CARNOSINE

Carnosine is an amino acid di-peptide (beta-alanyl-L-Histidine). It is partly hydrolyzed in the small intestine to the amino acids beta-alanine and histidine. Carnosine is found in its highest concentrations in the brain, the heart, and in muscle tissue. The enzyme that produces Carnosine from Beta-alanine and Histidine is localized intracellularly.

- powerful antioxidant – scavenges hydroxyl radicals and protects SOD (Super Oxide Dismutases = enzymes critical in protecting the brain; works with Glutathione) against peroxidation.

- protects and potentiates the immune system.

- protects cellular proteins from aging.

- protects against toxic carbonyl groups associated with aging.

- strengthens the heart and improves the circulation.

Clinical benefits from supplementation with Carnosine are seen in…

- Energy
- Immune response
- Inflammatory signaling
- Liver metabolism
- Glucose tolerance
- Cognition
- Memory
- Neuroplasticity
- Neuroprotection
- Sleep
- Blood pressure control
- Stem cell function
- Tissue regeneration
- Organ protection
- Bone marrow function
- Bone mass
- Muscle mass
- Senescence rate decreased.
- Age-related disorders decreased.

Carnosine plays an absolutely critical role in protecting against protein degradation, a major component of aging.

Carnosine, (like lipoic acid and Co-Enzyme Q10) is biologically active in protection against both anabolic & catabolic aging (Endogenous & Exogenous aging). It could thus have been included in both your Diphasic A.M. and your Diphasic P.M. It is such a powerful antioxidant that it would be right at home with your delta tocotrienol, gamma tocopherol, lipoic acid, and Co-Enzyme Q10 of your Diphasic P.M. (OXY-MAX). However, since it has protective effects against both excess steroids and against tumor growth, it is just as appropriately included in your Diphasic A.M. (ADAPTO-MAX).

Since it works in conjunction with Glutathione ("The Master Antioxidant"), it is ideal to partner with NAC + Glycine in your REJUVENATOR.

Consider these amazing health and youth-protecting benefits of carnosine:

- Carnosine is not only a powerful antioxidant; one study shows it is the only antioxidant to significantly protect cellular chromosomes from oxidative damage.

- Carnosine quenches the most destructive protein oxidizing agent, the hydroxyl radical.

- As a hydroxyl scavenger, Carnosine protects against fragmentation of zinc SOD and copper SOD by peroxide.

- Carnosine, though water soluble, works with and potentiates the antioxidant affect of lipid soluble alpha tocopherol during lipid peroxidation in liver microsomes. It is thus a major protector of the liver cytochrome P-450 system.

- Carnosine shows particular strength in protecting against lung fibrosis. In animal modules Carnosine completely eliminates mortality from toxin-induced lung injury.

- In an animal model of kidney damage caused by cisplatin (a chemotherapeutic agent) Carnosine prevents the common cisplatin-induced kidney oxidative damage, while maintaining organ structure and function.

- MDA-induced glycation in blood albumin and eye lens protein is inhibited by carnosine.

- Because of its ability to prevent cross-linking, carnosine has been shown to be effective in the treatment of senile cataracts, and in the prevention of cataracts.

- Carnosine has a rejuvenating effect on connective tissue cells and has been shown to benefit wound healing.

Anti-Aging = protection Against INFLAM-AGING

Carnosine is a major player in both Health Span and Life Span and is essential to cellular homeostasis by protection from a large array of cellular functions that erode with aging. It is protective of cell and tissue functions --- effects that are gradually diminished as carnosine concentration in muscle and serum decline with age, or in age-related diseases (such as Alzheimer's).

However, studies show that the drop in Carnosine with age can be compensated for by taking Carnosine as a supplement --- since it is intestinally absorbed, and its level in blood is maintained by re-absorption from renal tubules.

Carnosine can be absorbed in the small intestine, and a significant part of oral intake enters the blood intactly (not hydrolyzed). Absorption is enhanced by a more acidic intestinal lumen pH.

