**Carnosine**

Carnosine - Information about L-Carnosine

Alzheimer’s is an angiogenesis-dependent disease

Alzheimer’s disease seems to be an angiogenesis-dependent disorder (like cancer!). Development of anti-angiogenic drugs targeting the abnormal brain endothelial cell might be able to prevent and treat this disease. An editorial in *Lancet* suggests several laboratory and clinical approaches for testing the hypothesis.

Brain imaging shows rapid and massive brain cell loss in Alzheimer’s.

The main reason for brain cell destruction in Alzheimer’s is probably the inhibition of the proteasome, a protein which removes damaged and denatured proteins from the brain cells.

Carnosine protects the proteasome and hence fights Alzheimer’s disease. Carnosine is a dipeptide, also called a neuropeptide and neurotransmitter. Patients with Alzheimer’s disease develop extracellular deposits of amyloid protein and microscopic tangles of fibrils inside nerve cells. In experiments, treatment with carnosine was found to reduce or completely prevent cell damage caused by β-amyloid. Carnosine blocks and inactivates β-amyloid, so it protects neural tissues against dementia.

Moreover, carnosine protects the brain cells by fighting the highly toxic alpha, beta-unsaturated aldehyde acrolein which is formed during the peroxidation of polyunsaturated lipids, raising the possibility that it functions as a ‘toxicological second messenger’ during oxidative cell injury.

Recent research also confirms that the toxic unsaturated aldehyde crotonaldehyde (CA) contributes to carbonylation resulting in protein damage during lipid peroxidation. As carnosine combats all aldehydes, it offers another explanation for its benefits in prevention of Alzheimer’s disease and other conditions with oxidative stress. Moreover, carnosine protects proteasomes, protein molecules which detoxify the brain cells, and carnosine removes toxic heavy metals from the brain cells in a biochemical process called chelation.

Interest in carnosine has increased markedly over the last few years and many experts are predicting it will become the fundamental daily treatment for people of all ages, but in particular those approaching 40 and beyond.

In America, the UK, Australia, Japan, and in Scandinavia, anti-ageing specialists and nutritionist are recommending it as a valuable supplement. There are no known side effects or incompatibility with other drugs.

Laboratory research on cellular senescence (the end of the life cycle of dividing cells) suggests that these facts may not be coincidences. Carnosine has the remarkable ability to rejuvenate cells approaching senescence, restoring normal appearance and extending cellular life span.

How does carnosine rejuvenate cells? We do not yet know the full answer, but carnosine’s properties may point up key mechanisms of tissue and cell aging, as well as the anti-aging measures that counteract them.

Carnosine has been shown to have a wide repertoire of beneficial effects in the body. Mechanisms of action are explained in terms of:

- proton buffering (maintaining pH balance in the muscles in heavy exercise)
- heavy metal chelating (especially copper and zinc)
- free-radical and active sugar molecule scavenging (prevents glycation and carbonylation of proteins)
- preventing the modification of biomacromolecules thereby keeping their native functionality under oxidative stress
- proteasome protection

Physiological concentrations (20-30 micromoles, or mM) in standard media prolong the in-vitro lifespan of human fibroblast cells and strongly reduce the normal features of senescence (ageing). In laboratory animals, carnosine clearly improved the external appearance of experimental animals and produced apparent beneficial effects on behavioural parameters and average life span.

Age-related conditions that carnosine may be useful for include:

- neurological degeneration (Alzheimer’s, Parkinson’s, epilepsy depression, schizophrenia, mild cognitive impairment, dementia and stroke)
- Autistic Spectrum Disorders, Asperger’s syndrome, ADHD, dyslexia, dyspraxia, Tourette’s syndrome etc.
- cellular senescence in general
- cross-linking of the eye lens (cataracts)
- cross-linking of skin collagen (skin ageing)
formation of advanced glycation end products (AGES)
accumulation of damaged proteins
muscle atrophy
brain circulation deficit (stroke)
cardiovascular conditions
diabetes and its complications.

Carnosine as a multi-functional dietary supplement is a relatively novel discovery. It is an amazing physiological and 100 % natural super-antioxidant with numerous biological roles including (in addition to the above mentioned):

universal and versatile antioxidant activity
supporting muscle vitality
increasing muscle strength and endurance
speeding up recovery after sprints
inhibiting cellular damage caused by alcohol
acting as neurotransmitter or message-carrying chemical, in the brain and nerves.

Side-effects: None. Carnosine is non-toxic.

Pharmacology and biochemistry

Carnosine is a 100 % natural substance, a so-called dipeptide, formed of two amino acids (β-alanyl-L-histidine). It is often called a neuropeptide due to its brain-protective properties.

Carnosine is found naturally in healthy muscles, heart, brain, liver, kidneys and other tissues. The muscles contain about 20 µmol/g dry weight.

Figure 1. Chemical formula of L-Carnosine (NH2CH2CH2CONHCH(C4H5N2)CO2H )

Carnosine acts together with other biological antioxidants, e.g., vitamin E and vitamin C, zinc and selenium, and it spares their consumption in the tissues. Persons with latent vitamin E deficiency consume carnosine more than normally. [It is stressed that the intake of vitamin E is deficient in a major part of the general population, as suggested by epidemiological studies world wide.]

In the human body, the enzyme carnosine synthetase, forms carnosine from the amino acids alanine and histidine. This reaction occurs mainly in the brain and in the musculature. Another group of enzymes, called dipeptidases or carnosinases, in turn inactivate carnosine in the blood and other tissues. Many scientists behind carnosine, including Drs Kyriazis and Hipkiss (see later on) believe that some of the benefits of carnosine are derived after carnosine has been degraded by carnosinases to produce histidine and alanine, therefore degradation may be a good thing.

Meat is the main dietary source of carnosine. High doses of carnosine are necessary for therapeutic effect because the body naturally degrades carnosine with the enzyme carnosinase. Absorption of carnosine from food is 30% to 70 % (depending on the amount of various amino acids in the meal) and that of pure L-carnosine greater than 70%. A greater part of the absorption occurs in the small intestine (jejunum, but not in the ileum). From the blood carnosine moves into the muscles, brain and other tissues. The human plasma does not contain measurable quantities of carnosine, in other words a blood test does not detect a possible deficiency state.

[In contrast, equine plasma contains carnosine over 100 µmol/l. As a result of muscle injuries the content in the plasma increases, and determination of plasma carnosine can be used for detection of muscle injuries.]

