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AS WE SEE IT

Why Antioxidants Aren't Enough

Every second, a destructive process called “glycation” occurs throughout the body. Glycation can be described as the binding of a protein molecule to a glucose molecule resulting in the formation of damaged, non-functioning structures. Many age-related diseases such as arterial stiffening, cataract and neurological impairment are at least partially attributable to glycation. The glycation process is presently irreversible.

In the August 2001 issue of Life Extension magazine, an article reported on a compound called ALT-711 that has been shown to partially reverse glycation. Regrettably, the company trying to get ALT-711 through the FDA’s drug approval process is woefully under funded, and it may take years before this lifesaving compound becomes available...if ever.[1]

Life Extension has long argued that the high cost of gaining FDA-approval denies Americans access to life-saving compounds such as ALT-711.[2] It can take so long for a new compound to become an approved “drug”, that many companies run out of capital before they are able to comply with the FDA’s Byzantine regulatory procedures. The result is that Americans die even though potentially effective therapies sit in the FDA’s waiting room.

Since we cannot yet reverse the pathological effects of glycation, it becomes critical for those seeking to prevent premature aging to at least slow this lethal process.

Gaining control over our biochemistry

A recent study explains how certain chemical reactions, such as glycation, are so dangerous to the body. This paper pointed out that organisms survive by successfully integrating the countless chemical reactions that sustain their metabolism. Aging results largely from the chronic insults caused by chemical side-reactions that cumulatively degrade the structure and function of the organism.[3]



The most important of these “side-reactions” are oxidation and glycation. Oxidation occurs when free radicals attack biological molecules, removing an electron—just as iron oxidizes when it rusts. The oxidation of fats, called lipid peroxidation, sets off a chain reaction that generates large numbers of free radicals. Glycation is a series of reactions that irreversibly cross-links sugars to proteins, as happens when a chicken browns in the oven.

The body’s proteins are the most important targets of these reactions. From a biochemical point of view, the body is composed mostly of amino acid chains that we know as proteins. There is a telltale biochemical sign of serious protein damage called the carbonyl group, which becomes attached to proteins in oxidation or glycation reactions. The carbonyl group is actually carbon monoxide (CO), which blocks oxygen use and transport. “Carbonylated” proteins lose their elasticity and resist the body’s attempts to break them down. Later in life, about one-third of the body’s proteins become carbonylated in this way.

How does the body cope with these chronic assaults on proteins? Long-lived cells, such as neurons and muscle cells, contain high levels of a dipeptide called carnosine, made up of histidine and beta-alanine. Unlike ordinary antioxidants, carnosine blocks all the above-mentioned pathways of protein carbonylation.

It is now known that metals, especially copper, strongly promote these carbonylation pathways. Fortunately carnosine chelates



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(binds) excess copper and zinc so that they cannot promote carbonyl-forming reactions.

Protein Browning

Antioxidants protect proteins against oxidative damage caused by free radicals, but not against equally damaging sugars. When sugars (or sugar-containing reactive compounds such as aldehydes) cross-link proteins, the result is wrinkled skin, neurodegeneration, atherosclerosis and diabetic complications.

The glycation process that turns a chicken brown in the oven is exactly what happens to the proteins in our body as we age. When body proteins react with sugars they turn brown and fluorescent, lose elasticity, and cross-link to form insoluble masses that generate free radicals. The resulting AGEs (advanced glycation endproducts) accumulate in our collagen and skin, cornea, brain and nervous system, arteries and vital organs as we age. Unfortunately, they are highly resistant to the normal processes of protein turnover and renewal that maintain the healthy tone of youthful body tissues and organs.

Glycation and oxidation reinforce each other in a vicious circle. Glycation has long been considered a “fixative” of free radical damage, while glycated proteins act as free radical generators. A leading glycation researcher, Professor John Baynes of the University of South Carolina, suggests that we think of glycated proteins as amplifiers and integrators of oxidative damage.[3] Copper is the accelerant, stimulating oxidation, lipid peroxidation and glycation. A study by Professor Baynes and associates soon to be published in the Journal of Biological Chemistry shows that copper chelation is instrumental to glycation fighters, including carnosine.[4]

Consequently, it is necessary to suppress all of these interrelated factors to protect the body’s proteins. While antioxidants close the front door to oxidation, they leave open the back door to glycation, and the side door to metal toxicity. Antioxidants are simply not cut out to block the many biochemical pathways that damage proteins. Indeed, research conducted by Professor Baynes and associates shows that oxidation is not necessary for protein glycation and cross-linking, from which they conclude:

