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Mini-review

Possible Benefit of Dietary Carnosine towards Depressive Disorders

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ABSTRACT: Many stress-related and depressive disorders have been shown to be associated with one or more of the following; shortened telomeres, raised cortisol levels and increased susceptibility to age-related dysfunction. It is suggested here that insufficient availability of the neurological peptide, carnosine, may provide a biochemical link between stress- and depression-associated phenomena: there is evidence that carnosine can enhance cortisol metabolism, suppress telomere shortening and exert anti-aging activity in model systems. Dietary supplementation with carnosine has been shown to suppress stress in animals, and improve behaviour, cognition and well-being in human subjects. It is therefore proposed that the therapeutic potential of carnosine dietary supplementation towards stress-related and depressive disorders should be examined.

Key words: carnosine, telomeres, human, diet, supplementation, depression, cognition, stress, cortisol, aging

A recent paper [1] has shown that supplementation of human diets with carnosine (β-alanyl-L-histidine), a naturally-occurring neurobiological peptide, can provoke beneficial effects on exercise performance and quality of life. Another recent paper [2] has shown that major depressive disorder (MDD) is associated with reduced telomere length, increased susceptibility towards age-related dysfunction and raised cortisol levels in response to stress, while two other recent papers have described an association between decreased leukocyte telomere length and stress-associated disorders [3, 4]. It is objective of the present communication to suggest that (i) carnosine insufficiency could provide a link between stress and depression-associated phenomena and age-related dysfunction, and (ii) carnosine may possess therapeutic potential towards depression and stress-associated disorders when administered as a dietary supplement.

Carnosine and aging

Carnosine is a normal constituent of brain and muscle. In the brain carnosine is synthesized by and secreted from astrocytes: it is degraded to its constituent amino acids by either cellular carnosinase (CNDP1) or serum carnosinase (CNDP2), whose activities in the brain possibly increase in old age [5]. Carnosine and related peptides such as anserine and balenine can also be obtained via carnivorous diets but are absent from strict vegetarian diets.

Although characterized more than a century ago [6], the "true" function of carnosine remains elusive, thus the dipeptide has been described as enigmatic [7]. Evidence from animal and model studies suggests that carnosine is multifunctional. Cell culture studies show that carnosine can inhibit growth of transformed cells [8-10], delay

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cellular senescence [11], help to maintain telomere length [12] and promote generation of a more juvenile phenotype when added to senescent cells [11]. Carnosine can inhibit many deleterious biochemical phenomena thought to be associated with generation of the aged phenotype, these include protein damage (including cross-linking [13]) induced by reactive oxygen species [14], reactive nitrogen species [15,16], reducing sugars [13] and reactive carbonyl species such as malondialdehyde [17], 4-hydroxynonenal [18,19] and methylglyoxal [20]. Model animal studies show beneficial effects of the dipeptide towards a number of age-related physiological conditions including impaired wound healing [21, 22], Alzheimer's disease [23, 24], Parkinson's disease [25, 26], stroke [27, 28], atherosclerosis [29, 30], cataracts [31, 32] and diabetic kidney disease [33, 34]. In fact it has been claimed that carnosine may be a rapamycin mimetic (a well-recognized anti-aging agent) because many of their respective properties are so similar [35], and recent evidence supports this proposal [10].

Depression, cortisol, aging and carnosine

The paper by Gotlib *et al.* [2] illustrates a relationship between telomere length, serum cortisol levels and depression in female children. It has also been suggested that major depressive disorder (MDD) patients may be predisposed to the onset of much age-related pathology [see 2 and refs. therein for a more complete discussion]. Papers by Miller and Sadeh [3] and Shaleh *et al.* [4] detail a relationship between telomere erosion and stress-related depressive disorders. The nature of the relationship, if any, between, on the one hand, cortisol levels and depression and, on the other hand, telomere length and aging, is uncertain. Nevertheless it is possible that a common molecular entity exists whose activities link aging, telomeres, cortisol and behaviour. It is suggested here that carnosine could provide a therapeutic link between these phenomena because, as noted above, carnosine (i) can act as an anti-aging agent (mimicking rapamycin) including exerting beneficial effects on animal models of age-related brain dysfunction [23-28], (ii) can help to maintain telomere length [12], (iii) may enhance cortisol metabolism, at least in mice [36], (iv) ameliorates stress-induced changes in metabolism in restrained mice [37] and (v), when complexed with zinc, suppress the effects of cortisol on rat bone metabolism [38]. Interestingly, it has been suggested that carnosine's anti-stress effects in mice are mediated by modulating the stress-activated hypothalamic-pituitary-adrenal axis [37], whilst it has recently been shown that raised cortisol levels are present in Alzheimer's disease patients' cerebrospinal fluid, possibly arising from dysregulation of the hypothalamic-pituitary-adrenal axis [39]. These observations indicate a possible role for carnosine in controlling age-related neurological dysfunction via effects on the hypothalamic-pituitary-adrenal axis in human brain.

Carnosine supplementation affects brain function in chickens, rodents and humans

Carnosine supplementation can influence behaviour in chickens [40] and rodents [41, 42]; its ability to suppress anxiety in rats [42] could possibly be due to enhanced cortisol metabolism [36]. Interestingly, it has also been reported that carnosine (β-alanyl-histidine) and its reverse structure (i.e. histidinyl-β-alanine) exert the opposite behavioural effects in chickens [40, 43]. While the interpretation of this curious observation in very uncertain, it does at least indicate some structure-function relationship with respect to brain response to the peptides.

In humans, carnosine supplementation has been found to enhance cognition and/or well-being in at least five studies [1, 44-47]. Dietary supplementation with carnosine provoked beneficial effects on behaviour in autistic children [44], and improved cognitive function in patients suffering from Gulf War Illness [45], schizophrenia [46], and chronic heart failure [1]; the latter group also reported a significantly improvement in their quality of life [1]. A recent study has shown that carnosine plus anserine supplementation improved cognitive function and physical capacity in elderly humans [47]. These findings provide evidence that carnosine supplementation has therapeutic potential in humans, despite the presence of carnosinase which might be expected to counteract any efficacy that the dipeptide might elicit. It has however been shown that raised levels of kidney carnosinase does increase the probability of diabetic kidney disease in type-2 diabetics [34], which is probably due to increased destruction of the dipeptide. Nevertheless the fact that beneficial effects of carnosine supplementation have been detected in humans [1, 44-47] suggests that carnosinase activity is not necessarily an impediment to the dipeptide's efficacy in all cases.

Conclusion

Carnosine's ability to affect behaviour positively in humans when present as a dietary supplement supports the idea that carnosine should be explored for its therapeutic potential towards control of depression and post-traumatic stress disorder, as well as for the control of much age-related pathology, despite of the presence of carnosinase. However it would be expected that genetically-determined differences in carnosinase activity could influence any beneficial effects of the dipeptide, as

observed with respect to diabetic kidney disease [5, 33, 34].

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