The biological functions of carnosine include:

buffering the effects of lactic acid in the muscles (the pH remains neutral even in heavy physical exercise, such as sport sprints)
pluripotent antioxidative actions
ability to inactivate reactive oxygen species, scavenge free radicals
aldehyde-sequestering
prevention of glycation (Agirrova & Agirrov 2003)
prevention of carbonylation of proteins, i.e., ‘carnosinylation´)
function as neurotransmitter
protection of proteasomes
chelation of metals
action as neurotransmitter in the brain and nerves.

In summary, carnosine is an aldehyde scavenger, which is also able to remove the rubble (ultimate de-linking damaged proteins, sugars and phospholipids) and act as a key member in the building of the new more impervious towers. As a
dietary supplement, carnosine is a possible modulator of diabetic complications, atherosclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, autism, dyslexia, AD/HD, schizophrenia and related syndromes, as we will discuss below in more detail.

Copper and zinc are released during normal synaptic activity. However, in the presence of a mildly acidic environment which is a characteristic of Alzheimer's disease, they reduce to their ionic forms and become toxic to the nervous system. Research has shown that carnosine can buffer copper and zinc toxicity in the brain.

Carnosine has also been shown, in vitro (in the test tube), to inhibit non-enzymic glycosylation and cross-linking of proteins induced by reactive aldehydes, including aldose and ketose sugars, certain triose glycolytic intermediates, and malondialdehyde (MDA, a lipid peroxidation product). Carnosine also inhibits formation of MDA-induced protein-associated advanced glycosylation end products (AGEs) and formation of DNA-protein cross-links induced by acetaldehyde and formaldehyde.

The lipid peroxidation product malondialdehyde forms adducts with proteins that are detected during routine assays for protein carbonylation.

Short historic review

Carnosine was discovered and its structure determined in the very beginning of the 20th century by the Russian scientist W. S. Gulewich. It was the first and the simplest example of biologically active peptides (actually a dipeptide), opening the long list of widespread natural protein regulators of metabolism. The first decades were dedicated to studies of structure, distribution, and properties of the compound. It was understood that carnosine has a direct relation to the function of excitable tissues like muscles and the brain.

In 1953 another Russian scientist, S.E. Severin showed that carnosine effectively buffered lactic acid, produced by working muscles, and that adding carnosine substantially increased the contractility and endurance of the muscles. As the carnosine is consumed, the muscles accumulate lactic acid, the pH decreases, and the muscles get tired. When carnosine is added, the muscles recover almost immediately and contract like they never had been exhausted. This is known as the "Severin phenomenon".

Everybody who has some experience in sports has experienced how physical fatigue feels, and he or she will understand the immense importance of supplementation with carnosine in sports event.

Widespread interest in this natural non-toxic substance has only recently been increased, fuelled by dramatic Australian and British discoveries about its anti-aging actions. Carnosine's anti-ageing properties have only been extensively studied during the past few years even though we've known about it for almost a century. More striking research came in 2002 from the USA where Dr Michael Chez’ team reported data on the carnosine’s dramatic effects on autistic children.

Pluripotent superantioxidant

Carnosine is an antioxidant which stabilizes and protects the cell membrane. Specifically, as a water-soluble free radical scavenger it prevents lipid peroxidation within the cell membrane. Many antioxidants (like vitamins E and C) are aimed at preventing free radicals from entering the tissues, but have no effect after this first line of defence is broken. Free radicals cause oxidative stress in the body.

Carnosine reacts chemically all reactive oxygen species thus preventing oxidative stress.

Carnosine is not only effective in prevention, but it is also active after free radicals react to form other dangerous compounds, like lipid peroxides and secondary products. So, it protects the tissues from these damaging 'second-wave' chemicals. For example, a highly reactive lipid peroxidation end-product called malondialdehyde or MDA, a dangerous product of free radical reactions, is blocked by carnosine. MDA, if left uncontrolled, can cause damage to lipids, enzymes and DNA, and plays a part in the process of atherosclerosis, joint inflammation, cataract formation, and aging in general. Carnosine, by reacting and inactivating MDA, sacrifices itself in order to protect the amino acids on the protein molecule.

A rather unusual antioxidant property of carnosine is its ability to reduce concentrations of thiobarbituric acid reactive substances (TBARS).

Carnosine is a substance that protects and extends the functional life of the body's key building blocks-cells, proteins, DNA, and lipids and can be fairly called an agent of longevity.

Interacting with aldehydic lipid oxidation products, carnosine protects biological tissues from oxidation, since aldehydes can form adducts with DNA, proteins, enzymes, and lipoproteins, causing harmful alterations in their biological activity (Burcham et al. 2002).

Oxidative stress and trauma cause a reduction in carnosine levels, which may help explain the increased mortality in the
elderly following stressful events. That is why proper antioxidant defence is crucial for good health, in particular for elderly individuals. Carnosine is an all-in-one super antioxidant.

The anti-ageing properties of carnosine go far beyond its antioxidant properties, as you will soon learn.

Metal chelation:

Many investigators believe that carnosine exerts - at least partly - its beneficial health effect due to its ability to chelate metals (Miller and O'Dowd 2000, Chez et al. 2002). What does it mean in plain English? The term chelate, from the Greek ‘chele’ for ‘claw’, refers to the ability of a material to combine with excess metals in the cells and blood stream, so the liver and kidney can excrete them. Chelation therapy is normally given as a series of intravenous infusions containing disodium EDTA and various other substances like penicillamin.

Chelation therapy has been traditionally applied in Occupational Medicine, as it effectively removes toxic heavy metals (such as lead) from the body. In occupational health chelation therapy is strictly conventional medicine, not alternative medicine. However, chelation therapy is also used, at private clinics, as a complementary treatment for a number of other conditions than heavy metal intoxications, as it may provide the following benefits:

- Dilates constricted arteries
- Reduces high blood pressure
- Diminishes free radical activity
- Improves uptake of oxygen to the cells
- Removes toxic heavy metals from the body
- Improves memory
- Relieves pain in the extremities
- Increases elasticity of blood vessels
- Improves blood flow to the heart, brain, body organs, and legs
- Improves enzyme activity.

In the context of vaccination chelation with carnosine may be crucial, as it removes organic mercury (thiomersal or thimerosal) from a child. Organic mercury is present in most vaccines as an anti-microbial preservative, although it since the 1930’s has been recognised as a toxic substance affecting the central nervous system. Every vaccinated child and adult should take carnosine as a precaution in order to remove thimersal from the body as soon as possible.

Chelation therapy became a popular "alternative" treatment after EDTA was found effective in chelating and removing toxic metals from the blood, and some scientists postulated that hardened arteries could be softened if the calcium in their walls was removed. The first indication that EDTA treatment might benefit patients with atherosclerosis came from Clarke, Clarke, and Mosher, who, in 1956, reported that patients with occlusive peripheral vascular disease said they felt better after treatment with EDTA.

