Carnosine As a Natural Antioxidant and Geroprotector: From Molecular Mechanisms to Clinical Trials

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Carnosine is a protective dipeptide consisting of β-alanine and L-histidine. It demonstrates a number of useful features, including stimulation of brain and muscle microcirculation and a rejuvenating effect on cultured cells. Its activity is based on its antioxidant and antiglycating action that, in addition to heavy metal chelation and pH-buffering ability, makes carnosine an essential factor for preventing neurodegeneration and accumulation of senile features. Recently, carnosine was successfully used to treat patients after brain stroke or patients with Parkinson disease. We conclude that carnosine can be recommended for patients under oxidative stress as a natural remedy having high efficiency and no side effects.

Carnosine: A Versatile Antioxidant and Antiglycating Agent

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Carnosine (β-alanyl-L-histidine) has recently attracted much attention as a naturally occurring antioxidant and transition-metal ion sequestering agent. It has also been shown to act as an anti-glycating agent, inhibiting the formation of advanced glycation end products (AGEs). Through its distinctive combination of antioxidant and antiglycating properties, carnosine is able to attenuate cellular oxidative stress and can inhibit the intracellular formation of reactive oxygen species and reactive nitrogen species. By controlling oxidative stress, suppressing glycation, and chelating metal ions, carnosine is able to reduce harmful sequelae such as DNA damage. AGEs are known contributors to the pathology of Alzheimer's disease, and carnosine therefore merits serious attention as a possible therapeutic agent.

Carnosine: can understanding its actions on energy metabolism and protein homeostasis inform its therapeutic potential?

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The dipeptide carnosine (β-alanyl-L-histidine) has contrasting but beneficial effects on cellular activity. It delays cellular senescence and rejuvenates cultured senescent mammalian cells. However, it also inhibits the growth of cultured tumour cells. Based on studies in several organisms, we speculate that carnosine exerts these apparently opposing actions by affecting energy metabolism and/or protein homeostasis (proteostasis). Specific effects on energy metabolism include the dipeptide's influence on cellular ATP concentrations. Carnosine's ability to reduce the formation of altered proteins (typically adducts of methylglyoxal) and enhance proteolysis of aberrant polypeptides is indicative of its influence on proteostasis. Furthermore these dual actions might provide a rationale for the use of carnosine in the treatment or prevention of diverse age-related conditions where energy metabolism or proteostasis are compromised. These include cancer, Alzheimer's disease, Parkinson's disease and the complications of type-2 diabetes (nephropathy, cataracts, stroke and pain), which might all benefit from knowledge of carnosine's mode of action on human cells.
Carnosine decreased neuronal cell death through targeting glutamate system and astrocyte mitochondrial bioenergetics in cultured neuron/astrocyte exposed to OGD/recovery.

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Previously, we showed that carnosine upregulated the expression level of glutamate transporter 1 (GLT-1), which has been recognized as an important participant in the astrocyte-neuron lactate shuttle (ANLS), with ischemic model in vitro and in vivo. This study was designed to investigate the protective effect of carnosine on neuron/astrocyte co-cultures exposed to OGD/recovery, and to explore whether the ANLS or any other mechanism contributes to carnosine-induced neuroprotection on neuron/astrocyte. Co-cultures were treated with carnosine and exposed to OGD/recovery. Cell death and the extracellular levels of glutamate and GABA were measured. The mitochondrial respiration and glycolysis were detected by Seahorse Bioscience XF96 Extracellular Flux Analyzer. Results showed that carnosine decreased neuronal cell death, increased extracellular GABA level, and abolished the increase in extracellular glutamate and reversed the mitochondrial energy metabolism disorder induced by OGD/recovery. Carnosine also upregulated the mRNA level of neuronal glutamate transporter EAAC1 at 2 h after OGD. Dihydrokainate, a specific inhibitor of GLT-1, decreased glycolysis but it did not affect mitochondrial respiration of the cells, and it could not reverse the increase in mitochondrial OXPHOS induced by carnosine in the co-cultures. The levels of mRNAs for monocarboxylate transporter1, 4 (MCT1, 4), which were expressed in astrocytes, and MCT2, the main neuronal MCT, were significantly increased at the early stage of recovery. Carnosine only partly reversed the increased expression of astrocytic MCT1 and MCT4. These results suggest that regulating astrocytic energy metabolism and extracellular glutamate and GABA levels but not the ANLS are involved in the carnosine-induced neuroprotection.

