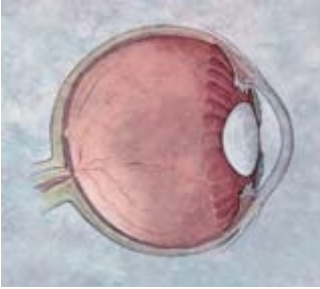


**REPORT****Alpha Lipoic Acid, Acetyl-L-Carnitine and Carnosine**

The Latest Significant Research on This Powerful Life Extension Trio

By Tim Batchelder, B.A.



A landmark study published in the Proceedings of the National Academy of Sciences<sup>1,2</sup> produced by noted biochemist Bruce Ames and a team of scientists describes the powerful synergistic abilities of lipoic acid and acetyl-L-carnitine to significantly combat aging. Together, these two nutrients are shown to help combat diabetes, maintain proper cognitive function, support heart health, support energy production, protect the body from radiation and chemical toxins, and maintain immunity. And, when combined with carnosine, a powerful trio for longevity is created.

**New Findings in the Fight Against Diabetes**

The story begins in the 1950's when Eli Lilly and Company backed the discovery of alpha lipoic acid (ALA) by a team led by Lester Reed in the Department of Chemistry at University of Texas, Austin. More recently a German pharmaceutical company Asta Medica has taken the lead in developing ALA for use in diabetic neuropathy. Today, acetyl-L-carnitine (ALC) and carnosine have joined the ranks of ALA in the fight against diabetes.

This supplement trio goes to the root of the problem of diabetes to control blood sugar levels. One recent study found that ALA increased glucose uptake from 40% (approximately the same amount as insulin) up to an impressive 300% (in insulin resistant muscles) in obese diabetic mice.<sup>1</sup> Leading antioxidant authority Lester Packer<sup>2</sup> notes that ALA works against insulin resistance by increasing the permeability of cell membranes, which is decreased by hyperglycemia and prevents uptake of glucose. ALC given at 1.0 milligram per kilogram per minute constant infusion increases glucose storage from 3.8 to 5.2 milligrams per kilogram per minute.<sup>3</sup> Carnosine also works to lower glucose in cases of hyperglycemia.<sup>4</sup>

One side effect of high sugar levels is damage to the nervous system, called neuropathy. Packer claims ALA can prevent or slow neuropathy experienced by up to 70% of diabetics<sup>5</sup> and it has been used in Germany for over 30 years for this application. ALA and evening primrose oil were found to improve blood flow and nerve function by lowering blood lipid risk factors in a recent study.<sup>6</sup> ALA improves circulation to the sciatic nerve, which is crucial for nerve function but is reduced in neuropathy by impaired acetylcholine-mediated vascular relaxation and accumulation of superoxide radicals.<sup>7</sup> ALA provides 85% protection against the 31% reduction in maximum endothelium relaxation to acetylcholine that occurs in diabetes by improving nitric oxide levels, vasodilation and cervical ganglion blood flow.<sup>8</sup> ALA is shown in another study to reverse the impairment of nitric oxide (NO)-mediated vasodilation in diabetes due to increased vascular oxidative stress.<sup>9</sup> In addition, protein glycation (denaturing) or cross linking by excessive glucose damages nervous, vascular, kidney, retinal and other tissues and carnosine is an effect anti-glycating agent due to its hydroxyl radical scavenging ability.<sup>10</sup> Carnosine's anti-protein glycation abilities make it very effective at delaying senescence in nervous system cells and other types of cells.<sup>11</sup>

High sugar levels can cause extensive damage to other body systems as well. For example, people with diabetes often suffer from a high incidence of eye cataracts (free radical damage to the non renewable proteins of the eye lens) since the cells of the eye lens are very susceptible to glucose damage. Eye lens cells use slower anaerobic (without oxygen) metabolism as transparent structures without mitochondria which puts them at greater risk for free radical damage. Fortunately, ALA can help this condition. Packer and his team suggest that about 60% of diabetes related cataracts can be prevented with ALA.<sup>12</sup> ALA works by recharging levels of the potent antioxidant glutathione, which is essential for protecting the eye lens. ALA can also help protect other organs from sugar damage. A recent study found that long term ALA supplementation in rats (30 milligrams per kilogram of body weight per day) prevented kidney injury (depletion of glutathione and accumulation of malondialdehyde) due to high blood sugar levels in people with diabetes.<sup>13</sup>

**Preventing Cognitive Decline**

Besides diabetes the other frontline application of ALA, ALC and carnosine has been in preventing disorders of cognitive decline. For example, ALC, first discovered in 1905, has recently become an important new target of drug and biotech companies as an Alzheimer's treatment block-buster drug. It is manufactured by Italy's Sigma-Tau as ALCAR, also known as Branigen (Glaxo), Nicetile (Sigma-Tau) and Normobren (Medosan).

