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Review

Glycation, ageing and carnosine: Are carnivorous diets beneficial?

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Abstract

Non-enzymic protein glycosylation (glycation) plays important roles in ageing and in diabetes and its secondary complications. Dietary constituents may play important roles in accelerating or suppressing glycation. It is suggested that carnivorous diets contain a potential anti-glycating agent, carnosine (β-alanyl-histidine), whilst vegetarians may lack intake of the dipeptide. The possible beneficial effects of carnosine and related structures on protein carbonyl stress, AGE formation, secondary diabetic complications and age-related neuropathology are discussed.

Keywords: Glycation; Carbonyls; Aldehydes; Carnosine; Ageing; Diabetes; Diet

1. Introduction

A number of recent papers (Ahmed, 2005; Suji and Sivakami, 2004; Chen et al., 2004; Davydov et al., 2004; Kikuchi et al., 2003; Miller et al., 2003) have (i) discussed the importance of non-enzymic protein glycosylation or glycation mediated by glucose (and more reactive aldehydes) in ageing, neurodegeneration, diabetes and its related complications and (ii) outlined possible mechanisms of intervention, pharmacological and dietary. In their review Davydov et al. (2004) emphasize the role of aldehydes as sources of protein modification and the importance of the ameliorating effects of aldehyde-scavenging enzymes generally, and Chen et al. (2004) highlight specifically the action of glyoxalase-1 against the deleterious effects of the highly reactive aldehyde methylglyoxal in Alzheimer's disease. Ahmed (2005) suggests the properties which putative, non-enzymic, anti-glycating agents should possess to help suppress aldehyde-mediated protein modification and consequential secondary diabetic complications. Suji and Sivakami (2004) discuss how diet might influence glycation and cite the observations of Krajcovicova-Kudlackova et al. (2002) who found that levels of advanced glycosylation end products (AGEs) in the plasma of vegetarians were higher than those detected in omnivours. As an explanation Krajcovicova-Kudlackova et al. (2002) suggested that the higher intake of fructose by the vegetarians induces the raised AGE plasma levels. There is, however, an additional or alternative explanation that should be considered.

2. Carnosine and aldehydes

The dipeptide carnosine (β-alanyl-L-histidine), discovered more than a century ago (Gulewitsch and Amiradzibi, 1900), is found exclusively in animal tissue, especially muscle (Maynard et al., 2001) and brain (de Marchis et al., 2000) sometimes in millimolar concentrations (see also Quinn et al., 1992 and Bonfanti et al., 1999 for reviews). There is an increasing body of evidence that shows that carnosine may be an effective anti-glycating agent, at least in model systems (Hipkiss et al., 1995, 1998b; Vinson and Howard, 1996; Hipkiss, 1998; Swearengin et al., 1999; Seidler, 2000; Burcham et al., 2002; Gugliucci et al., 2002; Ukeda et al., 2002; Argirova and Argirov, 2003; Gugliucci, 2003; Gugliucci and Menini, 2003; Gianelli et al., 2003; Liu

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et al., 2003; Monnier, 2003; Seidler et al., 2004; Hobart et al., 2004; Yan and Harding, in press) and cultured cells (Hipkiss et al., 1997; Wang et al., 2003). The dipeptide has been shown to inhibit formation of protein carbonyls and cross-links induced by reducing sugars and other reactive aldehydes e.g. malondialdehyde and methylglyoxal (Hipkiss et al., 1998a,b; Hipkiss and Chana, 1998; Hipkiss and Brownson, 2000). Furthermore, adducts formed by carnosine and deleterious aldehydes (e.g. acrolein and hydroxynonenal) have been characterized (Aldini et al., 2002; Carini et al., 2003; Liu et al., 2003). The dipeptide can also react with (i.e. carnosinylate) protein carbonyls (Brownson and Hipkiss, 2000) and suppress AGE formation (Hipkiss et al., 1998a) and AGE-induced protein modification (Hipkiss and Chana, 1998). NMR data obtained from human leg muscle indicates immobilization of a proportion of tissue carnosine, possible because it forms adducts with (i.e. carnosinylates) carbonyl groups present on oxidized phosphatidylcholine (Schroder et al., 2004).