I know some elderly people, who on a regular basis take EDTA chelation therapy on the Costa del Sol, Spain, and they claim it has kept them alive and healthy well into their golden years. The EDTA therapy is, however, expensive and cumbersome, as it is given intravenously as a slow infusion at a clinic. One session normally takes 3 hours, and one needs 10 to 20 sessions to clear the arteries.

Carnosine, as a dietary supplement, seems to have all the same chelating properties as EDTA, and it offers a possibility for an inexpensive oral chelation therapy. Carnosine has an ability to chelate pro-oxidative metals, such as copper, zinc and toxic heavy metals (arsenic, lead, mercury, cadmium, nickel).

Prevention of glycation (glycosylation)

Most recent research suggests that the most important action of carnosine may be its anti-glycation effect (Aldini et al 2002a, 2002b, Yeargans and Seidler 2003). Then what is this glycation? Let me try to explain it to you in a simple way.

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. Glycation alters protein structure and decreases biological activity. Glycated proteins, which accumulate in affected tissue, are reliable markers of disease. Many age-related diseases such as arterial stiffening, cataract and neurological impairment are at least partially attributable to glycation.

Carnosine, which prevents glycation, may also play a role in the disposal of glycated protein. Carnosinylation (the process where carnosine combines with denaturated molecules) tags glycated proteins for cell removal.

Glycation, also known in biochemistry as the Maillard reaction, occurring between proteins and glucose, is recognized as a major contributor to aging and perhaps cancer, as well as the complications arising from diabetes. Glucose provides the fuel for glycation, the insidious protein/glucose combination that (following several steps including the oxidation process)
results in the formation of an advanced glycation end product or AGEs.

Once AGEs are formed, they interact with neighbouring proteins to produce pathological cross links that toughen tissues. It has been speculated that no other molecule has the potential toxic effects on proteins as advanced glycation end products. Diabetic individuals form excessive amounts of AGEs earlier in life than non-diabetics, a process that disrupts the normality of organs that depend on flexibility for function. It has been shown that it is glycation that hardens the arteries of a diabetic individual.

AGEs trigger a cascade of destructive events as AGEs cling to cellular binding sites. One of the consequences of AGEs is a 50-fold increase in free radical formation. As diabetes, a condition of accelerated aging spawns a harvest of AGEs, the arteries, the lens and the retina of the eye, peripheral nerves and the kidneys are under specific attack. By opposing glycation, glomerular damage and the resulting inflammation and renal degeneration is reduced. Diabetic rats, not treated with glycation inhibitors, show a twofold increase in glomerular staining for advanced-glycation end products compared with a similar group of diabetic rats receiving treatment (Forbes et al., 2001).

Cataracts (another complication common to diabetics) are also likely to form as a result of glycation, while glycation inhibitors, like carnosine and calcium pyruvate protect against the damage. Supplementation with glycation inhibitors enable humans to prevent many of the adversities that accompany aging. Because carnosine structurally resembles the sites that glycating agents attack, it appears to sacrifice itself to spare the target. Carnosine also bolsters proteolytic pathways, i.e., the disposal of damaged and unneeded proteins.

Because of its anti-glycation actions, carnosine may be useful in preventing and treating diabetic complications such as cataract, neuropathy, arteriosclerosis and kidney failure. It can also be helpful to all of us since AGEs age us all, although not a rapidly as diabetics.

Carbonylation - Beyond antioxidants

Why do older people, and animals, look different than younger ones? This has to do with changes in the proteins of the body. Proteins are the substances most responsible for the daily functioning of living organisms, which gives protein deterioration its dramatic impact on the body's function and appearance. Many lines of research over the last decade converge on protein modification as a major pathway for aging and degenerative disease. These modifications result from oxidation (as by free radicals) and interrelated processes such as glycation.

Our body is made up largely of proteins. Because the body's antioxidant system and other lines of defence cannot completely protect proteins, they tend to undergo destructive changes as we age, due largely to oxidation, glycation and another process called carbonylation. In other words carbonyl groups (>C=O) adhere to the protein molecules (and phospholipids as well). As a result the proteins break up in a process called proteolysis. Since protein carbonylation clearly preceded the loss of membrane integrity, it may be associated with the toxic process leading to cell senescence and death. In order to understand the implications of the proteolytic decline and build up of aberrant proteins, it is necessary to revise the picture.

These interrelated protein denaturation and proteolysis include oxidation, carbonylation, cross-linking, glycation and advanced glycation endproduct (AGE) formation, as explained above. They figure prominently not only in the processes of ageing but also in its familiar signs such as skin aging, cataracts and neurodegeneration (i.e., loss of memory and dementia). A vast number of scientific studies, published by investigators in the east and west, show that carnosine is effective against all these forms of protein denaturation. Carnosine reacts with the carbonyl group and form an inert protein-carbonyl-carnosine adduct, thus protecting the proteins and reversing the denaturation.

Figure 4. This is how AGE-inhibitors act. Quenching of the carbonyl (bold arrow) is the main way of action. Carnosine and other AGE-inhibitors chelate metals, and hence they prevent the metals from catalysing oxidation and producing AGE’s (Price et al. 2001)

How does carnosine do this? Carnosine simply restores the normal cell cycle control. To understand how this can happen, consider an engine whose oil isn't changed regularly. When the detergent in the oil is used up, contaminants precipitate and sludge forms on vital engine parts. The sludge accumulates, impairing engine performance, until finally the engine dies. The body too needs an efficient sludge removal system. When protein "sludge" accumulates, the gears of the cell cycle can get clogged up. This could impair the efficiency of cell division, and perhaps more importantly, enable damaged cells to reproduce. The result is increasing chromosomal instability, leading to degeneration and cancer. Another possible outcome is cellular senescence, when the cell cycle grinds to a halt. Protein carbonylation thus becomes a potentially terminal condition. Carnosine behoves us to maintain healthy intact proteins and to ensure their timely turnover.

Carnosine seems to be far superior to traditional antioxidants, e.g., vitamin E and selenium, that are not as effective as we hoped in the past. They do suppress some of the many pathways involved, while having no effect upon the others, like glycation and carbonylation. 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 glycation and carbonylation is like attempting to build a house with only a screwdriver - an essential tool, but incapable
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 ageing 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.

Proteins are not the only molecules denaturated by carbonylation - phospholipids are carmorylated as well. And the carbonylation of phospholipids cause damage particularly in the central and peripheral nervous system, resulting in memory impairment and other deterioration of cognitive skills. As carnosine fights carbonylation of the phospholipids as well, it is now wonder that this dipeptide is a marvellous neuroprotectant, as we will see further on.