Without the need for oxidation chemistry for efficient browning of proteins by smaller sugars, therapeutic strategies that rely solely on antioxidant activity to inhibit the Maillard reaction [the “browning” process that follows glycation] may have limited efficacy.[5]

Nature doesn’t rely solely upon antioxidants to protect vital proteins in the brain, eye and muscle, and neither should the Life Extensionist. Rather, nature employs a multipurpose compound that scavenges free radicals, quenches reactive aldehydes and lipid peroxidation products, inhibits glycation and chelates toxic metals. A complete review of carnosine’s properties is beyond the scope of this article, however we note that carnosine has been shown to protect DNA, crystallin (eye lens protein), amyloid beta, the cellular antioxidants SOD and catalase, serum albumin and anti-thrombin III (an anticoagulant blood protein) from glycation. For further information, see the sidebar “Carnosine Summary” and the articles cited therein.

Alzheimer’s disease

Carnosine’s ability to chelate copper and zinc is especially important in the brain. These metals are neurotoxic at far lower concentrations than previously thought, yet are essential to the transmission of impulses across brain synapses. Nature’s solution to this problem is carnosine, without which normal brain activity would be neurotoxic. Carnosine has been shown to protect neurons from copper and zinc toxicity at concentrations similar to those found in the brain.[6]

The significance of these findings is underscored by the discovery that tiny amounts of zinc and especially copper stimulate the formation of senile plaques in Alzheimer’s disease, by causing amyloid-beta to aggregate.[7] Conversely copper-zinc chelators reverse this process, dissolving the plaques. Moreover, copper potentiates the neurotoxicity of amyloid-beta, turning it into a pro-oxidant.[8]

In the laboratory, the copper-zinc chelator clioquinol dissolves amyloid-beta deposits in postmortem brain tissue from Alzheimer’s disease patients. A new study extends these results to mice genetically prone to overproduce amyloid-beta.[9] Clioquinol cut amyloid deposits in half over a nine week period with no adverse effects. The mice treated with clioquinol also exhibited significantly improved scores on a behavioral rating scale.



Curiously, clioquinol was sold as an oral antibiotic until it was withdrawn from the market in the early 1970s due to overdose-related neurological side effects now thought to be prevented by vitamin B12 supplementation. Clioquinol is now in FDA-mandated Phase II clinical trials, and will require several years of testing before it could reenter the pharmaceutical market as a treatment for Alzheimer’s disease.

For the foreseeable future, the significance of clioquinol research lies in its validation of copper-zinc chelation as an effective therapeutic mechanism for Alzheimer's disease—a mechanism shared by an inexpensive natural agent that is currently available.



German scientists compared the ability of carnosine and anti-glycation drugs to block cross-linking of amyloid-beta, the process that generates senile plaques. One of the drugs, tenilsetam, has demonstrated clinical benefit in Alzheimer's disease; the other drug was aminoguanidine. They incubated amyloid-beta with fructose, a sugar abundant in the brain that cross-links proteins up to ten times faster than glucose. All of the anti-glycation agents tested, including carnosine, prevented amyloid-beta from cross-linking, keeping it nearly 100% soluble.[10]

This laboratory finding suggests that formation of senile plaques can be prevented by inhibiting glycation, and we have already seen that copper-zinc chelation dramatically cuts amyloid-beta deposits. The relatively high levels of carnosine in the brain are not surprising when one considers that carnosine combines these two mechanisms, anti-glycation and copper-zinc chelation, with additional neuroprotective and antioxidant functions.

Protecting brain chemistry

A new study shows that carnosine helps prevent the deterioration of brain chemistry as seen in Alzheimer's disease. The study compared the effects of carnosine and antioxidants on neurochemical functions in a rat strain that overproduces free radicals. The study measured three neurochemical parameters altered in Alzheimer's and other neurodegenerative diseases.[11]

First results of this study showed that carnosine protected thiol groups in brain proteins from oxidation. Thiol groups are essential to the stability and function of proteins. Cells employ glutathione (itself a thiol) to protect thiol-containing proteins from oxidative damage. According to a new study, protein thiol groups decline in Alzheimer's disease despite activation of the glutathione system to counteract oxidative stress.[12]