3. Diabetes, carnosine and glycation

Many of the secondary complications of diabetes result from protein glycation and oxidation (glycoxidation) (see Brownlee, 2001 and Ahmed, 2005 and Refs. therein) mediated by agents and processes against which carnosine may, theoretically, protect (Hipkiss, 1998); some preliminary supportive evidence from animal studies has been obtained (Hipkiss et al., 2001). Additionally there are a number of observations which suggest an inverse relationship between diabetes and carnosine: the concentration of carnosine in plasma of diabetic rats is reported to be lower than in plasma of normal animals (Nagai et al., 2003); erythrocyte carnosine levels are lower in human diabetics than in normal subjects (Gayova et al., 1999); carnosine can protect diabetic rat erythrocytes against acidic haemolysis (Korobov et al., 2000); Nagai and co-workers (Nagai et al., 2003; Yamano et al., 2001) propose that carnosine has a regulatory effect on rat blood glucose levels. Indeed carnosine seems to satisfy many of the requirements that Ahmed (2005) suggests that any putative glycation inhibitor should possess i.e. carbonyl scavenger (Hipkiss, 1998), metal ion chelator (Horning et al., 2000; Baran, 2000) and anti-oxidant (Kohen et al., 1988; Nagasawa et al., 2001; Fontana et al., 2002).

4. Protective roles of carnosine

Carnosine has some ameliorative effects on ageing at cellular and whole animal levels. Carnosine suppresses senescence in cultured human fibroblasts and even rejuvenates senescent cells (McFarland and Holliday, 1994, 1999). More recently, carnosine was shown to protect telomeres of cultured cells against oxidative damage (Shao et al., 2004). Beneficial effects of carnosine on the survival of senescence-accelerated mice (Yuneva et al., 1999; Boldyrev et al., 2004), *Drosophila* (Yuneva et al., 2002) and rodent fibroblasts (Kantha et al., 1996) have also been described. The processes responsible for these effects have not been defined but they are most likely consequences of carnosine's pluripotency (Hipkiss, 1998) as the dipeptide possess anti-oxidant (Kohen et al., 1988; Nagasawa et al., 2001; Fontana et al., 2002), copper-, calcium- and zinc-chelating (Horning et al., 2000; Baran, 2000) and glyoxylase-mimetic (Battah et al., 2002) activities, in addition to the aldehyde- and carbonyl-scavenging properties outlined above.

5. Could carnosine suppress carbonyl stress-induced pathology?

Carnosine's pluripotency may provide protective function, at a variety of levels, against the development of pathologies where glycoxidative events and the generation of protein carbonyls might be causative (see Levine, 2002; Dalle-Donne et al., 2003 for reviews). For example cataractogenesis is often a diabetes-related. Carnosine's potential here has been most clearly demonstrated by Barbizhayev and et al. who have repeatedly shown that carnosine and its acetylated pro-drug acetyl-carnosine has both therapeutic and rejuvenating actions against the cataracts in human and animal lenses (Barbizhayev, 2004; Barbizhayev et al., 2004, 2001).

Glycoxidation effects and their control are also thought to be important in neurodegenerative conditions (Shuvaev et al., 2001; Picklo et al., 2002; Reddy et al., 2002; Hipkiss, 2002; Kikuchi et al., 2003; Ghanbari et al., 2004; Ahmed et al., 2005). Chen et al. (2004) conclude that glyoxalase activity can attenuate neuronal methylglyoxal levels to suppress aldehyde-mediated tau modification and consequent aggregation in a mouse model of Alzheimer's disease. It is therefore at least conceivable that carnosine could supplement glyoxalase's action, both by dipeptide's aldehyde-scavenging action and its glyoxalase-mimetic activity (Battah et al., 2002). Experimental observation (Preston et al., 1998; Munch et al., 1997; Kim et al., 2002; Miyata and van Ypersele van Strihou, 2003; Boldyrev et al., 1997, 1999, 2003, 2004) provide some support for the suggestion that carnosine could be useful in ameliorating aspects of Parkinson's and Alzheimer's diseases. It may not be coincidental (Hipkiss, 2004) that the olfactory lobe, an area which has been implicated in the onset of these conditions, is normally carnosine enriched (Sassoe-Pognetto et al., 1993).

6. Carnosine's effects on humans

There is some evidence that suggests beneficial effects of the dipeptide in humans, despite the presence of serum and cellular carnosinases, enzymes which hydrolyse the dipeptide to histidine and β-alanine. Antonini et al. (2002) showed

that both meat and carnosine-supplemented diets increased total anti-oxidant activity in human sera. Chez et al. (2002) found that dietary carnosine-supplementation improved behaviour of autistic children. The mechanisms involved are totally unknown but carnosine's anti-oxidant and aldehyde-scavenging roles could be involved because the autistic brain shows signs of oxidative injury (McGinnis, 2004).