ALC works by preventing buildup of amyloid plaque that damages brain tissues and is emerging as a cause of cognitive disorders such as Alzheimer's. A new study shows that ALC helps control amyloid by inhibiting free radical action and preserving energy

production in the brain.<sup>14</sup> Similarly, ALA protects rat cortical neurons against cell death induced by amyloid induced free radical damage.<sup>15</sup> And carnosine works to inhibit advanced glycation end-products (AGEs), which cross-links proteins, renders them insoluble, accumulates in protein plaques and leads to oxidation of neurons.<sup>16</sup> AGE inhibitors such as carnosine may work by chelating copper,<sup>17</sup> which is linked to brain disorders such as Alzheimer's.

Chemical messengers like neurotransmitters are vital to maintaining cognitive function yet often decline with age. Fortunately, a new study shows that ALC improves synthesis of neurotransmitters such as acetylcholine and uptake of choline, both of which increases learning capacity (maze learning was used in this study).<sup>18</sup> ALC improves Alzheimer's by helping to maintain brain energy production, phospholipid metabolism and acetylcoenzyme A levels, the latter being used by the body to re-synthesize acetylcholine.<sup>19</sup> Degenerative ataxias are also slowed by ALC due to improved mitochondrial energy production, synthesis of acetylcholine, and antioxidant metabolism.<sup>20</sup> ALA also controls excitotoxicity (a condition of excess glutamate, the main excitatory neurotransmitter) and improves survival in animal models of Huntington's disease.<sup>21</sup>



ALA, ALC and carnosine work by preventing damage to nervous system tissues by free radicals. For example, one new study found that ALA protects against Alzheimer's by preventing the oxidative stress and energy depletion caused by deranged glucose metabolism and free radical production. In this study 600 milligrams of ALA was given daily to nine patients with Alzheimer's and related dementias for roughly a year and led to stabilization of cognitive function.<sup>22</sup> ALA and vitamin E work synergistically to prevent free radical damage to brain cells during stroke according to new research.<sup>23</sup> And it controls activity of a key enzyme in cell death, caspase-3 (CPP32), which increases in the hippocampus in rats with diabetes and cerebral ischemia by up to 80%.<sup>24</sup> Together ALA and ALC improve performance on memory tasks by lowering oxidative damage to mitochondria and improving mitochondrial function.<sup>25</sup> ALA and ALC also work synergistically to increase ambulatory activity, restore levels of ascorbate and lower levels of malondialdehyde (a product of lipid oxidation) in old rats more than either supplement alone.<sup>26</sup>

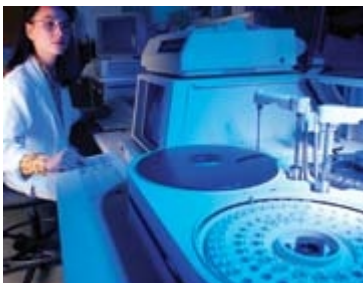
### **Keeping Cardiovascular Disease in Check**

Cardiovascular disease is the number one killer of Americans. We've heard this many times but how many people actually do something to prevent it? Fortunately, ALA, ALC and carnosine provide just the tools we need to take action against this frightening disorder.

High glucose levels oxidize low-density lipoproteins resulting in formation of foam cells and deposits of atherosclerotic plaques. As a result, people with diabetes suffer from higher rates of heart disease, stroke, and hypertension than the general population. Fortunately, ALA inhibits monocyte adhesion and endothelial activation, which leads to atherosclerosis due to oxidative stress.<sup>27</sup> Carnosine inhibits oxidation of low-density lipoprotein (LDL), which leads to atherosclerosis, by chelating (removing) copper, which oxidizes ascorbic acid.<sup>28</sup>

ALA prevents hyperglycemia induced hypertension in rats by lowering free radical production and raising glutathione levels.<sup>29</sup> It also prevents hypertension and protects against kidney and vascular injuries in rats by suppressing endothelin-1 (a substance produced in blood vessels that regulates their tone).<sup>30</sup> Carnosine is shown to suppress diabetes triggered increases in blood pressure by reacting with small carbonyl compounds (aldehydes and ketones) which accumulate on proteins during aging.<sup>31</sup>