Carnosine's Effect on Amyloid Fibril Formation and Induced Cytotoxicity of Lysozyme


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Carnosine, a common dipeptide in mammals, has previously been shown to dissemble alpha-crystallin amyloid fibrils. To date, the dipeptide's anti-fibrillogensis effect has not been thoroughly characterized in other proteins. For a more complete understanding of carnosine's mechanism of action in amyloid fibril inhibition, we have investigated the effect of the dipeptide on lysozyme fibril formation and induced cytotoxicity in human neuroblastoma SH-SY5Y cells. Our study demonstrates a positive correlation between the concentration and inhibitory effect of carnosine against lysozyme fibril formation. Molecular docking results show carnosine's mechanism of fibrillogenesis inhibition may be initiated by binding with the aggregation-prone region of the protein. The dipeptide attenuates the amyloid fibril-induced cytotoxicity of human neuronal cells by reducing both apoptotic and necrotic cell deaths. Our study provides solid support for carnosine's amyloid fibril inhibitory property and its effect against fibril-induced cytotoxicity in SH-SY5Y cells. The additional insights gained herein may pave way to the discovery of other small molecules that may exert similar effects against amyloid fibril formation and its associated neurodegenerative diseases.
Use of carnosine as a natural anti-senescence drug for human beings.


Carnosine is an endogenous free-radical scavenger. The latest research has indicated that apart from the function of protecting cells from oxidation-induced stress damage, carnosine appears to be able to extend the lifespan of cultured cells, rejuvenate senescent cells, inhibit the toxic effects of amyloid peptide (A beta), malondialdehyde, and hypochlorite to cells, inhibit glycosylation of proteins and protein-DNA and protein-protein cross-linking, and maintain cellular homeostasis. Also, carnosine seems to delay the impairment of eyesight with aging, effectively preventing and treating senile cataract and other age-related diseases. Therefore, carnosine may be applied to human being as a drug against aging.

Could carnosine or related structures suppress Alzheimer's disease?


Reactive oxygen species, reactive nitrogen species, copper and zinc ions, glycating agents and reactive aldehydes, protein cross-linking and proteolytic dysfunction may all contribute to Alzheimer's disease (AD). Carnosine (beta-alanyl-L-histidine) is a naturally-occurring, pluripotent, homeostatic agent. The olfactory lobe is normally enriched in carnosine and zinc. Loss of olfactory function and oxidative damage to olfactory tissue are early symptoms of AD. Amyloid peptide aggregates in AD brain are enriched in zinc ions. Carnosine can chelate zinc ions. Protein oxidation and glycation are integral components of the AD pathophysiology. Carnosine can suppress amyloid-beta peptide toxicity, inhibit production of oxygen free-radicals, scavenge hydroxyl radicals and reactive aldehydes, and suppresses protein glycation. Glycated protein accumulates in the cerebrospinal fluid (CSF) of AD patients. Homocarnosine levels in human CSF dramatically decline with age. CSF composition and turnover is controlled by the choroid plexus which possesses a specific transporter for carnosine and homocarnosine. Carnosine reacts with protein carbonyls and suppress the reactivity of glycated proteins. Carbonic anhydrase (CA) activity is diminished in AD patient brains. Administration of CA activators improves learning in animals. Carnosine is a CA activator. Protein cross-links (gamma-glutamyl-epsilon-amino) are present in neurofibrillary tangles in AD brain. gamma-Glutamyl-carnosine has been isolated from biological tissue. Carnosine stimulates vimentin expression in cultured human fibroblasts. The protease oxidised-protein-hydrolase is co-expressed with vimentin. Carnosine stimulates proteolysis in cultured myocytes and senescent cultured fibroblasts. These observations suggest that carnosine and related structures should be explored for therapeutic potential towards AD and other neurodegenerative disorders.