common antioxidants such as vitamin E and beta-carotene are not very soluble in water. Alpha-lipoic acid, because of its water solubility, may exert a protective effect against the formation of cataracts. This has been demonstrated in some animal models but there is not yet solid data for human trials.

Another area that is being investigated is atherosclerosis. As we learn more and more about atherosclerosis, there is strong evidence indicating that oxidation plays a key role in some of the early steps in depositing of cholesterol plaques in arterial walls. There is a strong possibility that alpha-lipoic acid will be protective against this. I think those are the two most exciting area of new research with alpha-lipoic acid.

Passwater: Dr. Clark, thank you for reviewing the scientific literature on the basic properties of alpha-lipoic acid with us.

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