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Biological Activity of Carnosine and its Role in Diabetic Nephropathy.

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ABSTRACT

In the present sort-review, a brief development of the structure, chemical and biological activities of carnosine dipeptide is initially carried out. The mechanisms by which carnosine prevents the development of diabetic nephropathy are then analyzed, demonstrating the role of carnosine in the binding of serum carnosinase which has been shown to be related to both the development and progression of diabetic nephropathy.

The effects of carnosine on factors such as transforming growth factor-β (TGF-β), serum carnosinase complexation, prevention of advanced glycation end products (AGEs) formation and potential targets such as glycine N-methyltransferase (GNMT), caspase -1 and Nrf2 pathway, are also analyzed.

1. Introduction

Carnosine was discovered and its structure determined at the beginning of the 20th century by the Russian scientist W.S. Gulewich.[1] It was the first and simplest example of a biologically active peptide. The first decades were devoted to studies of the structure and properties of the component. It was understood that carnosine has a direct relationship with the function of body tissues. In 1953 another Russian scientist, S. E. Severin, demonstrated that carnosine effectively prevented the action of lactic acid that causes a decrease in pH and weakens muscles. When carnosine is added, muscles recover their capacity for work almost immediately and contract as if they had never been exhausted. This is known as the "Severin effect".[2]

Lately there has been widespread interest in this natural non-toxic substance, boosted by important American, Russian and British discoveries about its

antiaging actions.[3-5] The most important research, however, was done in 2002 in the USA, where the team of Dr. Michael Chez reported data on the very significant effects of carnosine in autistic children.[6]

The MEDLINE database includes over 2000 published studies on carnosine.

Carnosine **(Figure 1)** is a natural dipeptide, consisting of β-alanine and L-histidine, linked together by a peptide bond.[7-8] Carnosine occurs in various muscle tissues of various organs and brain tissues.[9] The various regions that the molecule has such as the carboxyl group, the terminal amino group, the amino group of the amide bond and the imidazole ring give carnosine an increased buffering capacity that makes it able to protect against increased acidity created by the production of lactic acid inside muscle tissues after vigorous activity. [10-12] The average pK values of these groups are 2.64 for the carboxylate, 6.77 for the Nτ nitrogen of the imidazole ring, and 9.37 for the amino group. The existence of mobile hydrogens can explain the different tautomeric types.[13]

Figure 1. *The numbering of the neutral Carnosine ($carnH_4$)^0; N^3 is characterized as N***π** *while N^4 as N***τ**.[28]

Due to the fact that carnosine reacts with various active reagents such as hydroxyl radical, superoxide or "singlet" oxygen, it has been extensively reported that it has an antioxidant effect.[14-19] The carboxyl group, amino groups and N atoms of the imidazole ring make carnosine a biologically active dipeptide and an effective complexing agent and allow it to interact with metalloenzymes or with metal ions within the body such as copper, zinc, iron and calcium .[20-22] Attempts to characterize complexes of carnosine other than Cu(II) and a few of its compounds with Zn(II), with vanadium, cobalt, ruthenium and only one report of a complex of Ni(II) have been reported.[23-26]

Due to both its structure and its non-toxicity, carnosine exhibits a special biological activity. In this article, its actions, along with the important role of carnosine against diabetic nephropathy will be also discussed.

2. Biological activity of carnosine

Some of its main biological actions are:

- Significantly contributes to the maintenance of acid-base balance in the skeletal muscle buffer, when the H+ concentration increases, due to the production of lactic acid during intense physical exercise.33
- Antioxidant actions. [17, 29-32]
- Ability to inactivate reactive oxygen species, and to trap free radicals. [34,35]
- Binding of aldehydes. [36]
- prevention of glycosylation. [27]
- Prevention of carbonylation of proteins. [37]
- Function related to neurotransmitters. [38]
- Formation of chelate compounds with metals. [23-26]

In general, carnosine is a compound that binds aldehydes, reacts with glycosylated proteins,[39] sugars and phospholipids.[40] Thus, carnosine is a potential modulator against diabetic complications, atherosclerosis, Alzheimer's, Parkinson's, epilepsy, autism, dyslexia, Attention of deficit hyperactivity disorder (AD/HD), schizophrenia and related syndromes.

