Carnosine (beta-alanyl-L-histidine) (Fig. 1) is a naturally-occurring dipeptide composed of two amino acids alanine and histidine. While the majority of early research on carnosine was conducted in Russia following its discovery in 1900, Western scientists have recently begun to recognize the tremendous range of health benefits supported by this highly effective anti-aging nutrient.

Carnosine Declines with Age
Carnosine (not to be confused with L-carnitine) is found in highest concentrations in long-lived tissues such as skeletal muscle, cardiac muscle and brain.1 Muscle carnosine levels in humans decline 63 percent from age 10 to 70 (Fig. 2).2 This marked reduction in muscle carnosine concentration may be a cause of the age-related decline in muscle mass, strength and function. Stress, infections and trauma also cause carnosine levels to decline, which may help explain the increased mortality in the elderly following stressful events.

Carnosines Multiple Anti-Aging Mechanisms

The metabolic pathway shown in (Fig. 3) illustrates how carnosine participates in several important biological reactions, including methylation (giving rise to anserine or ophidine), hydrolysis (leading to histidine and beta-alanine), and decarboxylation (resulting in histamine formation, which interacts with beta-alanine to result in the formation of carnicine). Carnicine, a stable analog of carnosine, has been used experimentally to reverse cataracts. Carnosines two amino acids, histidine and alanine, are metabolized in the citric acid cycle. Alanine enters through the Coenzyme A pathway and histidine through the alpha-ketoglutarate pathway. Aging is associated with damage to cellular proteins, resulting in inter- and intra-molecular cross-linking. Carnosine protects cellular proteins from such metabolic damage in at least two ways. First, as an antioxidant, carnosine prevents the formation of oxidized sugars, or glycosyl radicals, also called advanced glycosylation end products (AGEs).3 Second, carnosine bonds with potentially harmful carbonyl groups that attack and bind with proteins imbedded in the cellular membrane, and neutralizes them. Both of these processes have important implications for anti-aging therapy, in that carnosine not only prevents damaging cross-links from forming, it eliminates cross-links that have previously formed, thus restoring normal membrane function.4

Closely related to this auto-regulation ability are carnosines effects as an anti-inflammatory and immunoregulatory nutrient. Carnosine suppresses...
excess immunoreaction in immature mice, and stimulates immunoreaction in aged mice. In this regard, carnosine activates both B and T lymphocytes. By increasing the respiratory burst and interleukin-1-beta production of human neutrophils, carnosine acts to up-regulate the immune response.

Carnosine also has profound cell membrane-stabilizing effects. Other important actions of carnosine include proton buffering, heavy metal chelating, anti-cross-linking and even neurotransmitter properties. (For more on the cross-linkage theory of aging, see the series on VRPs website at http://www.vrp.com/art/704.asp.)

**Therapeutic Uses for Carnosine**

A wide range of therapeutic uses have been proposed for this remarkable substance (Fig. 4). As early as 1935, carnosine was recognized as a treatment for polyarthritis. As time has passed, the number of conditions alleviated by carnosine has grown, and earlier research has been corroborated.

**Stroke Prevention and Treatment**

In Russia, scientists performed a series of experiments in rats, in which the animals’ common carotid arteries were clamped for 45 minutes, resulting in a loss of oxygen to their brains. Thirty minutes before the operation, carnosine at a dose of 250 mg/kg of the animals’ bodyweight was administered intraperitoneally (by injection). Fifty-five percent of the control animals died, and those that survived had greatly impaired cognitive performance (determined by their performance on a maze test). Remarkably, only 17 percent of the animals that were pre-treated with carnosine died; cognitive function among those surviving was restored to pre-experimental levels. Other studies by the same group produced similar results. Two of the scientists speculated that these pronounced anti-ischemic (oxygen-sparing) effects of carnosine in the brain (and heart) are due to a combination of its antioxidant, membrane-protecting, and chelating properties, proton buffering capacity, and regulation of macrophage (white blood cells) function. Based on these studies in rats, the scientists recommended that carnosine be used for stroke-prevention and treatment in humans.

