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Carnosine, diabetes and Alzheimer's disease

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"It has been proposed that carnosine can inhibit generation of many of the protein alterations accompanying aging, especially those associated with AD and diabetes and its complications."

The perspective by Maher and Schubert in this issue of *Expert Review of Neurotherapeutics* discusses the possible association between Alzheimer's disease (AD) and Type 2 diabetes (T2D) metabolism and, in particular, the likelihood that these conditions have common causative agents [1]. The paper also comments on the relative paucity of potential therapeutic agents towards these conditions, possibly because of the mindset of the major pharmaceutical companies that seek a single critical molecular target for their drugs. Instead, the authors suggest that a more broad-brush, multisite attack should be employed, based upon the basic biology of the diseases. The authors propose that any hypothetical potential therapeutic agent should be an anti-inflammatory agent, which is also an antioxidant that chelates metal ions, in addition to possessing antiglycating activity with the ability to scavenge dicarbonyls, such as methylglyoxal, and suppress advanced glycation end product formation and reactivity. It should be noted that the processes that the hypothetical therapeutic should suppress or inhibit also describe the principal factors that promote the accumulation of altered proteins and which accompany (or cause) animal and human aging [2].

In order to search for effective agents that might possess the proposed protective properties, Maher and Schubert suggest that the natural pharmacopeia (natural products made by plants) might provide a source of therapeutic compounds [1]. However, it can be argued that long-lived tissues of long-lived animal species might also contain suitable protective agents that help to suppress the formation of altered proteins, especially when an animal is young. A particular example is the dipeptide carnosine (β-alanyl-L-histidine), which, along with related compounds (e.g., anserine, homocarnosine and balanine), is found in the brain and muscles of mammals, birds and fish, sometimes at surprisingly high concentrations [3,4]. However, carnosine and its related structures have been described as enigmatic and forgotten [5]. This is unfortunate, because carnosine appears to satisfy most of the requirements for efficacy that Maher and Schubert suggested in their article [1]. It has been proposed that carnosine can inhibit generation of many of the protein alterations accompanying aging [6], especially those associated with AD [7] and diabetes and its complications [8].

"...certain antiepileptic drugs raise brain carnosine or homocarnosine levels in the brains of mice and humans."

Carnosine is an antioxidant [9–11] and antiglycating agent that inhibits sugar-mediated protein crosslinking [12–14] and also chelates a number of metal ions (including copper and zinc) [15]. Carnosine reacts with methylglyoxal [16,17] and it has been described as a glyoxalase mimetic [18]. The dipeptide can react with a number of deleterious aldehydic products of lipid peroxidation (i.e., acetaldehyde, acrolein, formaldehyde, malondialdehyde and hydroxynonenal) and thereby suppress their toxicity [19–22]. Carnosine can also react with glycated proteins and inhibit advanced glycation end product formation. [23] There is also some evidence from animal studies that carnosine can inhibit some of the deleterious effects of a high fructose diet [24].

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Carnosine suppresses cell senescence in cultured human fibroblasts (and even rejuvenates senescent cells) [25,26], and delays aging in senescence-accelerated mice [27] and *Drosophila* [28]. Carnosine has been shown to interfere with amyloid peptide reactivity [29–31] and to suppress the progression of the secondary complications of diabetes in mice [32], especially diabetic kidney disease in mice and humans [33–35]. There is also evidence showing that carnosine can protect against ischemia when added either prior to or even following an ischemic episode [36–39]. Consequently, carnosine has been described as an anti-aging peptide [40–42]. There is some evidence suggesting that tissues levels of carnosine may decline with age [43–45]. While carnosine is absent from cerebrospinal fluid (CSF) in humans, levels of homocarnosine, a carnosine homolog, declines in human CSF by up to sevenfold [46,47]. It may be significant that AD is associated with increased levels of glycated proteins in the CSF [48–50].

> "...the fact that carnosine and many of its related structures are not patentable may be an impediment to their immediate exploration..."

Carnosine's apparent anti-aging activity possibly derives from its pluripotency, although its potential efficacy as a dietary supplement in humans is uncertain. This is due to the presence of the enzyme carnosinase in human blood, which cleaves the dipeptide into its component amino acids β-alanine and histidine. It has been argued that the presence of carnosinase therefore limits carnosine's use as a potential drug, however, it should be pointed out that ingestion of β-alanine can promote an increase in muscle carnosine levels in humans [51]. If this is so, then this may counter the argument that the presence of serum carnosinase will suppress the potential efficacy of carnosine, because the carnosinase will simply increase β-alanine levels for resynthesis of carnosine at the relevant tissues (β-alanine availability is the limiting factor in carnosine synthesis). An alternative approach would be to present the carnosine in a form that carnosinase does not attack, such as acetylcarnosine or the decarboxylated form, carcinine [52]. To access the brain, serum carnosinase may be avoided by using an intranasal delivery route.

It is also interesting to note that certain antiepileptic drugs raise brain carnosine or homocarnosine levels in the brains of mice and humans [53,54]. This may provide an alternative mechanism by which brain levels of the dipeptides might be selectively increased. It may be relevant to note that certain antiepileptic drugs also suppress aging in some animal models, although the mechanisms involved remain uncertain [55,56].

In conclusion, it is suggested that carnosine, an almost non-toxic natural product, satisfies the criteria proposed by Maher and Schubert [1], that lead compounds should possess for eventual development of drugs to combat AD and T2D. There is evidence of carnosine's efficacy from animal models. Unfortunately, as noted in general by Maher and Schubert [1], the fact that carnosine and many of its related structures are not patentable may be an impediment to their immediate exploration by the commercial sector. Perhaps charities and the public sector might be encouraged to explore carnosine's therapeutic potential to help keep at bay these two conditions that threaten to overwhelm future medical provision.

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