Carnosine prevents senescence, induces rejuvenation, and has geroprotective effect, likely by its wide spectrum of actions, including protein carbonylation and degradation of damaged proteins. Carnosine also reduces damage to telomeres and their shortening rate in fibroblasts.

Carnosine mimics the geroprotecting action of Rapamycin by inhibition of mTOR signaling. Carnosine increases Life Span by 20% in senescence-accelerated mice.

Carnosine has been shown in mice to inhibit tumor growth and mortality --- likely by inhibition of glycolysis (an anti-Anaerobic effect), which is essential to cancer growth (Warburg's Effect).

In physiological conditions, Carnosine has dual activity. First, it directly reduces oxidative damage by quenching hydroxyl radicals, Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and by protecting against carbonyl groups. Those direct antioxidant benefits of Carnosine play a major role in improving Health Span --- as a defender against Exogenous Aging.

The secondary or indirect effects of Carnosine are to improve the enzymatic and non-enzymatic antioxidant activities conducted intracellularly. These include particularly enhancing depleted Glutathione defenses and SOD antioxidant activity. Here we see the longevity benefits of Carnosine --- as it protects against Endogenous Aging, thus increasing Life Span.

With its antioxidant and anti-inflammatory and anti-aging benefits, Carnosine prevents the formation of Advanced Glycation End Products (AGE) and Advanced Lipoxidation End Products (ALE). Carnosine has a dual effect here --- not only protecting against the production of these pro-inflammatory compounds, but also protects against cellular damage caused by these inflammatory end-products. In human skin fibroblasts, Carnosine is more effective than N-acetylcysteine (NAC) in avoiding cell damage induced by AGEs and ALEs. [CAUTION: NAC is effective (and not damaging) only to the extent it can be combined with Glycine to form Glutathione.]

- Carnosine has been shown to rejuvenate cells approaching senescence by extending the life over which those cells will continue to divide with the frequency typical of youth. In tissue cultures supplemented with carnosine, cells retain a youthful appearance and have an extended cellular life span. This ability for carnosine to increase cellular life span holds true even for old cells. One study showed a 67% increase in cellular life span with carnosine supplementation.

- Extending the study of carnosine's Life Span increasing property from tissue cultures into living organisms, studies show that mice supplemented with carnosine live an average of 20% longer than un-supplemented mice and are twice as likely to reach old age in a healthy state.

In summary, the available data show that Carnosine has sweeping rejuvenating effects. These effects include significant improvement in cellular fitness, damage control, and repair. The clinical impacts of Carnosine ensure maintenance of youthful phenotype --- by promoting longer Health Span and longer Life Span. It is one of the few true "rejuvenins".

Autonomic Nerve Effects = Sympathetic/Parasympathetic

The wide range of biological activities of Carnosine is attributable to its circadian/dysphasic resetting of clock genes. That resetting of clock genes is mediated via control of the autonomic nervous system. Specifically, in response to stresses as illustrated by experimental jetlag, the sympathetic system is inhibited, and the parasympathetic system is activated. Experimentally, this shift from sympathetic to parasympathetic activity shows up in the circadian resynchronization of the heart clock --- an obvious place to monitor Sympathetic/Parasympathetic Metabolic Balance.

Carnosine regulates the pyruvate dehydrogenase complex in the mitochondrial matrix that converts the pyruvate derived from glycolysis to acetyl-coenzyme A, so that its oxidation by the Krebs cycle produces energy in the mitochondria. Carnosine is thus categorized as an anti-fatigue agent.