Although zinc and/or copper are found in many neuronal pathways in the brain, concentrations of zinc and copper in the olfactory bulb (the target of input afferents from sensory neurons in the nose) are among the highest in the Central Nervous System (C.N.S.). The role of zinc and copper in the C.N.S. is the modulation of neuronal excitability. However, zinc and copper have also been implicated in a variety of neurological conditions including Alzheimer's disease, Parkinson's disease, stroke, and seizures. Trombley et al. have reviewed the modulatory effects that carnosine may have on the ability of zinc and copper to influence neuronal excitability and ex-

ert neurotoxic effects on the olfactory system.[41]

Aldini et al. studied and explained the mechanism of action of carnosine as an inhibitor of cytotoxic α, β-unsaturated aldehydes using 4-hydroxy-trans-2,3-nonenal (HNE) as a model aldehyde. It was shown that in phosphate buffer pH 7.4 carnosine was 10 times more active as an HNE inhibitor than L-histidine and N-acetyl-carnosine while β-alanine was completely ineffective. This indicates that the two cognate amino acids act synergistically as a dipeptide and excess β-alanine catalyzes the addition of histidine to HNE. Two classes of carnosine reaction products are identified, in a pH-dependent equilibrium: (a) a "Michael" adduct, stabilized as a five-membered cyclic hemiacetal ring, and (b) a macrocyclic imine derivative. The addition chemistry of carnosine to HNE appears to begin with the formation of a reversible α, β-unsaturated imine and proceeds with ring closure via an intramolecular "Michael" addition. [42]

3. The important role of carnosine against diabetic nephropathy

Diabetic nephropathy (DN) is a common microvascular complication of diabetes and the main cause of end-stage nephropathy (ESRD). Inflammation and fibrosis play an important role in the development and progression of DN. 48 The risk of diabetic nephropathy is partially genetically determined. Diabetic nephropathy is linked to a gene locus on chromosome 18q22.3-q23.

B. Janssen et al. aimed to identify the causative gene, on chromosome 18, and study the mechanism by which the product of this gene could be involved in the development of diabetic nephropathy. The effect of carnosine on the production of extracellular matrix components and transforming growth factor-β (TGF-β) after exposure to 5 and 25 mmol/l d-glucose was studied in cultured human podocytes and mesangial cells, respectively. A trinucleotide repeat in exon 2 of the CNDP1 gene, coding for a leucine repeat in the leader peptide of the carnosinase-1 precursor, was associated with nephropathy.

Carnosine inhibited the increased production of fibronectin and collagen type VI in podocytes and the increased production of TGF-β in mesangial cells induced by 25 mmol/l glucose. Diabetic patients with the CNDP1 Mannheim variant are less susceptible for nephropathy. [27]

Also, J.H. Kang, in his study demonstrated that carnosine and homocarnosine inhibited the production of hydroxyl radicals in the L-3,4-dihydroxyphenylalanine/Fe^{3+} (DOPA) system. The results suggest that carnosine and homocarnosine act as scavengers of hydroxyl radicals to protect against DNA damage. It is suggested that carnosine and homocarnosine may be explored as potential therapeutic agents for pathologies involving DNA damage by DOPA oxidation. [43]

Recent biochemical and clinical evidence implicates human serum carnosinase in a variety of pathological conditions, such as neurological disorders and diabetic nephropathy, suggesting that this enzyme is of greatest interest as a novel drug target. The study by Vistoli et al.,44 was conducted to elucidate the role of serum carnosinase and its catalytic activity and to analyze the mechanism by which citrate ions increase the catalytic activity of carnosinase.

A homologous model of the enzyme was obtained based on β-alanine synthetase and its active center was found to bind known substrates carnosine, homocarnosine and anserine with bonds that favor catalysis. Citrate ions appear to bind at only three well-defined sites involving both ions and hydrogen bonds. Molecular dynamics simulations demonstrate that citrate has a marked effect on the three-dimensional structure of carnosinase, increasing the binding capacity of carnosine on the catalytic side. This is one of the first reports to demonstrate the molecular mechanism of an allosteric enzyme activator using molecular dynamics simulations.