Second, carnosine protected against excitotoxicity, a common pathway to Alzheimer's and other neurological disorders. Excitotoxicity is toxic overactivity of the neurotransmitter glutamate, the main transmitter of excitatory impulses in the brain. There is considerable evidence that excitotoxic complications determine the long-term effects of stroke, and are largely responsible for the toxic effects of senile plaques in Alzheimer's disease.[13,14] The study found that carnosine prevented an increase in the density of glutamate binding sites (NMDA receptors), which would have increased excitotoxicity and led to memory derangement. This reinforces earlier findings that carnosine protects brain cells from the excitotoxic effects of glutamate analogs.[15]

Third, carnosine prevented degradation of the enzyme (Na/K-ATPase) that drives the cell's sodium-potassium pump. Impairment of this enzyme, as occurs in Alzheimer's disease, interferes with the ability of brain cells to regulate calcium levels.[16] Calcium is a key signaling molecule in neurons, which use ion pumps to maintain a low intracellular calcium level.

The failure to properly regulate cellular calcium levels is thought to be a major cause of brain aging and Alzheimer's disease. The influx of calcium ions into brain cells—as happens when the sodium-potassium pump fails—makes them more vulnerable to excitotoxicity, and eventually leads to cell death.[17,18]

Carnosine thus preserved the integrity of brain proteins, neurotransmission and ion regulation under conditions of oxidative stress. The disruption of these neurochemical functions in Alzheimer's disease magnifies the toxicity of amyloid-beta, the material that makes up the senile plaques—the pathological hallmark of the disease. This study thus complements recent findings that carnosine protects brain biochemistry and extends life span in senescence-accelerated mice.[19]

Beyond antioxidants

Carnosine Summary

- Safe, naturally present in the body
- Extends lifespan 20% in senescence-accelerated mice
 - Dramatically improved behavior & appearance of old mice
 - Preserved brain biochemical functions
- Rejuvenates senescent human cells in culture
 - Increased cell life span
 - Restored youthful appearance and growth patterns to cells approaching senescence
- Most effective natural glycation fighter
 - Protects proteins from cross-linking
 - Protects against formation of AGEs (advanced glycation endproducts)
 - Protects proteins from AGE toxicity
- Multifunctional protein protector

Protein carbonylation in its many forms is an underlying cause of neurodegenerative disease, and of aging processes along with their signs such as skin wrinkling. Traditional antioxidants suppress some of the many pathways involved, while having no effect upon the others.

It has been established beyond question that antioxidants perform a crucial biochemical function in preventing reactive oxygen damage. However expecting an antioxidant to protect proteins against every form of carbonylation is like attempting to build a house with only a screwdriver—an essential tool, but incapable of replacing the rest of the toolbox. Carnosine, nature's multipurpose tool for protein protection, was designed by evolution to control the many factors that cooperate in degrading the body's proteins.

The chemical side-reactions that erode biological structure and function in the course of aging result from toxic effects of the most basic elements in the body's chemistry—oxygen, sugars, lipids and essential metals. We cannot do without these biochemical elements, but nutritional science is now giving us the understanding to better control their side effects.

The key levers, such as CoQ10, carnosine and full-spectrum vitamin E, operate naturally in the body. With wise nutritional supplementation we can gain increased leverage over the battle between chemistry and biology as we age. If drugs such as ALT-711 are approved in time, many of us may be able to reverse the lifelong degenerative effects of glycation.

Wishing you a long and prosperous life,



Paul Wand, M.D.

P.S. For further information about glycation, please refer to the January 2001 issue of Life Extension magazine.

- Protects against formation of protein carbonyls, the hallmark of protein damage
- Inhibits damaged proteins from damaging healthy proteins
- Helps preserve normal protein turnover
- Aids recycling of damaged proteins
- Protects against metal toxicity
 - Chelates copper and zinc
 - Naturally protects against copper-zinc toxicity in the brain
 - Copper-zinc chelators dissolve Alzheimer's disease plaques
- Versatile antioxidant & aldehyde scavenger
 - Quenches hydroxyl, superoxide and peroxy radicals
 - Suppresses lipid peroxidation
 - Superior protection of chromosomes from oxygen damage

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- Protects brain proteins & chemistry
- Protects brain cells from excitotoxicity
- Inhibits cross-linking of amyloid-beta into Alzheimer's disease plaques
- Sharply reduces lipid peroxidation in brains of senescence-accelerated mice
- Safeguards brain chemistry in rats overproducing free radicals

For details, please refer to the Life Extension magazine articles "Carnosine: Nature's Pluripotent Life Extension Agent" and "Carnosine and Cellular Senescence" in the January 2001 issue.

When it comes to protecting the body's proteins, new research leaves yesterday's solutions behind. We look over the horizon at tomorrow's answers to a fundamental problem of biological life.

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