7. Diets and carnosine

It is suggested that macromolecular glycation and associated pathologies induced by sugars, deleterious aldehydes and ketones, (Brownlee, 2001) and glycotoxins produced during cooking (Koschinsky et al., 1997), might be ameliorated by carnivorous diets containing carnosine and possibly the related peptides, acetyl-carnosine, homocarnosine and anserine. In contrast any diet which is exclusively vegetarian would lack carnosine, a likely anti-glycating agent; therefore the observations of Krajcovicova-Kudlackova et al. (2002) might be explained by a deficiency of carnosine in a vegetarian diet, thereby permitting the increased AGE formation and reactivity detected in vegetarians.

There is little clear evidence to either support or refute the proposal that a carnivorous diet or carnosine-supplementation suppresses glycation and secondary diabetic complications in humans. This is probably because the components of human carnivorous diets have yet to be considered as potentially protective (but see McCarty, 2005). However the author has received anecdotal ''evidence'' from medical practitioners who report that their carnivorous diabetic patients appear to control their secondary complications better than vegetarian diabetics. Clearly the situation is complex as vegetarians are often more fastidious than carnivores about their health and diets; the latter might consume more dietary carnosine but any accompanied increased intake of animal fat may mask the any benefit which carnosine might exert.

Nevertheless it is suggested that carnosine-rich diets could become increasingly important in old age. Some studies have shown that tissue levels of carnosine decline with age (Johnson and Hammer, 1992; Stuerenburg and Kunze, 1999; Stuerenburg, 2000) and the concentration of a related structure, homocarnosine, in human cerebrospinal fluid apparently may decline between 4- and 10-fold with age (Huang et al., 2005). The latter observation could be important in age-related neuropathology as Ahmed et al. (2005) have recently reported an association between Alzheimer's disease and raised levels of protein glycation products in cerebrospinal fluid (CSF). One conjectures whether homocarnosine normally suppresses protein glycation in the young CSF, but a progressive decline in the concentration of this dipeptide permits increasing CSF protein glycation.

8. The carnosinase paradox

Clearly serum and tissue carnosinases could present major obstacles towards any ameliorative actions of carnosine in vivo. However hydrolysis of the dipeptide into β-alanine and histidine would immediately double the molarity of available amino groups for aldehyde-scavenging etc. Consequently carnosinase activity need not be regarded as counterproductive with respect to carnosine's anti-glycating and aldehyde/carbonyl scavenging actions.

9. Other putative anti-glycating agents

It should be pointed out that a number of other naturally occurring putative anti-glycating agents have been proposed, these include polyamines (Gugliucci and Menini, 2003), pyridoxamine (Baynes, 2002; Amarnath et al., 2004), thiamine (Hammes et al., 2003) and various Chinese herb extracts (Yokozawa and Nakagawa, 2004; Tang et al., 2004: Kim et al., 2004); other possible carbonyl scavengers include aminoguanidine (Thornalley, 2003) and D-penicillamine (see Wondrak et al., 2002; Rahbar and Figarola, 2003; Monnier, 2003 for extensive lists). However that carnosine possess remarkably low toxicity and is found exclusively in animal tissues indicates the possibly utility of carnivorous diets, or diets supplemented with carnosine, for combating glycation/glycoxidation of proteins and aminolipids, especially in diabetics.

10. Conclusions

It is clear that much research is required to determine whether carnivorous diets or carnosine-supplementation do in fact suppress protein glycation and the secondary complications of diabetes. Similarly it is unknown whether carnosine and related dipeptides (e.g. homocarnosine) exerts any protection action with respect to Alzheimer's disease or other neurodegenerative conditions where glycoxidative events are involved. The present discussion has outlined a case for more research in this area, but because carnosine and homocarnosine cannot be patented one wonders whether the likely absence of any large financial profit from such studies would hinder investigation. Conversely, however, should such studies reveal that carnosine, homocarnosine or carnivorous diets do benefit to human health, their relatively low costs might be considered to be more socially desirable than expensive patented pharmaceuticals.

Note added in Proof

Following submission of this manuscript Lee et al. (2005) have reported that both carnosine and histidine suppress some diabetic symptoms in mice, consistent with the proposals outlined here.

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