Low doses of Carnosine may regulate the levels of plasma Free Fatty Acids mobilized from white adipose tissue. It is concluded that low doses of Carnosine regulate the lipolytic processes in adipose tissue through facilitation of the sympathetic nervous system, which is driven by Histamine neurons through the H1 receptor --- and, that the Beta-(3)-receptor sympathetic nerves may be involved in this enhanced lipolytic response. ----- High doses of Carnosine, on the other hand, may decrease lipolysis by suppressing sympathetic nerve activity via the H(3)-receptor, and the muscarinic (parasympathetic) receptor maybe related to this response.

Carnosine affects the activity of sympathetic and parasympathetic nerves innervating the adrenal glands, liver, kidney, pancreas, stomach, and white and brown adipose tissues --- thereby causing changes in blood pressure, blood glucose, appetite, lipolysis, and thermogenesis. Carnosine-mediated changes in neurotransmission and other physiological functions are eliminated by H1 or H3 receptor antagonists.

Carnosine released from skeletal muscle during exercise may be transported to the Hypothalamus and hydrolyzed. The resulting Histidine may subsequently be converted to Histamine, which could be responsible for the effects of Carnosine on neurotransmission and physiological function. Thus, Carnosine appears to influence hypoglycemic, hypotensive, and lipolytic activity through regulation of autonomic nerves, and with the involvement of the Hypothalamus and Histamine.

Brain Function and Protection Against INFLAM-AGING

- The reason such a high carnosine concentration is found in the brain is because there, carnosine protects against cross-linking, glycation, excito-toxic brain cell destruction, and oxidative damage.

- Carnosine can rescue neurons from zinc- and copper-mediated neurotoxicity, suggesting that one function of carnosine may be as an endogenous neuroprotective agent.

- In animal studies, it has been shown that carnosine protects the brain in simulated ischemic stroke.

- The copper-zinc compounds that contribute to amyloid-beta plaque formation are inhibited by carnosine.

- Not only does carnosine protect against the formation of amyloid-beta senile plaques, but also protects the cells that line the brain blood vessels from damage by those plaques that do form.

- Carnosine protects the brain against both lipid peroxidation and against damage from excess alcohol.

- Carnosine not only has anti-ischemic effects in the brain, but in the heart as well.

In animal studies, Carnosine demonstrates particular protective effects on the brain. In response to Neurotoxins --- Carnosine supplementation reduces MDA and other markers of oxidative damage, while eliminating protein carbonyls and arresting the senescence-accelerated damage of both xenobiotics (such as alcohol, chemotherapy agents, etc.), and the age-accelerating effects of hypobaric hypoxia.

Carnosine's protective effects on the brain are evidenced by its inhibition of beta-amyloid polymerization, and the neurotoxicity of amyloid beta. In animal studies, Carnosine reduces the accumulation of amyloid, and fully restores mitochondrial function in affected brain cells. In mice on a high corn oil diet, Carnosine prevents cognitive decline.

Similarly, in animal models of neurotoxicity, by several mechanisms, Carnosine's antioxidant and anti-inflammatory effects are protective. A pilot study in humans shows that Carnosine (1.5 grams per day) increases the efficiency of DOPA, decreases plasma protein carbonyls, increases SOD, and improves clinical symptoms such as rigidity of hands and legs, leading to increased hand and leg movements.

One study shows that in 31 children with Autistic Spectrum Disorder, 800 mg Carnosine daily for 8 weeks yielded significant improvements. The Gilliam Autism Rating Scale and the Receptive One-Word Picture Vocabulary Test improved. A metabolomic study reveals decreased urinary Carnosine, Beta-alanine, and Histidine in children with Autistic Spectrum Disorder.

Carnosine treatment (2g daily for three months) in adults --- improved some cognitive tests such as the Strategic Target Detection Test.

Persian Gulf War Veterans affected by cogitative disfunction termed Gulf War Illness showed improved cognitive function in response to Carnosine supplementation (1.5g daily for twelve weeks).

Immune System Anti-Inflammatory Benefits

- Carnosine has immunopotentiating properties. It protects the immune system from immuno suppression by hydrocortisone, by anti-tumor drugs, and many other immunosuppressive drugs.