In sports and body building carnosine is involved in the detoxification pathway of reactive aldehydes from lipid peroxidation generated in skeletal muscle during physical endurance (Aldini et al. 2002a,b). Hence carnosine protects the skeletal muscles from injury, increases muscle strength and endurance and speed up recovery after strenuous exercise, as I will explain in detail later on in this review.

Anti-ageing Benefits Combined

Carnosine has so many youthful benefits it almost seems difficult to see how one simple dipeptide can have such a tremendous effect on rejuvenating the body. Carnosine has an outstanding ability to rejuvenate old cells (senescence cells) into healthy cells. It has always been thought that old cells could not be rejuvenated until carnosine was studied.

It currently appears that most cells can only divide so many times, but the higher the carnosine levels the more times cells can divide. Therefore, the healthier we can keep the cells by keeping older cells from aging as fast, the longer the time between cell divisions, the longer life can be.

Carnosine extends cultured human fibroblast life-span, kills transformed cells, protects cells against aldehydes, against an ß-amyloid peptide fragment (characteristic in Alzheimer’s disease), and against alpha-Synuclein produced in Parkinson’s disease, and it inhibits, at least in vitro (in the test tube), protein glycation and DNA/protein cross-linking.

In a recent article, 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 (Hipkiss 2002), and ‘in vivo’ animal experiments in which carnosine prevented the development of visible features of aging.

In that study, carnosine significantly delayed the appearance of skin ulcers, periopthalmic lesions, spinal lordokyphosis and behavioural responses of aged animals. In another recent article, Russian scientists reported that not only did the carnosine-fed mice appear much more youthful than controls, but experienced a 20% increase in lifespan. And rumours have it that Boris Yeltsin (the Russian ex-president) has been on the "Russian supervitamin", i.e., carnosine, for some time, as he now looks ten years younger.

Carnosine intake reduces urinary malondialdehyde (MDA). There is clearly a dose-response effect until the daily intake reaches 500 mg. Higher daily dosage does not increase the effect on MDA reduction (Source: Dr Kyriaziz).

Carnosine rejuvenates the skin

In normal cells, replicative senescence results from loss of telomeric repeats after several rounds of cell division. This generates a DNA-damage signal that activates p53. Some anticancer drugs induce cell senescence by inducing this DNA-damage response in both normal and malignant cells. Carnosine, in contrast, has a striking ability to reverse the signs of aging in skin cells (fibroblasts) approaching senescence and to restore normal appearance and extend the life span of skin cells (fibroblasts). These functions are attributed to carnosine’s effects against all forms of protein and phospholipid modification. The limited capacity of the cell to perpetuate itself through division is called the Hayflick Limit.

The Hayflick Limit has to do with the mortality of our cells. Most cells regenerate themselves by dividing to form a pair of new cells. As early as in 1961 Dr L. Hayflick discovered that cells eventually reach a limit beyond which they cannot continue to divide. In a now-famous series of experiments, Hayflick demonstrated that cultured human fibroblasts (connective tissue cells) can divide only about 60 to 80 times. By young adulthood, fibroblasts have 30 to 40 divisions left, while in old age no more than 10 to 20 remain. When a cell reaches this "Hayflick Limit" it enters into a twilight state called cellular senescence. Senescent cells are very much alive, yet they are distorted in both form and function.

The human fibroblasts are suitable for cultivation and observation in laboratory. Cultures of senescent cells cannot be mistaken for younger cells, which are uniform in appearance and line up in parallel arrays. By contrast, senescent cells exhibit a grainy appearance and take on odd shapes and sizes. They lose the ability to organise themselves in a regular pattern. These striking changes are called the senescent phenotype.
In a remarkable series of experiments, Australian scientists, led by Dr McFarland, have shown that carnosine rejuvenates cells as they approach senescence. What is most exciting is the ability of carnosine to reverse the signs of aging in cells approaching senescence. When the scientists transferred late-passage fibroblasts to a culture medium containing carnosine, they exhibited a rejuvenated appearance and often an enhanced capacity to divide. They again grew in the characteristic whorled growth patterns of young fibroblasts, and resumed a uniform appearance. But when they transferred the fibroblasts back to a medium lacking carnosine, the signs of senescence quickly reappeared. The scientists switched late-passage fibroblasts back and forth several times between the culture media. They consistently observed that the carnosine culture medium restored the juvenile cell phenotype within days, whereas the standard culture medium brought back the senescent cell phenotype. The carnosine medium also increased life span, even for old cells.

These results have been confirmed by British investigators, led by professor Alain Hipkiss, who showed that carnosine actually lengthens the life span of human fibroblast.

They write: "Carnosine can delay senescence in cultured human fibroblasts and reverse the senescent phenotype, restoring a more juvenile appearance. As better antioxidants/free-radical scavengers than carnosine do not demonstrate these antisenescent effects, additional properties of carnosine must contribute to its antisenescent activity. Having shown that carnosine can react with protein carbonyls, thereby generating "carnosinylated" polypeptides using model systems, we propose that similar adducts are generated in senescent cells exposed to carnosine.

Polypeptide-carnosine adducts have been recently detected in beef products that are relatively rich in carnosine, and carnosine’s reaction with carbonyl functions generated during amino acid deamidation has also been described. Growth of cultured human fibroblasts with carnosine stimulated proteolysis of long-labeled proteins as the cells approached their "Hayflick limit," consistent with the idea that carnosine ameliorates the senescence-associated proteolytic decline." (Hipkiss et al. 2002).

This research team is a candidate to receive the Anti-Ageing Science Award at Chicago University.

Carnosine’s revitalizing effects on cultured fibroblasts may explain why it improves post-surgical wound healing.

Why does the skin wrinkle? Senescent cells, keratinocytes and fibroblasts, behave in deviant ways and they appear to accumulate with age in human skin. They generate more metalloproteinase enzymes that break down proteins in the surrounding extra cellular matrix (the fabric that holds together cells, lymph nodes and blood vessels). They also generate adhesion molecules that contribute to hardening of arteries. Senescent cells express genes that have long-range, pleiotropic effects - degradative enzymes, growth factors, and inflammatory cytokines. Thus, relatively few senescent cells might compromise skin function and integrity. Senescent cells accumulate with age in all organs and tissues, where they resist programmed cell death (apoptosis) and contribute to age-related degeneration. Moreover, by altering the tissue micro environment, senescent cells may also contribute to the rise in cancer that occurs with age.