Zn(II) located in the catalytic domain and involved in interactions with His106, Gly115, Asp139, Glu173, Glu174 and two water molecules appear in β-alanine synthase **(Figure 2).**

Emerging evidence suggests that dysregulation of cellular redox homeostasis and chronic inflammatory processes are involved in the pathogenesis of kid-

ney disorders. In this light, the endogenous dipeptide carnosine (β-alanyl-L-histidine) and hydrogen sulfide (H2S) exert cytoprotective actions through modulation of redox-dependent resistance pathways during oxidative stress and inflammation.[45]

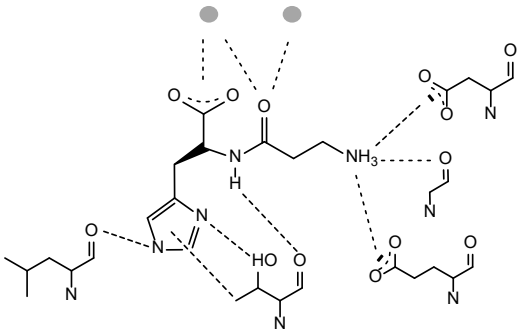

Figure 2. *Two-dimensional representation of the interaction pattern between carnosinase and the carnosine substrate. The model shows how the enzyme recognizes (binds) the amino group, the carboxyl group, and the unsubstituted imidazole ring. The amide bond is simultaneously bound for recognition and polarized for catalysis.*

High levels of transforming growth factor β (TGFβ) in urine stimulate the normal pathway (ALK 5, Smad 2/3) and the alternative pathway ALK 1, Smad 1/5). Activation of the canonical pathway causes accumulation of extracellular matrix in the glomerular basement membrane (GBM) and mesangium. In addition, activation of the alternative pathway causes podocyte injury that causes foot process elimination. It has been clinically shown that the use of oral carnosine supplementation can reduce TGFβ levels in patients with type 2 diabetes mellitus. [46]

It is well established that the formation of advanced glycation end products (AGEs) is a significant problem in uremic patients undergoing peritoneal dialysis (PD). In this way in a related study, peritoneal dialysis solutions (1.5% dextrose) were incubated with human serum albumin (HSA) or collagen (type IV) with or without 10 mmol/L of each of carnosine, anserine, homocarnosine, histidine, and aminoguanidine. The rate of AGE formation was monitored by fluorescence spectrophotometry.

It was found that carnosine and related compounds showed effective regression of AGE formation in both types of proteins in both long-term and short-term exposure to PD fluids with an efficacy rate of the order carnosine > homocarnosine > anserine, aminoguanidine > histidine in long-term time exposure and homocarnosine > carnosine > aminoguanidine > anserine > histidine in short-term exposure. [47]

Glycine N-methyltransferase is a multifunctional protein that regulates the cellular pool of methyl groups by controlling the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH).

Recent studies by Liu X.Q. et. al., showed that carnosine reversed the onset, clinical symptoms, and renal tubular damage in DN patients. More specifically, glycine N-methyltransferase (GNMT), a multifunctional protein that regulates the cellular pool of methyl groups by controlling the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), was significantly down-regulated in the serum of DN type 1 patients and in renal tissues of DN mice. Using tubular epithelial cells (TECs), it was confirmed that increased GNMT expression mimics the protective role of carnosine in reducing inflammation and fibrosis while inhibition of GNMT expression abolished the protective effects of carnosine. In this particular research, using web-prediction algorithms, cellular thermal shift assay (CETSA) and molecular docking, it was shown that the carnosine molecule is a target of GNMT. [48]

Caspase-1 was identified as interleukin-1β-converting enzyme (ICE, caspase-1) and was initially identified as the protease responsible for the maturation of pro-interleukin (IL)-1β to its pro-inflammatory, biologically active form. In a recent study, capase-1 and gadermin D were found to be increased in renal biopsy tissue of DN patients. This study was the first to demonstrate a novel role for carnosine in ameliorating podocyte injury by inhibiting apoptosis through targeting caspase-1. Thus,

carnosine may have potential as a therapeutic agent in the treatment of DN by targeting caspase-1. [49]

The nuclear factor erythroid 2–related factor 2 (Nrf2) is an emerging regulator of cellular resistance to oxidants. 50 In the recent review article by Caruso G. et. al. evidence on the therapeutic potential of carnosine, as an endogenous antidote, that can rescue the Nrf2 pathway and subsequently reverse drug-induced cardiotoxicity and neurotoxicity is reviewed. [51]

3. Conclusions

The effect of carnosine on factors such as transforming growth factor-β (TGF-β), serum carnosinase complexation, prevention of advanced glycation end products (AGEs) formation and potential targets such as glycine N-methyltransferase (GNMT), caspase -1 and Nrf2 pathway, make the carnosine molecule an important factor either in preventing the manifestation of DN or in preventing its progression. □

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