- Carnosine inhibits histamine-induced suppression of lymphocyte proliferation. Thus, it is classified among H-2 histamine blockers.

Carnosine appears to stimulate the production of constitutional Nitric Oxide (--- particularly critical to endothelial function and vasodilation), while inhibiting the production of inducible Nitric Oxide (--- which is associated with pro-inflammatory peroxynitrites). In brain cell cultures treated with lipopolysaccharide (endotoxin from undesirable gut microbiota), and with Interferon-γ, Carnosine protects against NO-induced cell death.

Cardio – Vascular Benefits

Carnosine supports blood pressure control, and that antihypertensive effect probably results from vasodilation (anti-Sympathetic).

Yet, despite its capacity for lowering blood pressure, Carnosine actually potentiates cardiac contractility. As in its effect on skeletal muscles, this effect is likely associated with a combination of pH buffering and improved calcium handling (excitation – contraction coupling).

- Carnosine has been shown to increase the strength of heart contractility by enhancing calcium response in heart cells.

Carnosine protects against homocysteine toxicity, with no change of the blood homocysteine level. Elevated homocysteine is a worker of INFLAM-AGING and, is an independent risk factor for cardiovascular disease.

Glycemic Control = Protection Against Diabetes

Many studies show a role of Carnosine in the regulation of blood glucose --- and that control is mediated via the autonomic nervous system. Specifically --- Carnosine lowers blood sugar by inhibiting excess sympathetic nerve activity and facilitating parasympathetic activity. The suppressive effect on hyperglycemia maybe achieved by Carnosine's regulating autonomic nerve balance via a Histamine-3 (H3) receptor.

- Observation in animal studies: A certain amount of ingested Carnosine (0.01% or 0.001%), but not a larger amount (0.1%), given with diet, suppresses induced hyperglycemia.

- Histidine injection into certain areas of the brain suppresses induced hyperglycemia.

- Diphenhydramine (an H1 antagonist, as well as an Alpha-fluoro-methylhistidine inhibitor of histamine synthesis), reduces induced hyperglycemia.

- Plasma Carnosine concentration is significantly lower in hyperglycemic rats.

A recent and thorough meta-analysis shows substantial evidence that supplementation with Carnosine (and to a certain extent with Beta-alanine) decreases fasting glucose in those with Insulin Resistance. Significantly, it causes no decrease in fasting glucose in subjects with normal glycemic control.

This meta-analysis shows equally substantial evidence that Carnosine (and to a certain extent Beta-alanine) supplementation decreases elevated HbA1c.

The analysis shows a significant but lesser effect of supplementation to decrease Insulin Resistance --- and also to decrease fasting insulin.

Data from many animal studies supports the findings of the meta-analysis, thus strengthening confidence in the results.

The proposed mechanism by which Carnosine provides a beneficial effect in those with poor glycemic control is through its ability to stabilize reactive carbonyl species. These toxic products increase with increasing loss of glycemic control --- damaged proteins, lipids, and DNA --- inducing inflammation and Insulin Resistance, and impairing insulin secretion. By scavenging these products, Carnosine reduces their reactivity, allowing them to be safely metabolized or excreted.

- Glycated proteins produce 50 times more free radicals than non-glycated proteins. Carnosine is the most effective anti-glycating agent ever found.

- Carnosine's anti-glycation benefits are particularly important for diabetic patients since most complications of poor glycemic control involve the formation of Advanced Glycation End-products (AGE).

- As part of its anti-glycation activity, carnosine reacts with aldehydes and ketones (toxic carbonyl groups) that accumulate on proteins during aging (and which occur in high concentration at a premature age when glycemic control is lost).

- Carnosine is an effective antioxidant in defense against malondialdehyde (MDA). MDA causes protein cross-linking and formation of AGEs. Carnosine has been shown to prevent MDA from inducing protein cross-linking.