Muscle, muscle disorders

When man ages from 20 to 70 years of age, the lean body mass (muscles) decline by 20 %, and muscular strength and endurance decline likewise. The carnosine concentration and the antioxidant effect of carnosine decreases by half as age increases. This marked reduction in muscle carnosine concentration may be a cause of the age-related decline in muscle mass, strength and endurance.

The active, strong so-called fast muscle fibres contain much carnosine, while weak and atrophied fibres contain little. The Russian scientist Severin observed already in the 1950’s that addition carnosine to the liquid where exhausted isolated from muscle was incubated, immediately restored the full muscle energy. The Australian team, led by Dr MacFarlane, has recently shown that supplementation with carnosine increases the strength and endurance of tired muscles. The more you take carnosine, the higher is the content in your muscles.

Carnosine has a role in the following neuromuscular disorders, too:

ALS (amyotrophic lateral sclerosis)
Duchenne’s muscle dystrophy
FSH muscular dystrophy
myastenia gravis (MG), polymyositis
medicine-related muscle diseases (e.g., statins)
late-onset-mitochondrial myopathy.

The role of carnosine in neuromuscular diseases has been investigated scientifically, and the results suggest supplementation with carnosine. While carnosine does not cure these grave disorders, it halts the oxidative stress and may increase the contractility of the muscles and add some strength and endurance.
Patients with Duchenne’s dystrophy have only half of the normal carnosine content in their muscles. Therefore it seems pertinent to recommend carnosine as supplement.

Carnosine in sports

The Russian scientist E. S. Severin showed as early as in 1953 that carnosine significantly contributes to the physicochemical buffering in skeletal muscles, which maintains acid-base balance when a large quantity of H(+) is produced in association with lactic acid accumulation during high-intensity exercise. Carnosine accounts for up to 30% of the buffering capacity of the body. Recent studies confirm that increased muscle carnosine concentrations lead to increased intramuscular hydrogen ion (H+) buffering capacity (Dunnet and Harris 1999, Dunnet et al. 2002) and that pre-exercise carnosine regulates the intracellular pH (pH(I)) of oxidative and glycolytic muscle fibres (Damon et al. 2003).

In fact, carnosine buffers most effectively lactate at the neutral pH area. We all know that when lactic acid in strenuous work accumulates in our muscles, and the pH falls, we get tired and ultimately exhausted. As muscle carnosine concentration reduces with age, also our muscular strength and endurance decline as we age. Supplementation with carnosine seems to restore the muscular carnosine concentration and thus increase the strength, endurance and speed up the recovery.

Figs. Buffer capacities of carnosine and histidine. Calculations based on Henderson-Haseelbalch formula. The buffer capacity of carnosine is superior compared to histidine, in particular in the neutral pH range 7 to 8. Buffer capacity refers to the amount of acid or base needed to change the pH of a solvent by one unit (Matti Heikonen, personal information.)

Carnosine helps the function of the calcium pump in the sarcoplasmic reticulum in the muscle cells and keeps the calcium channels open. In the lack of carnosine, the pump ceases to function and the channels close, as a result of acidity, lipid peroxidation and accumulation of malondialdehyde (MDA).

Carnosine fights all these harmful reactions, and it seems to be an ideal physiologic supplement in sports. Carnosine is not considered as a doping substance.

Fig. 5. Carnosine (30 nM) increases significantly the amount of calcium (Ca2+) liberated from the muscle. Black columns = carnosine supplementation, white columns = without carnosine (the pH falls and closes the calcium channels (see Rubtsov 2001). In sports and body building carnosine is involved in the detoxification pathway of reactive aldehydes from lipid peroxidation generated in skeletal muscle during physical endurance (Aldini et al. 2002a,b). Hence carnosine protects the skeletal muscles from injury, increases muscle strength and endurance and speed up recovery after strenuous exercise, as suggested by scientific tests.

Ergometre test

Japanese investigators examined the relations among the skeletal muscle carnosine concentration, fibre-type distribution, and high-intensity exercise performance among 11 healthy men. Muscle biopsy samples were taken from the vastus lateralis at rest and the carnosine concentration was determined by the use of an amino acid autoanalyzer. The fiber-type distribution was determined by the staining intensity of myosin adenosine triphosphatase (ATPase). The high-intensity exercise performance was assessed by the use of 30 second maximal cycle ergometre sprinting. A significant correlation was demonstrated between the carnosine concentration and the type IIX fibre composition. The carnosine concentration was significantly correlated with the mean power per body mass during the 30-s sprinting. When dividing the sprinting into 6 phases (0-5, 6-10, 11-15, 16-20, 21-25, 26-30 s), significant correlations were observed between the carnosine concentration and the mean power per body mass of the final 2 phases. These results indicated that the carnosine concentration could be an important factor in determining the high-intensity exercise performance.

Evidently, carnosine prevents muscular injuries and speed up recovery times in sports. One of the explanations is that high-intensity performance causes oxidative stress in the musculature, which in turn eats up the carnosine stores. The free radicals cause lipid peroxidation as well as carbonylation of proteins and phospholipids. As stated before, carnosine combats these reactions, provided, that there is enough of it in the muscles.

Research suggests that the minimum quantity is 2.5 mM in order to halt lipid peroxidation and 1 mM to stop carbonylation. In one study rats were fed carnosine for 13 months, and it was noted that the carnosine concentration in their skeletal muscles increased significantly, and at the same time lipidperoxidation and carbonylation diminished. This relevant study proved that carnosine indeed, in physiological circumstances prevents lipid peroxidation and protein carbonylation (Nagasawa ym 2001).

Another study on rats indicated that the carnosine concentration in the soleus muscle increased 5-fold and the histidine content 2-fold in 8 weeks, when the rats were given 1.8 % carnosine in the food. There is reason to believe that the same occurs in man. Therefore carnosine seems to be the ideal supplement for athletes.
Figure 6. Carnosine inhibits effectively accumulation of lactate, as result of hypoxia, in rat brain. Hypoxia was experimentally induced by ligating four arteries. 1=rats supplemented with carnosine, 2=controls. The columns indicate the lactate concentration before ligature (a) and thereafter (b) 35-45 minutes, (c) 90-100 min and (d) 150-170 min (Stvolinsky ja Dobrota 2000).

Sexual functions improved

Production of nitric oxide (NO) in the penis is a pre-requisite for starting and maintaining erection. Carnosine is the natural substrate for NO. In other words our body makes NO out of carnosine (Alaghband-Zadeh ym 2001). Therefore, supplementation with carnosine automatically improves potency.