Heart health is closely tied to how well heart cells can make energy and protect themselves from free radical attack. Recent research suggests that carnosine increases heart contractility by releasing calcium in calcium-regulated proteins in cardiac muscle cells.<sup>32</sup> ALA improves numerous functions in the heart including oxygen uptake, ATP levels, cardiac output, pyruvate (energy) production, lactate (a waste product) accumulation and glucose and glycogen (energy) storage and breakdown. It also protects glutathione and controls hydroxyl radicals, which may account for its anti-aging, heart supporting function.<sup>33</sup> Finally, ALA is found to protect against reperfusion arrhythmias and lipid peroxidation induced by ferrous ions and ascorbate.<sup>34</sup>



### **New Solutions for HIV-AIDS and Cancer**

Another recent application of ALA, ALC and carnosine that has caught the attention of drug and biotechnology companies is for immune disorders such as cancer and HIV-AIDS. For example, Polaprezinc an ultra-safe Japanese drug made from carnosine and zinc is shown to help fight certain cancers but has yet to be approved by the FDA for use in the U.S. One recent study noted that ALA is toxic to leukemia cell lines, inhibits proliferation of mitogen-stimulated human peripheral blood lymphocytes, and increases interleukin-2.<sup>35</sup> ALA synergistically enhances vitamin C cytotoxicity against hollow fibre tumors and unlike ascorbate, is equally effective against proliferating and non-proliferating cells.<sup>36</sup>



## REPORT

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ALC helps maintain liver function, which is essential for detoxification. One new study found that ALC almost completely restores the age-dependent decline in oxygen consumption, gluconeogenesis, urea synthesis, and ketogenesis found in the liver of old rats to the levels found in young rats.<sup>37</sup> ALC also helps prevent hepatotoxicity and increases survival during chemotherapy with hepatotoxic alkylating agents for cancer.<sup>38</sup> ALC and ALA are useful in treating muscle and nerve mitochondrial toxicity caused by nucleoside analog reverse transcriptase inhibitor therapy for HIV-AIDS.<sup>39</sup> ALC also enhances detoxification of ethanol in the liver as well as the unpleasant side effects of detoxification. For example, it significantly reduces the onset of tremors in ethanol withdrawal syndrome as well as the level of ethanol intake in alcohol-preferring rats.<sup>40</sup> One new study shows that ALA (and its chemical cousin alpha-lipoamide (LM) may work as an antioxidant by chelating iron which is involved in cell death by lysosomal rupture.<sup>41</sup> Further, since it has a particular affinity for the liver ALA can also treat liver damage from mushroom poisoning, snake venom, acetaldehyde and viral hepatitis. ALA was studied extensively in the 1950s for radiation protection and was found to be more effective than other common radio-protectants such as cysteamine. It was put to use for victims of Chernobyl, and as a sulfur compound, can bind and eliminate heavy metals. ALA is also shown to decrease smoking-related lipid peroxidation.<sup>42</sup> Finally, carnosine is a potent radioprotectant and prevents damage by cold, hyperthermia, and hypoxia.<sup>43</sup>



#### Support for Energy, Muscle Recovery and Weight Loss

Exercise creates a heavy load of free radical activity, which makes it a natural target for powerful antioxidants like ALA, ALC and carnosine. Several recent studies have looked at how these compounds work to protect muscle tissue during exercise and maintain energy stores. For example, one study noted that carnosine inhibits lipid peroxidation and oxidative modification of protein in muscle tissue.<sup>44</sup> It works as a pH buffer to protect muscle cells from oxidation under the acidic conditions of muscular exertion. Similar, ALA decreases lipid peroxidation and lactic acid accumulation and increases levels of glutathione, vitamins C and E and the activities of mitochondrial enzymes, which prevents tissue damage and improves ATP (energy) synthesis.<sup>45</sup> ALA also helps Chronic Fatigue Syndrome.<sup>46</sup> Finally, ALA and exercise interact in an additive fashion to improve insulin action in insulin-resistant skeletal muscles in obese rats.<sup>47</sup>

#### Conclusion

The surge of recent research on the synergies and anti-aging benefits of ALA, ALC and carnosine is making them an important addition to any supplement plan. What is so exciting is the versatility of these antioxidant compounds, which seem to work in so many body systems, from the nervous system to the cardiovascular, musculoskeletal and immune systems. In doing so they are able to

effectively combat the major diseases of our time including diabetes, cognitive decline and Alzheimer's, heart disease, obesity and immune disorders such as cancer and HIV-AIDS.

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