

# Would Carnosine or a Carnivorous Diet Help Suppress Aging and Associated Pathologies?

ALAN R. HIPKISS

*Centre for Experimental Therapeutics, William Harvey Research Institute, Barts' and the London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK*

**ABSTRACT:** Carnosine ( $\beta$ -alanyl-L-histidine) is found exclusively in animal tissues. Carnosine has the potential to suppress many of the biochemical changes (e.g., protein oxidation, glycation, AGE formation, and cross-linking) that accompany aging and associated pathologies. Glycation, generation of advanced glycosylation end-products (AGEs), and formation of protein carbonyl groups play important roles in aging, diabetes, its secondary complications, and neurodegenerative conditions. Due to carnosine's antiglycating activity, reactivity toward deleterious carbonyls, zinc- and copper-chelating activity and low toxicity, carnosine and related structures could be effective against age-related protein carbonyl stress. It is suggested that carnivorous diets could be beneficial because of their carnosine content, as the dipeptide has been shown to suppress some diabetic complications in mice. It is also suggested that carnosine's therapeutic potential should be explored with respect to neurodegeneration. Olfactory tissue is normally enriched in carnosine, but olfactory dysfunction is frequently associated with neurodegeneration. Olfactory administration of carnosine could provide a direct route to compromised tissue, avoiding serum carnosinases.

**KEYWORDS:** glycation; anti glycaters; AGEs; carbonyls; chelators

## INTRODUCTION

Nonenzymic protein glycosylation or glycation mediated by glucose (and more reactive aldehydes) contributes to aging, neurodegeneration, diabetes, and related complications.<sup>1-3</sup> Aldehydes are major sources of protein modification, while aldehyde-scavenging enzymes<sup>4</sup> and glyoxalase-1 activity, which

Address for correspondence: Alan R. Hipkiss, Centre for Experimental Therapeutics, William Harvey Research Institute, Barts' and the London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, U.K. Voice: 44-(0)20-7882-6032; fax: 44-(0)20-7882-6037.  
e-mail: alanandjill@lineone.net

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detoxify the highly reactive aldehyde methylglyoxal,<sup>5</sup> together with nonenzymic aldehyde scavengers<sup>6</sup> provide protection against these deleterious agents. Diet can influence glycation,<sup>2</sup> and levels of advanced glycosylation end-products (AGEs) in vegetarian diabetic plasma are higher than those detected in omnivores,<sup>7</sup> possibly because of the higher intake of fructose by vegetarians.<sup>7</sup> An alternative explanation, however, is discussed below.

## CARNOSINE AND ALDEHYDES

The dipeptide carnosine ( $\beta$ -alanyl-L-histidine), found exclusively in animal tissue, sometimes in millimolar concentrations, inhibits formation of protein carbonyls and cross-links induced by reducing sugars and other reactive aldehydes, such as malondialdehyde and methylglyoxal (see Ref. 6 and references therein). Adducts formed by carnosine and acrolein and hydroxynonenal have been characterized and detected in muscle tissue.<sup>6</sup> The dipeptide reacts with (i.e., carnosinylates) protein carbonyls and suppresses AGE formation, and AGE-induced protein modification.<sup>6</sup> Carnosinylation of carbonyl groups in oxidized muscle tissue phosphatidylcholine has been reported.<sup>6</sup>

## DIABETES, CARNOSINE, AND GLYCATION

Secondary complications of diabetes often result from protein glycation and oxidation (glycoxidation)<sup>1,9</sup> caused by agents against which carnosine may, theoretically, protect,<sup>6</sup> as evidenced by the following; plasma carnosine concentration is lower in diabetic rats than in normal animals; erythrocyte carnosine levels are lower in human diabetics than in normal subjects; carnosine protects diabetic rat erythrocytes against acidic hemolysis; and carnosine exerts regulatory effects on rat blood glucose levels.<sup>6</sup> In addition to its glyoxalase-mimetic action,<sup>8</sup> carnosine is a carbonyl scavenger, metal ion chelator, and antioxidant,<sup>6</sup> satisfying the requirements for a putative glycation inhibitor.<sup>1</sup> Its ability to alleviate diabetic deterioration in mice<sup>10</sup> further substantiates this proposal.