Cataracts

Carnosine not only inhibits the formation of AGEs - one of the main causative processes leading to cataracts - it can also protect normal proteins from the toxic effects of AGEs that have already formed. An elegant experiment carried out at King's College, University of London, made this point (Brownson C et al., 2000; Hipkiss AR et al., 2000). The scientists employed a glycating agent called methylglyoxal (MG) that reacts with lysine and arginine residues in body proteins. The scientists used MG to glycate ovalbumin (egg white protein). This produced a brown coloured solution typical of the "browning" effect of glycation. They then incubated the glycated albumin with a normal protein, a-crystallin, from the lens of the eye. The glycated albumin formed cross-links with the crystallin, but this was inhibited by carnosine.

Patients with Alzheimer's disease and Parkinson's disease may have an increased occurrence rate of glaucoma (Bayer et al. 2002). This is due to the fact that several harmful biochemical reactions occur simultaneously in all these conditions, i.e., oxidative stress, glycation, formation of AGES and carbonylation. As carnosine inhibits all the processes, it seems to be an ideal dietary supplement for individuals who are in the risk of developing, or have already any of these conditions.

Carnosine eye drops have been shown to delay vision senescence in humans, being effective in 100% of cases of primary senile cataract and 80% of cases of mature senile cataract (Wang AM et al. 2000). L-carnosine eye drops are able to enter both the aqueous and lipid parts of the eye, and they have been shown to prevent and repair light-induced DNA strand breaks in the eye. In Russia, carnosine eye drops are approved in humans for the treatment of many eye diseases.

Diabetes and its complications

A diabetic person excretes in the urine a lot of sugar and other substances, proteins (amino acids such as arginine, carnosine and taurine) and magnesium. As diabetes enhances glycation and the patient is deficient in carnosine, the arteries tend to harden. It is why the incidence of arteriosclerosis, myocardial infarctions and stroke is tree-fold amongst diabetics.

Carnosine is known to be a substance that, via the H3-receptors in the autonomous nervous system, controls the levels of blood sugar. Animal tests suggest that pregnant rats low in carnosine have an increased risk of getting diabetic offspring. This is explained by the fact that carnosine improves the foetal glucose tolerance. So, carnosine may be a beneficial supplement for all diabetic mothers-to-be, as it may lower their children's risk of diabetes.

Carnosine is recommended for all diabetics as it lowers the risk of the complications, i.e., heart events, stroke, peripheral artery hardening, kidney and eye problems.

Cardiovascular diseases

The healthy heart muscle (myocardium) contains naturally some carnosine, but carnosine supplementation increases significantly the strength and endurance of the heart muscle. Contractile failure of myocardial cells is a common cause of mortality in ischemic heart disease. According to a recent pharmacological study, carnosine improves myocardial contractility during hypoxia as well as verapamil, a calcium channel blocker frequently prescribed for the treatment of heart disease (Bharadwaj et al. 2002) and therefore carnosine opens completely new horizons in treatment of myocardial insufficiency (Gamez Navarro 2000, Zaloga et al 1997).

Fig. 7. The contractility of the left ventricle of an isolated rat heart and the pulse wave increase significantly with carnosine. (a) Initial status, (b) 5 nM carnosine, (c) 10 nM carnosine (Robets ja Zaloga 2000).

Carnosine exerts a number of beneficial effects in the heart and blood vessels, such as:

- increases the force of heart muscle contractions
- lowers elevated blood pressure
- protects against oxygen deficiency (hypoxia or ischaemia) in coronary heart disease
prevents oxidation of LDL cholesterol and thereby arteriosclerosis.

Carnosine may be used widely for treating the heart's reduced pumping efficiency, the hallmark of heart failure. Moreover, carnosine fights leptin, the obesity hormone. This hormone is elevated many times over in the blood of obese and overweight individuals and it raises blood pressure.

Stroke

Russian scientists set out to determine the effect of carnosine upon rats programmed to develop strokes. The first experiment focused upon carnosine as a revitalizer in hypoxic animals, i.e., those exposed to low oxygen levels. When oxygen-deprived animals were revitalized with normal levels of oxygen, the carnosine treated rats were able to stand after 4.3 minutes, as compared to 6.3 minutes in the untreated group.

Figure 8. Carnosine prevents accumulation of lactose as a result of experimental hypoxia in the rat brain. Hypoxia was induced by ligating four brain arteries. 1= rats on carnosine, 2= controls. The columns indicate the concentrations of lactate before closure of the arteries (a) and thereafter (b) 35-45 minutes, (c) 90-100 min and (d) 150-170 minutes (Stvolinsky and Dobrota 2000).

In the second study, a stroke was simulated in the animals by arterial occlusion. The scientists found that carnosine acts as a neuroprotector in the ischaemic (lack of oxygenated blood) brain. Rats treated with carnosine displayed more normal electrocardiograms, less lactate accumulation (a common measure of injury severity), and better cerebral blood flow.

In summary, carnosine seem to be a superb dietary supplement for prevention and treatment of all kind of cardiovascular events.

Neurological and psychiatric disorders

Carnosine is a versatile neuro-protectant

Evolution has arranged so that young and healthy brain will contain considerable amounts of carnosine which protects these most precious cells against damage and degeneration. The protective mechanisms are the antioxidant function, prevention of glycation and carbonylation, as explained above. In addition, carnosine protects proteasomes which have a central role in the disposal of carbonylated proteins. Carnosine simply stops proteins deforming and could pave the way for the prevention and slowing down Alzheimer’s disease and perhaps other types of dementia and mild cognitive impairment.

In chronic brain disorders, Alzheimer’s and Parkinson’s diseases, epilepsy, depression and schizophrenia, oxidation stress prevails and, in addition, all the other hazardous interrelated reactions occur at a high rate. The glycation denatured proteins and phospholipids, and produced AGE’s which in turn add fuel to the oxidation of the lipids in the cell membranes. Oxidative stress increases the activity of an enzyme called phospholipase A2 (PLA2), which in turn break down fatty acids of the cell membranes. All these reactions interfere with the neurotransmitters.

Carnosine antagonizes oxidative stress (Boldyrev et al, 1999) as well as all the following harmful reactions. Carnosine also works as a neurotransmitter, an anticonvulsant and a chelator (Chez et al. 2002). It is therefore a versatile neuroprotectant against all neurological and psychiatric syndromes and disorders.

Alzheimer’s disease and mild cognitive impairment (MCI)

Alzheimer’s disease is a degenerative disorder of the brain which causes progressive decline in memory and general cognitive abilities. Slowly and inexorably, the disease attacks nerve cells in all parts of the cortex of the brain, as well as some surrounding structures, thereby impairing a person’s abilities to govern emotions, recognize errors and patterns, coordinate movement, and remember. At the last, an afflicted person loses all memory and mental functioning. There is no recovery.