**Heart Disease and Hypertension**

Scientists at Wake Forest University School of Medicine compared the effects of carnosine with the cardiac drug isoproteronol on isolated rat hearts. They found that carnosine had inotropic action (increased the force of heart contractions) equal to isoproteronol, without the adverse effects of the drug (most frequently, ventricular fibrillation). In addition to improving cardiac contractions, the scientists found that carnosine decreased vascular tone (thereby reducing the heart afterload) and protected the heart from ischemia. They recommended that carnosine be considered in the therapy of (congestive) heart failure, hypertension, and for prevention or treatment of heart attacks.

**Cataracts, Glaucoma and Vision Improvement**

Carnosine-containing eyedrops have demonstrated efficacy in treating a variety of ophthalmic conditions, including corneal diseases, cataracts, glaucoma and increased intraocular pressure, and impaired vision from any cause. In 1997, clinical trials were conducted on 109 ophthalmic patients with carnosine-containing eyedrops.

The results confirmed accelerated healing of corneal erosions, trophic keratitis, post-herpetic epitheliopathy, primary and secondary corneal dystrophy, and bullous keratopathy. Most striking, however, was the ability of carnosine to eliminate existing cataracts. Carnosine actually restores the proteins in the lens by removing the carbonyl groups, as described...
earlier. Furthermore, carnosine is thought to function as a molecular water pump. In earlier experiments it was demonstrated that applying carnosine to the conjunctiva (the membrane covering the eye) caused a decrease in normal intraocular pressure and reduced prostaglandin-induced ocular hypertension (related to glaucoma).

Scientists in China reported that carnosine-containing eyedrops used to treat 96 cataract patients over 60 years of age resulted in 100 percent improvement in primary senile cataract, and 80 percent in those with mature senile cataract. In patients under 60, who did not have cataracts, carnosine was reported to alleviate eye tiredness and improve eyesight.

N-acetyl carnosine, the acetylated form of carnosine, has also been extensively tested for its ability to resolve cataracts. Although N-acetyl carnosine is not as potent an antioxidant as L-carnosine, it is believed to last longer in the tissues. And while proponents claim that N-acetyl carnosine is superior to L-carnosine in resolving cataracts when applied topically to the eye, there are no comparative studies proving that either form of carnosine is superior in this regard.

What is remarkable to me is that anything is capable of reversing cataracts as it seems to me to be as difficult as unfrying an egg. Nevertheless, I have known a number of patients who have used both versions of carnosine-containing eyedrops, with generally gratifying and satisfying results in conformance with the published studies.

Hearing Loss
Carnosine may even help to improve hearing. Carnosine was administered to rats at a dose of 200 mg/kg bodyweight 12 hours before and again 30 minutes prior to noise exposure sufficient to damage the auditory apparatus of untreated animals. Carnosine administration significantly reduced the severity of damage to the auditory apparatus in the treated animals.

Wound Healing and Immunity
Carnosine also accelerates wound healing, modulates immune responses, and increases immunocompetence.

Ulcers
As far back as 1936, carnosine was shown to be effective in both treating and preventing gastric ulcers. In a more recent study, oral carnosine significantly inhibited erosions in both the stomach and duodenum, and has been demonstrated to be effective in inhibiting H. pylori, the pathogen responsible for causing gastric ulcers and stomach cancer. In Japan, a complex of zinc and carnosine (generic name, Polaprezinc) is approved as an anti-ulcer drug.

