

REPORT

The Anti-Aging Effects of Carnosine



Proteins are the substances most responsible for the daily functioning of living organisms. Destruction to proteins can be caused by oxidation (as by free radicals) and protein-sugar reactions (glycation). Once too many proteins lose their ability to function, the body becomes prone to degenerative diseases and premature aging.¹ Carnosine, an amino acid compound, has been shown to specifically protect against the age-related degradation of protein.

Carnosine quenches the most destructive protein-oxidizing agent (the hydroxyl radical). One study showed carnosine was the only antioxidant to significantly protect cellular chromosomes from oxidative damage.² Antioxidants cannot completely protect proteins. Nature's second line of defense is to repair or remove damaged proteins.³ This is where carnosine demonstrates its most profound anti-aging effect.

Protein degradation occurs as a result of cross-linking and the formation of advanced glycation end products (AGE). These changes figure prominently in the processes of aging and its typical signs such as skin wrinkling and brain degeneration.^{4,5} Studies show that carnosine is effective against cross-linking and the formation of advanced glycation end products (AGE).^{6,7} Glycated proteins produce 50-fold more free radicals than nonglycated proteins and carnosine may be the most effective anti-glycating agent known.

An example of carnosine's defense against protein degradation is provided by MDA (malondialdehyde).⁸ MDA causes protein cross-linking and AGE formation. Carnosine has been shown to inhibit MDA-induced glycation in blood albumin and eye lens protein.⁹ Carnosine has also been shown to keep MDA from inducing protein cross-linking.¹⁰ One study showed that carnosine actually decreased MDA levels in mice.

Carnosine is highly concentrated in the brain. The reason is that the brain uses carnosine to protect against cross-linking, glycation, excitotoxicity and oxidation. Animal studies show that carnosine provides broad protective effects in simulated ischemic stroke.¹¹

Abnormal copper and zinc metabolism stimulates senile plaque formation in Alzheimer's disease. Chelators of these metals dissolve plaques in the laboratory. Carnosine is a potent copper-zinc chelating agent that can inhibit the cross-linking of amyloid-beta that leads to brain cell plaque formation. A signature of Alzheimer's disease is impairment of brain arterial and capillary system. Carnosine has been shown to protect the cells that line brain blood vessels from damage by amyloid-beta as well as byproducts of lipid oxidation and alcohol metabolism.¹²

Carnosine extends cellular life span

Our bodies are comprised of cells that replace themselves by dividing. There is a genetic limit as to how many times our cells will continue to replicate themselves via healthy division processes. Once enough cells reach their genetic reproductive limit, the organism (our body) is no longer able to sustain life functions and succumbs to disease or death. Carnosine appears to extend the period of time that cells will continue to divide in a youthful manner.

Laboratory research suggests that carnosine has the ability to rejuvenate cells approaching the end of the life cycle of dividing cells, restoring normal appearance and extending cellular life span.¹³ When scientists transferred late-passage fibroblasts (a type of skin cell) to a culture medium containing carnosine, they exhibited a rejuvenated appearance and often an enhanced capacity to divide.¹⁴ The carnosine medium increased life span, even for old cells. Cells transferred to the carnosine medium attained a life span of 413 days, compared to 126 to 139 days for the control cells. This study showed that carnosine induced a remarkable 67% increase in cellular life span.

WHY WE NEED SUPPLEMENTAL CARNOSINE

Carnosine levels in the body decline with age. Muscle levels decrease 63% from age 10 to age 70, which may account for the reduction in muscle mass and

These aged cells also grew in the characteristic patterns of young cells, and resumed a uniform appearance in the presence of carnosine. But when they transferred the aged cells back to a medium lacking carnosine, the signs of senescence quickly reappeared. The scientists switched late-passage cells back and forth several times between the culture media. Carnosine consistently restored the youthful cell phenotype within days, whereas the standard culture medium (without carnosine) brought back the senescence cell phenotype. How does carnosine revitalize cells in culture? Some researchers propose that carnosine may rejuvenate cells by reducing the formation of abnormal proteins, or by stimulating the removal of old proteins.⁹

Carnosine extends organism life span

A study tested the effect of carnosine on life span and indicators of aging in senescence-accelerated mice. Carnosine extended the life span of the treated mice by 20% on average, compared to the mice not fed carnosine.¹⁵ The mice given carnosine were about twice as likely to reach the "ripe old age" of 12 months as untreated mice.