Apart from the progressive destruction of nerve cells, a wide range of abnormalities can be seen in the brains of patients who have died from Alzheimer's, including extra cellular deposits of amyloid protein and microscopic tangles of fibrils inside nerve cells. In experiments, treatment with carnosine was found to reduce or completely prevent cell damage caused by beta amyloid, the substance found in the brain of Alzheimer's disease patients. Beta amyloid can interact with certain RAGE receptors causing damage to the nerves and arteries of the brain. Carnosine blocks and inactivates beta amyloid, so it protects neural tissues against dementia.

Moreover, carnosine protects the brain cells by fighting the highly toxic alpha,beta-unsaturated aldehyde acrolein which is formed during the peroxidation of polyunsaturated lipids, raising the possibility that it functions as a ‘toxicological second messenger’ during oxidative cell injury (Burcham et al. 2000).

Recent research also confirms that the toxic unsaturated aldehyde crotonaldehyde (CA) contributes to carbonylation
resulting in protein damage during lipid peroxidation (Fontaine et al 2002). As carnosine combats all aldehydes, it offers another explanation for its benefits in prevention of Alzheimer’s disease and other conditions with oxidative stress.

Metal chelation by carnosine may prevent and slow down Alzheimers.

Laboratory studies have reported excessive amounts of metal ions such as zinc, copper in Alzheimer’s brain. Such ions may possibly change the chemical architecture of normal beta amyloid, making it more harmful. A mildly acidic environment appears to be important in the process that binds these metals to beta amyloid. Experts observe that such conditions (acidic environment and higher levels of zinc and copper) commonly occur as part of the inflammatory response to local injury. Carnosine has the unique ability to chelate copper, zinc and other metals, and to remove them from the body, as explained above in the section Metal Chelation. This may be an important function of carnosine in preventing and slowing down Alzheimer’s and other degenerative brain disorders.

Mild cognitive impairment

Mild cognitive impairment (MCI) is a recently described syndrome that is currently thought of as a transition phase between healthy cognitive ageing and dementia. Recent evidence suggests that the aetiologcal heterogeneity among individuals with MCI could be greater than previously reported. For example, cerebrovascular disease seems to be underestimated as a potential cause of MCI. The general nature of MCI makes accurate accounting of the prevalence, prognosis, and potential benefit from treatment somewhat difficult. However, carnosine, as a potent neuroprotetntant, seems to be an ideal supplement for people with apparent or suspected mild cognitive impairment.

Parkinson’s disease

The ultimate cause, on the atomic level, are toxic free radicals and their toxic metabolites, which damage certain cells in the brain. H2O2 and TPA (tetracanoylphorbolacetate) are such radicals, and they are able to kill brain cells prematurely. Carnosine has been shown to prevent these radicals and it is thus protecting the brain cells (Kang et al. 2002 b).

Lewy particles in the brain of Parkinson patients accumulate a substance called alpha-Synuclein, which accelerates the disease. This substance is produced due to oxidative stress. Carnosine is able to combat both oxidative stress and accumulation of alpha-Synuclein (Kim et al. 2002).

Carnosine is already recommended by some researchers for (Nguimfack Mbodie 2002).

Epilepsy and schizophrenia

These chronic diseases belong to those conditions where oxidative stress and carbonylation damage the brain cells. Carnosine effectively fights these reactions, and is therefore apt as a diatery supplement for these patients (Petroff et al. 2000; 2001, Nguimfack Mbodie 2002). Carnosine is an anticonculsant( Chez. et al. 2002).

Stroke

Laboratory animal experiments suggest that supplementation with carnosine protects the brain cells against ischaemia (lack of oxygen) which occurs during and after stoke. In one study, experimental ischemic injury resulted in 67% mortality of the rats. In the group of animals pre-treated with carnosine the mortality was only 30% (Stvolinsky et al. 2000). In a similar British study, the mortality after ischemic attack decreased from 55% to 17% (Gallant et al. 2000). An increasing number of researchers advocate carnosine as a benefical supplement for secondary prevention of stroke (Suslina et al. 2000, Stvolinsky and Dobrota 2000, Khaspekov et al. 2002, Tabakman et al. 2002).

Figure 9. Carnosine inhibits accumulation of lactic acid as a result of ischaemia in the rat brain. In this experiment iscaesmia was caused by ligating four brain arteries. 1 = rats supplemented with carnosine, 2 = controls. The columns indicate the lactate concentration before ligature (a) and thereafter (b) 35-45 minutes, (c) 90-100 min and (d) 150-170 min (Stvolinsky andDobrota 2000)

Autistic spectrum disorders

There has been a major breakthrough by a Chicago neurologist, Dr Micheal Chez, in the treatment of autistic Spectrum Disorders (autism and Asperser’s syndrome). Since 2001 he has treated almost 1,000 autistic children with carnosine, and, according to Dr Chez, 80 to 90 per cent improve considerably within eight weeks. Carnosine acts in the frontal part of the brain where it combines with transmitters deep in the brain, says Dr Chez.

Parents with autistic children are saying that supplementation with carnosine helped their kids. Rose Stodola a mother of autistic child said in a TV interview, "Almost immediately within the first week I noticed a change. " “The gym teacher came up to me and said my gosh he's like a different child,” added Maureen Sieger. Four-year-old Nicholas Stodola would not talk to anybody. But then he took carnosine and there was a noticeable change.
Dr. Charles Chez found that kind of change was typical for 80 percent of these and other autistic children. Some jumped eight months in their reading scores and their behaviour also changed. "Response time, and eye contact and social awareness improved, play skills improved as a general rule", the children's neurologist says.

What's really exciting is that carnosine works by stabilizing and protecting brain cells and helping patients like Nicholas. And this may be just the beginning. Carnosine may help patients with Alzheimer's, an illness similar to autism and it has already helped some Alzheimer patients. Carnosine's also helped some other children. Dr. Chez says, "We've had parents report improved reading skills with dyslexic tendencies...just improved test scores with kids who've had borderline attention disorder." Soon other parents may have the same reaction Nicholas' have. "Carnosine and Dr. Chez have given us our son back," says Mrs. Stodola. Some non-autistic adults claim carnosine makes them more alert and improves their memory.

Dr Chez' team has conducted a scientific double-blind study on 31 autistic children. The daily dose of pure L-carnosine was 400 mg and no adverse side-effects have been observed. The report has been accepted for publication in the Journal of Child Neurology.

Other health benefits

As far back as 1936, carnosine was found to be of help in the treatment and prevention of gastric ulcers. In a more recent study, oral carnosine significantly inhibited erosions in both the stomach and duodenum (Truitsina, et. al.1997). Those with gastric and duodenal ulcers thus might benefit from supplementing with this amazing dipeptide.