Muscle Energy

Carnosine improves muscle function in three ways. First, as an acid pH buffer, it buffers the lactic acid formed in anerobic exercise. Second, Carnosine opposes the oxidative damage incurred during exercise. Third, Carnosine (especially in the presence of adequate magnesium (as in Activator)) normalizes the excitation-contraction coupling of the calcium sensitivity of muscle contractile function. This benefit is particularly apparent in fast-twitch fibers. Fast-twitch (Type II white) fibers contain 30-100% more Carnosine than slow-twitch (Type I, red) fibers.

Athletes who excel in sprint-type and high-intensity exercise, such as 100-meter sprinters, short-track skaters, etc., have an abundance of Type II B fibers and those fibers are rich in Carnosine. Endurance-type athletes such as marathon runners and triathletes have an abundance of Type I slow-twitch fibers, which are much lower in Carnosine.

Testosterone increases muscle Carnosine content. Castration of mice reduces the muscle Carnosine level by 40%, while testosterone administration to female mice increases muscle Carnosine content by 268%. The benefit of testosterone is associated with increased expression of the Taurine / Beta-alanine transporter.

The lower muscle Carnosine content of old age is mainly the result of a decrease that occurs during early adulthood (even shortly after puberty) rather than a steady decrease from early adulthood to elderly age.

The synthesis rate of Carnosine in muscle cells is rate-limited by the availability of Beta-alanine, rather than Histidine. Histidine, as an essential amino acid, is present in the blood in sufficient concentrations that it will not be a limiting factor. The endogenous supply of Beta-alanine, however, is dependent on hepatic synthesis from uracil degradation.

The dietary supply of Beta-alanine is of relevance. The average daily intake of Beta-alanine from an omnivore diet has been calculated at approximately 330 mg/day, nearly all of which is derived from meat, fish, and poultry. Chicken and Turkey white meat (higher in Type II fibers), along with tuna, are the best dietary sources. Beef, pork, venison, and rabbit contain significantly less Beta-alanine. Some fishes contain virtually no Beta-alanine. The Beta-alanine content is decreased to the degree meat is cooked, and curing of meat decreases the content by 35%.

Dairy and vegetable products do not contain Beta-alanine. Vegetarians have more than 20% lower muscle Carnosine than those on an omnivorous diet. Raising the dietary intake of Beta-alanine is an effective and powerful means to induce muscle Carnosine loading.

Daily ingestion of a very high dose of Carnosine (13g/day) for four weeks will elevate muscle Carnosine content of healthy volunteers by 65%. Interestingly, a similar increase is obtained when ingesting pure Beta-alanine, rather than Carnosine. Beta-alanine supplementation (1.6 – 6.4g/day for several weeks) has been shown in multiple studies to increase muscle Carnosine.

Muscle tissue also acts as a reservoir of Carnosine. Muscle can store and then release, as appropriate, Carnosine into the interstitium and into the circulation --- for transport to other tissues needing Carnosine and/or its constituents, beta-alanine, and histidine.

- In humans, carnosine levels decline with age. Muscle carnosine concentration decreases 63% from age 10 to age 70.

- Carnosine not only serves as an antioxidant in muscle, but also as a pH buffer. It protects muscle cell membranes from oxidation under the acidic conditions of muscular exercise.

- Carnosine dramatically improves exercise recovery (but does not increase performance, which means that it is not an "ergogenic aid," but rather facilitates the anabolic response to exercise).

- Carnosine quickly restores muscle contraction capability after fatigue.

- In studies using lab animals, exercise by a running wheel increases Carnosine synthesis in the leg muscle, and elevates plasma Carnosine concentration, then enhances the breakdown of Carnosine in the inactive period.

- These findings suggest a possibility that Carnosine released from muscles during exercise functions to reduce the blood glucose level through the regulation of the autonomic nerves --- and that regulation involves conversion of Carnosine to Histidine, then to Histamine.