Carnosine did not alter the 15 month maximum life span of the senescence-accelerated mouse strain, but it did significantly raise the number of mice surviving to old age. Carnosine distinctly improved the appearance of the aged mice, whose coat fullness and color remained much closer to that of young animals. Significantly more carnosine-treated mice had glossy coats (44% vs. 5%), while fewer had skin ulcers (14% vs. 36%).

The researchers also measured biochemical indicators associated with brain aging. Carnosine treated mice had significantly lower levels of toxic MDA (malondialdehyde) in their brain cell membranes. MAO-B (monoamine oxidase B) activity was 44% lower in the carnosine-treated mice, indicating maintenance of youthful dopamine metabolism. Aging humans produce too much MAO-B, and this is thought to contribute to certain types of brain cell damage. Glutamate binding to its cellular receptors nearly doubled in the carnosine treated group, which may explain the more normal behavioral reactivity of the carnosine-fed mice.

This longevity study showed that carnosine significantly improved most measures of appearance, physiological health, behavior, and brain biochemistry, as well as extending life span. The researchers concluded that "carnosine-treated animals can be characterized as more resistant to the development of features of aging."

Carnosine chelates copper and zinc

Copper and zinc are neurological double-edged swords. While the body cannot live without them, new research confirms that they can also be neurotoxic. Abnormal copper-zinc metabolism is implicated in Alzheimer's disease, stroke, seizures, and many other diseases with neurological components. Copper and zinc appear to be needed to modulate synaptic transmission, but can become neurotoxins at the concentrations reached when they are released from synaptic terminals. The brain must buffer these metals so that they can perform their functions without neurotoxicity. The new research on copper-zinc toxicity shows that carnosine provides that buffering action.¹⁶ When scientists exposed rat neurons to physiological concentrations of copper or zinc the neurons died. However carnosine at a modest physiological concentration protected the neurons from the toxic effects of these metals.

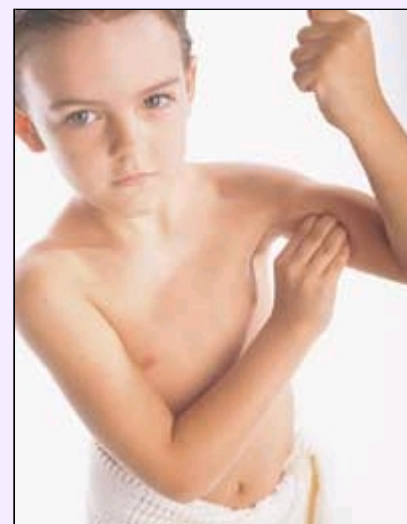
A spate of recent research papers point to the role of abnormal copper and zinc metabolism in the development of Alzheimer's disease. This abnormal copper and zinc metabolism contributes to amyloid-beta formation and toxicity through a host of mechanisms.^{17,18} These findings on copper and zinc as Alzheimer's disease promoters led scientists to investigate the effect of metal chelators on amyloid-beta plaques. A recent laboratory experiment by an international team of scientists found that chelators of copper and zinc solubilize (dissolve) aggregates of amyloid-beta in post-mortem human tissue samples from the brains of Alzheimer's disease patients.¹⁹ They hypothesize that:

"Agents that specifically chelate copper and zinc ions but preserve magnesium and calcium may be of therapeutic value in Alzheimer's disease."

function seen in aging humans.* Carnosine acts not only as an antioxidant in muscle, but also as a pH buffer.** In this way it keeps on protecting muscle cell membranes from oxidation under the acidic conditions of muscular exertion. Carnosine enables the heart muscle to contract more efficiently through enhancement of calcium response in heart cells.*** Muscle levels of carnosine correlate with the maximum life span of animal species.