Peptic ulcer disease and non ulcer dyspepsia (NUD) wreak havoc on millions of individuals worldwide. They are a source of morbidity and expense from over-the-counter (OTC) and prescription drugs, diagnosis and treatment. One of the prime causative factors of ulcers, both in the stomach and upper small intestine, is the spiral-shaped bacterium Helicobacter pylori. More than 75 per cent of people with gastric ulcers are infected with H. pylori. Infected humans (estimated to be at least half of the global population) are the likely vector for infecting others. Perhaps the second most significant causative factor in ulcers is the use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and similar OTC substances. These drugs inhibit the beneficial enzyme cyclooxygenase, which maintains the integrity of the upper GI tract and promotes blood flow to the stomach. Despite the advent of a class of NSAIDs that display greater inhibition in affecting one of the forms of cyclooxygenase (COX-2 inhibitors), all NSAIDs are attended by the risk of ulcerative complications.

Other actions, include:

- immune booster and inflammation reducer
- wound healing properties
- protection against radiation damage (both preventing damage and reversing the post-radiation syndrome)
- prevention of cancer

Carnosine for long-life

Mounting research suggests that carnosine has anti-aging potential due to its unique abilities to protect and extends the functional life of the body's key building blocks, i.e., cells, proteins, DNA and lipids. Carnosine may be fairly called an agent of longlivety. When that agent is safe, naturally present in the body and in food, and has demonstrated prolongation of life span in animals and cultured human cells, it is fundamental to any life extension program.

How does carnosine prolong life span? We do not yet know the full answer, but carnosine's properties may point up key mechanisms of tissue and cell aging, as well as the anti-aging measures that counteract them.

Do carnosine's rejuvenating effects on cells extend to the entire organism? Similar anti-senescence effects have now been demonstrated in mice. A Russian study tested the effect of carnosine on life span and indicators of senescence in senescence-accelerated mice. Half the mice were given carnosine in their drinking water starting at two months of age. Carnosine extended the life span of the treated mice by 20% on average, compared to the mice not fed carnosine.

Figure 10. The average life span (months) of the mice. (a) group supplemented with carnosine, (b) and (c) two control groups. The differences appeared after 6 to 16 months; the survival rate )% is higher amongst the mice on carnosine (see Gallant et al. 2000).

Carnosine did not alter the 15 month maximum life span of the senescence-accelerated mice strain, but it did significantly raise the number of mice surviving to old age. The mice given carnosine were about twice as likely to reach the "ripe old age" of 12 months as untreated mice. It also improved indicators of senescence measured at the "old age" of ten months.

Carnosine distinctly improved the appearance of the aged mice, whose coat fullness and colour remained much closer to that of young animals. Significantly more carnosine-treated mice had glossy coats (44% vs. 5%), while significantly fewer...
had skin ulcers (14% vs. 36%). However, carnosine did not affect the loss or texture of hair. Carnosine significantly reduced the rates of spinal lordokyphosis (spinal curvature) and periopthalmic lesions, but did not affect corneal opacities.

The sharpest contrast between the treated and untreated mice was seen in their behaviour. Only 9% of the untreated mice displayed normal behavioural reactivity, compared to 58% of the carnosine treated mice.

The researchers also measured biochemical indicators associated with brain aging. Brain membranes of the carnosine treated mice had significantly lower levels of MDA (malondialdehyde), a highly toxic product of membrane lipid oxidation. MAO-B (monoamine oxidase B) activity was 44% lower in the carnosine-treated mice, indicating maintenance of dopamine metabolism. Glutamate binding to its cellular receptors nearly doubled in the carnosine treated group. Since glutamate is the main excitatory neurotransmitter, this may explain the more normal behavioural reactivity of the carnosine-fed mice.

This study showed that carnosine significantly improved most measures of appearance, physiological health, behaviour, and brain biochemistry—as well as extended life span—in senescence-accelerated mice. The researchers therefore conclude that "carnosine-treated animals can be characterized as more resistant to the development of features of aging" (Boldyrev AA et al., 1999).

Carnosine as medicine and dietary supplement

A wide range of therapeutic uses have been proposed for this remarkable substance. As early as 1935, carnosine was recognized as a treatment for polyarthritis. Carnosine has the remarkable ability to down-regulate cellular and enzymatic processes when in excess, and up-regulate them when suppressed.

Several recent studies suggest that a combination of zinc and carnosine provide gastric mucosal protection against various irritants and are effective as anti-ulcerogenic substances (Odashima et al. 2002). For example, carnosine decreases platelet aggregation in patients with abnormal clotting tendencies ("thins the blood"), and increases platelet aggregation in patients with low clotting indices. Carnosine has protective effects on blood cell membranes, enhancing their survival, and has demonstrated cell membrane-stabilizing effects, offering protection against chemical-induced hemolytic anemia.

Table 1. Carnosine as complementary therapy
(Disorder/disease and year of commence)

1. Arthritis (polyarthritis) 1935
2. Gastric and duodenal ulcers 1936
3. Wound healing 1940
4. Hypertension (blood pressure) 1941
5. Antibiotic effect 1969
6. Adrenal cortex effect 1976
7. Alleviation of sleep 1977
8. Treatment of trauma 1980
10. Coronary heart disease 1989
12. Cataracts 1989
13. Anti-carcinogenic effect 1989
15. Prevention of radiation damage 1990
Summary:

safe, naturally present in food and in the body
versatile antioxidant and aldehyde scavenger
quenches hydroxyl, superoxide and peroxyl radicals
superior protection of chromosomes from oxygen damage
suppresses lipid peroxidation
most effective natural glycation fighter
inhibits formation of AGEs
protects proteins from AGE toxicity
protects proteins from cross-linking
multifunctional protein and phospholipid protector
protects against formation of protein carbonyls, the hallmark of protein damage
inhibits damaged proteins from damaging healthy proteins
aids recycling of damaged proteins by protecting the proteasomes
helps preserve normal protein turnover
extends lifespan 20% in senescence-accelerated mice
dramatically improves behavior and appearance of old mice
dramatical effect in Autistic Spectrum Disorders
protects brain cells from excitotoxicity
protects brain proteins (proteasomes) and biochemistry
preserves brain biochemical functions
functions as neurotransmitter
safeguards brain chemistry in disorders overproducing free radicals
rejuvenates senescent human cells in culture
increases cell life span
restores youthful appearance and growth patterns to cells approaching senescence
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
inhibits cross-linking of amyloid-beta into Alzheimer’s disease plaques