Parasites
In experimental animals (guinea pigs) infected by the liver parasite, Schistosoma mansoni, carnosine has been found to alleviate metabolic disturbances (elevation in serum alkaline phosphatase, gamma-glutamyl transferase, aspartate aminotransferase and procollagen III peptide [as a marker of liver fibrosis]). Administration of carnosine (10 mg/day) for 15 days, begun at the time of infection, reduced the worm burden and egg count, and dramatically reduced the procollagen III peptide level. This is a chronic, virulent infection, for which no safe, effective treatment is known. The fact that a low dose of carnosine has demonstrated such dramatic results provides an intriguing possibility that higher doses would be even more effective.

Neuromuscular Diseases
Skeletal muscle strength and mass decrease inexorably with age, and the incidence of several neuromuscular diseases (e.g., amyotrophic lateral sclerosis [ALS], myasthenia gravis, polymyositis, drug-induced myopathies, late-onset mitochondrial myopathy) increases with age. Carnosine concentration in muscle declines with age, and the decline of carnosine has been proposed as one of the causes of age-related decline in muscle strength and mass, as well as a cause of specific neuromuscular diseases such as ALS or polymyositis.

Dietary carnosine concentrations can dramatically increase muscle carnosine levels. When rats were fed a diet containing 1.8 percent carnosine for eight weeks, muscle carnosine concentrations increased fivefold. Muscle carnosine concentrations, in turn, relate directly to muscle performance. In a study of 11 healthy males, Japanese scientists found that carnosine not only prevents lactic acid buildup in high-intensity exercise, resulting in reduced fatigue and muscle pain, but that those with the highest concentrations of carnosine had the best performance in terms of strength, speed and endurance.

Neuroprotectant Autism and Other Neurological Diseases
Carnosine has been shown to have neurotransmitter-like actions, and may act as both a neuromodulator and a neuroprotective agent. In this regard, scientists have speculated on carnosines possible role as adjunctive therapy in...
Alzheimers disease, Parkinsons disease, stroke and seizures.34 Building on these hypotheses, physicians in Chicago studied the effect of carnosine on 31 children suffering from autism, using what was then considered a high dose 800 mg per day. The effects of this regimen were evaluated by using a number of standard behavioral and cognitive rating scales. After eight weeks, children on L-carnosine showed statistically significant improvements on the Gilliam Autism Rating Scale (total score and the Behavior, Socialization and Communication subscales) and the Receptive One-Word Picture Vocabulary test, as well as improved trends on the other measures used. No improvement was seen with placebo.35

Anti-Aging/Life-Extending Effects
Cells grown in culture have a limited capability to replicate before they begin to show signs of old age, and die. The viability of the cells grown in culture is measured in population doublings. Dr. Leonard Hayflick determined that normal fetal human fibroblasts (usually obtained from skin, lung, or foreskins) have a population doubling potential (PD) of about 50 times. This has become known as the Hayflick Limit. Cells originally taken from adults of various ages have a reduced PD, based on the age of the donor (i.e., the older the donor, the fewer PDs) (Fig. 5).

Although some scientists have questioned whether such esoteric research has anything to do with human aging, others believe that if a means can be found to extend the lifespan of cells grown in culture, it may have important anti-aging implications.

Using carnosine added to culture medium in physiologic amounts (i.e., concentrations that approximate those of human tissue), scientists in Australia36,37 and Ireland38 have successfully broken the Hayflick limit. In a series of studies, using cells cultured with and without carnosine, the Australian team repeatedly obtained increased survival of their cultures, ranging from six to 11 PDs more than the control cultures (Fig. 6).

In other studies, the researchers added carnosine to cell cultures that were clearly showing signs of old age, and noted a rejuvenation of their appearance to that of younger cells. Finally, they intentionally contaminated some of the cell cultures with cancer cells. As the cancer cells began to proliferate and take over the culture, the scientists added carnosine to the culture medium. Within three weeks, the cancer cells were completely gone, and the cell culture went on to a normal lifespan. This led the authors to speculate about the potential anti-cancer properties of carnosine.