## PROTECTIVE ROLES OF CARNOSINE

Carnosine can ameliorate aging at cellular and whole-animal levels (see Ref. 6 and citations therein). It suppresses senescence in cultured human fibroblasts and even rejuvenates senescent cells and protects their telomeres against oxidative damage. Beneficial effects of carnosine on survival of senescence-accelerated mice, *Drosophila*, and rodent fibroblasts have been reported, most likely due to carnosine's pluripotency.<sup>6</sup>

## COULD CARNOSINE SUPPRESS CARBONYL STRESS-INDUCED PATHOLOGY?

Carnosine can suppress murine diabetes<sup>10</sup> and cataractogenesis, especially when supplied as its acetylated pro-drug, acetyl-carnosine.<sup>6</sup>

Glycooxidation is important in neurodegeneration.<sup>11-14</sup> Glyoxalase activity attenuates neuronal methylglyoxal levels, suppressing aldehyde-mediated tau modification and aggregation in a mouse model of Alzheimer's disease.<sup>3</sup> Theoretically, carnosine could supplement glyoxalase's action, both by dipeptide's aldehyde-scavenging action<sup>6</sup> and its glyoxalase-mimetic activity,<sup>8</sup> and the dipeptide ameliorates aspects of Parkinson's and Alzheimer's diseases.<sup>15-20</sup> The olfactory lobe, an area implicated in the onset of neurodegeneration, is normally carnosine-enriched.<sup>21-23</sup> One therefore speculates whether olfactory administration of carnosine could be beneficial.

## CARNOSINE'S EFFECTS ON HUMANS

Carnosine may be beneficial in humans, despite the presence of serum and cellular carnosinases, which destroy the dipeptide as meat and carnosine-supplemented diets increase total antioxidant activity in human sera.<sup>24</sup> Dietary carnosine supplementation improved the behavior of autistic children.<sup>25</sup> The mechanisms involved are unknown, but carnosine's antioxidant and aldehyde-scavenging roles could be involved because the autistic brain shows signs of oxidative injury,<sup>26</sup> possible due to a lowered glyoxalase 1 activity.<sup>27</sup>

## DIETS AND CARNOSINE

Macromolecular glycation by sugars and associated glycotoxins, deleterious aldehydes and ketones, together with associated pathologies, might be ameliorated by carnivorous diets containing carnosine and possibly the related peptides, acetyl-carnosine, homocarnosine, and anserine. As an exclusively vegetarian diet would lack carnosine, the observations of Krajcovicova-Kudlackova *et al.*,<sup>7</sup> who observed more AGEs in vegetarian plasma than in omnivores, might be explained by a deficiency of carnosine in a vegetarian diet, which could permit the increased AGE formation observed in vegetarians.

There is little evidence that either supports or refutes the proposal that either a carnivorous diet or carnosine supplementation suppresses glycation and secondary diabetic complications in humans. This is most likely because the components of human carnivorous diets have yet to be regarded as protective (but see McCarty).<sup>28</sup>

It has very recently been shown, however, that a low activity of the enzyme that destroys carnosine, carnosinase, decreases the susceptibility to diabetic

nephropathy,<sup>31</sup> an observation consistent with the proposal that carnosine is protective *in vivo*.

Carnosine-rich diets could be important in old age as tissue levels of the dipeptide apparently decline with age.<sup>6</sup> The related structure, homocarnosine, present in human cerebrospinal fluid, decreases with age by more than 10-fold,<sup>29</sup> which could be important as an association has been reported between Alzheimer's disease and raised levels of protein glycation products in cerebrospinal fluid (CSF).<sup>30</sup> Could homocarnosine suppress protein glycation in young CSF, but does the decline in the concentration of this dipeptide permit increased protein glycation in the CSF?

## CONCLUSIONS

Much more research is required to determine whether carnivorous diets or carnosine supplementation suppress protein glycation and the secondary complications of diabetes, and whether carnosine and/or related peptides (e.g., homocarnosine) exert any protection action toward Alzheimer's disease or other human neurodegenerative conditions in which glycoxidative events are involved.

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