Carnosine has been shown to rejuvenate connective tissue cells, which may explain its beneficial effects on wound healing. Damaged proteins accumulate and cross-link in the skin, causing wrinkles and loss of elasticity. Protein cross-linking is also involved in cataract formation. Carnosine has been shown to be effective in the treatment of senile cataracts in dogs,+ and in the prevention of cataract development in rabbits.

The multiplicity of pathological effects caused by protein degradation places this problem beyond the scope of simple antioxidants.++ Carnosine is the most promising broad-spectrum shield against protein degradation.



* Stuerenburg HJ, Kunze K. Concentrations of free carnosine (a putative membrane-protective antioxidant) in human muscle biopsies and rat muscles. Arch Gerontol Geriatr. 1999;29:107-113.

** Burcham PC, Kerr PG, Fontaine

Carnosine fits this metal chelating profile, offering pH buffering and hydroxyl radical scavenging actions in addition. Not only does carnosine chelate copper and zinc, but the presence of copper and zinc ions enhances carnosine's potency as a scavenger of the superoxide radical.²⁰

Microvascular damage is the harbinger of Alzheimer's disease, preceding its other pathological features, possibly by impairing delivery of nutrients to the brain.²¹ An experiment on rat brain blood vessel walls shows that carnosine prevents this damage.¹² In another experiment carried out by the same British team, carnosine protected brain blood vessel cells from damage by MDA (malondialdehyde), a toxic product of lipid peroxidation. Carnosine inhibited protein cross-linking, while protecting cellular and mitochondrial function.²² A third experiment showed that carnosine also protects cells against the toxicity of acetaldehyde, which is produced when alcohol is metabolized.¹²

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REPORT

The Anti-Aging Effects of Carnosine

Carnosine protects against excitotoxicity and stroke

Many neurological disorders are caused by excitotoxicity.²³ This brain cell damaging effect is often caused by excessive sensitivity to glutamate, the main excitatory neurotransmitter. Excitotoxicity triggers a cascade of events including membrane polarization, ending in cell death.

It is probable that excitotoxic complications determine the long-term effects of stroke. In Alzheimer's disease, laboratory experiments show that amyloid-beta induces cultured neurons to undergo excitotoxic death.

Experimental evidence shows that carnosine protects cells against excitotoxic death. A Russian study showed that rat cerebellar cells incubated in carnosine were resistant to excitotoxic cell death from toxic glutamate analogs.²⁴

Two further Russian studies tested carnosine in animal experiments designed to simulate stroke. In the first experiment, rats were exposed to low pressure hypoxia.¹¹ Rats given carnosine beforehand were able to keep standing and breathing almost twice as long as the others. After the hypoxia, carnosine treated rats were able to stand after 4.3 minutes, as compared to 6.3 minutes for the untreated rats.

The second experiment simulated stroke through arterial occlusion. The scientists found that carnosine acts as a neuroprotector in the ischemic (blood-deprived) brain. Rats treated with carnosine displayed a more normal EEG, less lactate accumulation (a common measure of injury severity), and better cerebral blood flow restoration.²⁵

Carnosine and skin aging

While the epidermis (outer skin layer) changes only subtly with age, profound changes take place in the dermis (inner skin layer). In the dermis, the population of fibroblasts (connective tissue cells) is cut in half by age 80. Collagen becomes disorganized with broken fibers, while the extracellular matrix shows widespread destruction.

Protein degradation damages all components of the epidermis and dermis, leading to loss of elasticity, wrinkles, macromolecular disorganization, loss of extracellular matrix, and reduced capacity for wound repair, all of which are characteristics of aged skin. Collagen, the protein substance of connective tissue, tends to cross-link with age. It is well known that collagen is cross-linked in the course of glycation and the consequent formation of AGEs (advanced glycation end products). This robs the skin of elasticity and youthful tone.