In a recent article in International Anti-Aging Systems Anti-Aging Bulletin, Dr Marios Kyriazis reported that his patients who take carnosine supplements often receive comments that they simply look younger. This may be a reflection of the phenomenon observed in in vitro experiments which show that carnosine actually rejuvenates older cells in culture,36 and in vivo animal experiments in which carnosine prevented the development of visible features of aging.39 In that study, carnosine significantly delayed the appearance of skin ulcers, periophthalmic lesions, spinal lordokyphosis and behavioral responses, such as activity and passive avoidance (all characteristic of aged animals). In several other recent articles, Russian scientists reported that carnosine-fed mice not only appeared much more youthful than controls, but they also experienced a 20 percent increase in lifespan (Fig. 7).17,40 In a subsequent study, Yuneva and his associates demonstrated carnosines ability to also extend the lifespan of male fruit flies (Drosophila melanogaster).41

Dosage
Carnosine is an extremely non-toxic and safe substance. Boldyrev and other authors have reported that absorption of carnosine is excellent, perhaps exceeding 70 percent.

The antioxidant properties of carnosine are enhanced when it is taken with other antioxidants. (For example, when vitamin E is taken with carnosine, levels of both substances are higher in cardiac muscle than when either is taken alone.9 Consequently, I recommend taking fat-soluble antioxidants like vitamin E, CoQ10, and lipoic acid.
(which is unique, in being both fat- and water-soluble) in combination with carnosine. The optimum dosage of carnosine is still a matter of conjecture. Dr. Marios Kyriazis, the first clinician in the world to use carnosine on a regular basis in his practice recommends 50-200 mg/day to his patients. In his excellent book, Carnosine and Other Elixirs of Youth, Dr. Kyriazis reported that noticeable benefits have been observed by his patients at this modest intake level. He also indicated that the University of London Dr. Alan Hipkiss, one of the world’s leading researchers on carnosine believed these doses to be adequate for preventive purposes.

Nevertheless, Dr. Kyriazis conceded that these recommendations might change if ongoing research indicated that higher doses would be even more effective. Higher doses 800 mg per day were used in the study on autistic children, cited above. In his book, Dr. Kyriazis mentions that Russian physicians use 1,000 to 3,000 mg per day to treat cancer patients.

In a U.S. patent assigned to Peptide Technology Limited, carnosine use has been patented for the prevention and treatment of the complications of diabetes. The doses discussed in the patent ranged from 20 to 2,000 mg per kg body weight per day. For a 150-pound person, that would be a dose ranging from about 1,400 mg per day, to 140 gm per day, although the preferred recommended dose was in the range of 100 to 200 mg/kg body weight per day. For most of us for the foreseeable future, the limiting factor of dosage will most likely be the cost.

Criteria for Selecting Anti-Aging Nutrients for This Series

For this series of articles reviewing top anti-aging nutrients, Ward Dean, MD, has selected substances based on several criteria:

1. The mechanism by which the substance is believed to act. Most substances discussed are involved in one or more theories of aging (i.e., antioxidants/free radical theory; cross-linkage inhibitors/cross-linkage theory; hormone receptor sensitizers/neuroendocrine theory, etc).
2. The health-enhancing effect of the substance.
3. Whether the substance has shown the capability to reverse or restore a biomarker to a more youthful state.
4. Has the substance demonstrated the ability to extend the maximum lifespan of one or more experimental organisms?
5. Practical considerations: An individual pill capacity how many capsules/tablets is a person willing to take? Cost and availability for example, some substances are beyond the reach of many people due to high cost or other impediments (i.e., legal issues, availability, requirement for a prescription, etc.).

Based on these criteria, the series of articles presents what Dr. Dean considers to be the most effective anti-aging/life extending substances readily available today. The substances featured are presented in no particular order. The first article in the series focused on DHEA, published in the June 2004 issue; part 2, on CoQ10, appeared in July; part 3, on Melatonin, was featured in August; and part 4, on DMAE, was published in September.

References


