# Carnosine

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Carnosine (beta-alanyl-L-histidine) is a dipeptide of the amino acids beta-alanine and histidine. It is highly concentrated in muscle and brain tissues.

Carnosine has several mechanisms of action, including

- Antioxidant
- Anti-glycating agent; inhibits advanced glycation end product formation
- May inhibit some of the deleterious effects of a high fructose diet
- Chelates divalent metal ions, including copper and zinc
- Suppresses toxicity of deleterious aldehydic products of lipid peroxidation, including acetaldehyde, acrolein, formaldehyde, malondialdehyde and hydroxynonel
- Neuroprotective

## Cataracts

Cataract, opacification of the lens, is one of the commonest causes of loss of useful vision during aging, with an estimated 16 million people world-wide affected. (Babizhayev 2010)

Cataract formation represents a serious problem in the elderly, with approximately 25% of the population aged >65 years and about 50% aged >80 years experiencing a serious loss of vision as a result of this condition. Not only do cataracts diminish quality of life, they also impose a severe strain on global healthcare budgets. In the US, 43% of all visits to ophthalmologists by Medicare patients are associated with cataract. Surgery represents the standard treatment of this condition, and 1.35 million cataract operations are performed annually in the US, costing 3.5 billion US dollars (year of costing, 1998). Unfortunately, the costs of surgical treatment and the fact that the number of patients exceeds surgical capacities result in many patients being blinded by cataracts worldwide. This situation is particularly serious in developing countries; worldwide 17 million people are blind because of cataract formation, and the problem will grow in parallel with aging of the population. In any event, surgical removal of cataracts may not represent the optimal solution. Although generally recognised as being one of the safest operations, there is a significant

complication rate associated with this surgical procedure. Opacification of the posterior lens capsule occurs in 30-50% of patients within 2 years of cataract removal and requires laser treatment, a further 0.8% experience retinal detachments, approximately 1% are rehospitalised for corneal problems, and about 0.1% develop endophthalmitis. Although the risks are small, the large number of procedures performed means that 26,000 individuals develop serious complications as a result of cataract surgery annually in the US alone. Thus, risk and cost factors drive the investigation of pharmaceutical approaches to the maintenance of lens transparency. (Babizhayev, Deyev et al. 2004)

## Carnosine for Cataracts

N-acetyl-carnosine may be beneficial in preventing and treating cataracts.

Carnosine has been shown to act as a competitive inhibitor of the non-enzymatic glycosylation of proteins. Thus, carnosine may prevent and reverse (de-link) the formation of the advanced glycation end-products (AGEs), whose accumulation in the ocular tissues has been proposed to play a direct role in the etiology and pathogenesis of cataract and diabetic ocular complications (DOC). (Babizhayev and Kasus-Jacobi 2009)

Carnosine treatment delayed the progression of cataracts in diabetic rats, and the delay was statistically significant on the fourth week of diabetes ($p<0.05$, when compared with untreated moderately diabetic rats). (Yan, Guo et al. 2008)

Mildly denaturing conditions induce bovine alpha-crystallin, the major structural lens protein, to self-assemble into fibrillar structures in vitro. L- and D-carnosine was shown to have protective effects on alpha-crystallin amyloid fibril formation, and may be beneficieal for cataract disease. (Attanasio, Cataldo et al. 2009)

N-acetylcarnosine is a therapeutic tool to manage age-related cataracts in human and in canine eyes. (Babizhayev, Deyev et al. 2004)

Oral carnosine (1g/kg body weight/day)supplementation prevents vascular damage in experimental diabetic retinopathy in rats. (Pfister, Riedl et al. 2011)

## Can-C Eye Drops

Innovative Vision Products, Inc. (IVP)'s scientists developed the lubricant eye drops (Can-C) designed as 1% N-acetylcarnosine (NAC) prodrug of L-carnosine containing a mucoadhesive cellulose-based compound combined with corneal absorption promoters in a sustained drug delivery system.

A recent clinical study assessed vision before and after 9 month term of topical ocular administration of NAC lubricant eye drops or placebo in 75

symptomatic patients with age-related uncomplicated cataracts in one or both eyes, with acuity in one eye of 20/40 or worse (best-corrected distance), and no previous cataract surgery in either eye and no other ocular abnormality and 72 non-cataract subjects ranged in age from 54 to 78 years. Following 9 months of treatment with NAC lubricant eye drops, most patients' glare scores were improved or returned to normal in disability glare tests with Halometer DG. Improvement in disability glare was accompanied with independent improvement in acuity. Furthermore, patients with the poorest pretreatment vision were as likely to regain certain better visual function after 9 months of treatment with N-acetylcarnosine lubricant eye drops as those with the worth pretreatment vision. (Babizhayev, Burke et al. 2009)

N-acetylcarnosine (as the ophthalmic drug Can-C), has been found to be suitable for the nonsurgical prevention and treatment of age-related cataracts. This molecule protects the crystalline lens from oxidative stress-induced damage, and in a recent clinical trial it was shown to produce an effective, safe and long-term improvement in sight. When administered topically to the eye in the form of Can-C, N-acetylcarnosine functions as a time-release prodrug form of L-carnosine resistant to hydrolysis with carnosinase. N-acetylcarnosine has potential as an in vivo universal antioxidant because of its ability to protect against oxidative stress in the lipid phase of biological cellular membranes and in the aqueous environment by a gradual intraocular turnover into L-carnosine. In our study the clinical effects of a topical solution of N-acetylcarnosine (Can-C) on lens opacities were examined in patients with cataracts and in canines with age-related cataracts. These data showed that N-acetylcarnosine is effective in the management of age-related cataract reversal and prevention both in human and in canine eyes. (Babizhayev, Deyev et al. 2004)

### Carnosine and Aspirin Eye Drops

A recent study found that a combination of carnosine and aspirin in eye drops are effective against the onset and development of diabetic cataract in rats. (Shi, Yan et al. 2009)

### Polaprezinc

Zinc complex of L-carnosine (L-CAZ; generic name Polaprezinc) is the first drug for oral administration in which zinc plays an essential role. L-CAZ was approved as an anti-ulcer drug of membrane protection type. (Matsukura and Tanaka 2000)

Polaprezinc was shown to protect against radiation-induced apoptosis in rat jejunal crypt cells. (Matsuu-Matsuyama, Shichijo et al. 2008)

Polaprezinc protects mice against endotoxin shock. (Ohata, Moriyama et al. 2010)

Polaprezinc attenuates the Helicobacter pylori-induced gastric mucosal leucocyte activation in Mongolian gerbils. (Suzuki, Mori et al. 2001)

Polaprezinc (Zinc L-carnosine) is a potent inducer of anti-oxidative stress enzyme, heme oxygenase (HO)-1 - a new mechanism of gastric mucosal protection. (Ueda, Ueyama et al. 2009)

A randomized, double-blind, placebo-controlled, multi-center study found that Polaprezinc is effective for patients with taste disorders. The group of patients given 68 mg zinc showed a significant improvement in their gustatory sensitivity compared with the placebo group. The most common side effects observed were increase in serum triglyceride and serum alkaline phosphatase, decrease in serum iron, and some gastrointestinal incidents, although they were not serious. (Sakagami, Ikeda et al. 2009)

### Carnosinase

Carnosinase is an enzyme that hydrolyzes carnosine (amino-acyl-l-histidine) and other dipeptides containing l-histidine into their constituent amino acids.

### Adverse Effects

In animal models, supplemental carnosine can increase corticosterone levels, which may explain the hyperactivity sometimes seen in high doses. (Tomonaga, Tachibana et al. 2004)

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