Once AGEs form, they can directly induce the cross-linking of collagen even in the absence of glucose and oxidation reactions. Researchers have found that neither antioxidants nor metal chelators can inhibit direct cross-linking of collagen by AGEs. Only an anti-glycating agent, in one case the drug aminoguanidine, could inhibit this process. According to several published studies, carnosine offers a superior efficacy and toxicity profile compared to aminoguanidine.²

Carnosine rejuvenates senescent fibroblasts (connective tissue cells).¹⁴ This helps to explain a series of research findings that carnosine significantly improves post-surgical wound healing. A Japanese study showed that carnosine enhances granulation, a healing process in which proliferating fibroblasts and blood vessels temporarily fill a tissue defect.²⁶ A Brazilian study showed that granulation tissue matured faster, with a higher level of collagen biosynthesis, in carnosine treated rats.²⁷ This is not surprising in view of carnosine's ability to extend the replicative potential of cultured fibroblasts. These studies further suggest that carnosine can restore the body's regenerative potential.

HOW CARNOSINE PROTECTS AGAINST BRAIN DEGENERATION

The brain's rich supply of oxygen, glucose, membrane lipids and metals may explain why it is also richly endowed with carnosine. Carnosine suppresses oxidative stress, lipid peroxidation, pathological protein-sugar interactions and copper-zinc toxicity. Moreover, carnosine's ability to forestall cellular senescence may help sustain the long lives of neurons, which do not divide to form new cells.

A major source of oxidative damage and cellular dysfunction in the brain is the oxidation of lipids in the membranes of brain cells.* This generates highly toxic byproducts

The skin makes visible the changes that occur throughout the body as damaged proteins. The life cycles of cells and proteins may regulate both our appearance as we age and how long we live. By preserving the integrity and regular turnover of protein, carnosine is a key defense against the downward spirals of degeneration that occur as part of the aging process.²⁸

Summary

Carnosine stands out as a promising multi-modal life extension discovery. It extends life span at the level of the cell and of the organism. The scientific evidence indicates that carnosine could help to preserve the structural, functional and genetic integrity of the body in a natural way.

Some of the age-related conditions that carnosine may help to prevent (and treat) include:

- Neurological degeneration
- Cellular senescence (cell aging)
- Cross-linking of the eye lens
- Accumulation of damaged proteins
- Muscle atrophy
- Brain circulatory deficit
- Cross-linking of skin collagen
- LDL cholesterol oxidation
- DNA chromosome damage
- Formation of advanced glycation end products (AGEs)

Life Extension members can obtain the recommended 1000 mg daily dose of carnosine by taking either two capsules a day of Super Carnosine Caps or six capsules a day of the Chronoforte formula. Both of these formulas are now fortified with a potent dose of water-soluble quercetin.

that damage proteins and inhibit the synthesis of protein and DNA. Lipid peroxidation is particularly significant in Alzheimer's disease, where it is most prominent in the vicinity of senile plaques.^{**} Carnosine dramatically reduces the levels of lipid peroxidation products.

When mice were stressed with electric shocks for two hours, significant increases in lipid peroxidation products in the brain and blood were observed, with decreased antioxidant activity levels.^{***} However, mice treated with carnosine before the shocks showed opposite effects. After the same series of shocks, their brain and blood lipid peroxidation product levels were more than 85% lower than in the untreated mice. Brain SOD antioxidant activity was six times higher in the carnosine fed mice compared to the untreated mice. When stress was induced, it caused a depression in levels of essential membrane phospholipids by 9% while carnosine treatment actually raised them by 26%. Carnosine also protected against a step in the glycation process, protected cells from damage by lipid

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peroxidation toxins and increased the "flowability" of cell membranes.

In Alzheimer's disease, lipid peroxidation toxins are thought to interfere with critical membrane proteins involved in cellular signaling and in transporting ions, glucose and glutamate. Carnosine appears to protect against many of the pathologies that have been identified in the Alzheimer's disease process.

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