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Carnosine in Aging-Induced Neurodegeneration: A Promising Approach towards Better Tomorrow for Geriatrics

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Short Communication

Natural aging develops a negative association with the ability to respond everyday's stress related physiological conditions and develops a positive consequence with health deterioration and death [1]. Aging in fact, has its own detrimental effects on the molecules, cells, gross morphology and the normal function of the brain and body as a whole. During aging the brain shrinkages with a loss of its weight and volume, more specifically the grey matter of the brain with the neuronal cell death [2-4]. Among the brain regions the prefrontal cortex and hippocampus affects most during aging [2,3,5] with their region specific executive functions and processing rate of information [6]. The losses of dendrites and neurons have been shown to be associated with various age related neuro diseases [7-9]. In different aging-induced neurodegenerative diseases the senile plaque formation due to amyloid beta peptide deposition may be the signs of clinical mutations of genes, coding for Amyloid Precursor Protein (APP) or presenilins (PS1 and PS2) [10,11]. In consequences of the gene mutation, the reflection in biochemical alteration makes the scenario of senile plaque formation perfect. Previously, Fukumoto et al. [12] have shown that not only in aging-induced neurodegenerative diseases but also in the non-diseased aging pathology the presence of senile plaques are found with the same characteristics of amyloid beta protein deposition in different brain regions. It has been found that during aging different brain neurotransmitters (e.g., serotonin, dopamine) decline [13-15] with an increase of its monoamine metabolizing enzyme and mitochondrial dysfunction which may lead to form Reactive Oxygen Species (ROS) [16,17]. These damaged mitochondria are removed and degraded by the autophagic pathway [18] but the key regulator of autophagy, baclin-1, and expression is reduced in aging brain [19]. This may in-turn lead to accumulate the dysfunctional and degenerated mitochondria which in general up regulates the ROS generation. This ROS with the help of nitric oxide produces RNS and these ROS and RNS through the activation of Apoptosis Signal-regulating Kinase 1 (ASK 1), induced by Amyloid Beta (Aβ) cause neuronal cell death [20]. The production of amyloid beta from the Amyloid Precursor Protein (APP) is enhanced with the aging process and produces more Aβ by the increased activation of secretases (β and γ) [21,22]. The Neurofibrillary Tangles (NFTs) are another hallmark of pathological brain aging. The NFTs are formed due to hyperphosphorylation of tau protein. The Aβ-tau together plays a role towards more vulnerability of aging-induced neuro diseases [23] including dysfunction of mitochondria [17,24] and the function of different neurotransmitters (such as serotonin, glutamate, GABA, acetylcholine) [15,25-37]. As mentioned previously aging increases ROS and declines antioxidant system which in turn develops the antioxidant-ROS imbalance within the system. This imbalance makes an accumulation of ROS and may cause the cellular senescence and reduces the life span [38]. Arking [38] has also shown that the oxidative stress is minimum and the antioxidant activity is much higher in the long lived animals than in the short lived animals. This promising observation leads to deal with the antioxidant molecules, such as vitamin C, α-lipoic acid, resveratol, carnitine, carnosine, vitamin E etc and others to challenge or delay the aging process [39]. Among the antioxidant molecules, carnosine (a dipeptide) is one of them having some unique properties makes it special and different from others.

Carnosine was first discovered by Gulewitch and Amiradzibi [40], the Russian chemists, during their search for unidentified nitrogen-containing not-protein compounds in Liebig's meat extract. It (carnosine) is an endogenous smallest (dipeptide) biomolecule containing two amino acids, Alanine (β) and Histidine (L) [41,42]. Carnosine has a metal chelating [43] and pH buffering [44] properties. Carnosine has also a gene regulatory property [45], anti-senescence activity [46] and inhibits the metastasis [47]. This carnosine can react with methylglyoxal (MG), a metabolic product

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of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, and other metabolic aldehyde-mediated macromolecular damage [48,49]. In physiological condition carnosine, in one hand can react with the oxidant molecules to scavange and on the other hand prevents the oxidative damages through both the enzymatic and non-enzymatic mechanisms. Carnosine is present in the blood [41], skeletal muscle and in olfactory bulb of the brain in mammals [42]. It also presents in other brain regions but at concentration 10-1000 folds less than the skeletal muscle contains [43]. It is degraded by an enzyme, carnosinase [50,51] and synthesized in the biological system by carnosine synthase (formerly carnosine synthatase) enzyme in presence of the rate limiting amino acid, β-alanine [52]. There are two forms of carnosinase: One is serum Carnosinase (CN1) [53] present in serum, Cerebro Spinal Fluid (CSF) and brain and the other one is tissue Carnosinase (CN2), which is present in liver, spleen and kidney as non-specific cytosolic dipeptidase [54]. CN1 has very specific substrate specificity and the CN2 has a wider range of substrate specificities [43]. It is [55] and Bellia et al**.** [56] have shown that serum carnosinase activity is increased and the brain regional carnosine is reduced with aging. Margles [55] has also shown that the olfactory bulb is enriched with carnosine and smelling sense is lost (hyposmia) with the loss of carnosine concentration in aging-induced diseases. In oxidative and nitrosative driven neuro diseases carnosine acts as a potent neuroprotectant by scavenging the reactive oxygen species such as singlet oxygen (O_2^{-}), hydroxyl radicals ($OH^{\cdot}$) [43,57,58] by modulating the cytoprotective enzymes such as Superoxide Dismutase (SOD), heat shock proteins (HSPs) and Heme Oxygenase-1 (HO-1) [59-61] as well as counteract the metal-induced neurotoxicity [62] having antioxidant and antiglycating properties [58,63,64]. This biomolecule inhibits the 6-hydroxydopamine (6-OHDA)-induced stress in endoplasmic reticulum of SH-SY5Y neuroblastoma cell lines [65]. Carnosine reduces the glutamate levels and helps to protect the glutamate transporter-1 (GLT-1) expression in astrocytes exposed to ischemia [66]. In addition, Margles [55] and Hipkiss [64] have shown that age associated phenomenon of advance glycation end products (AGEs) is the result of the reaction between sugar aldehyde and amino group. They have also found that carnosine inhibits the sugar-induced β-A4-amyloidogenic peptide aggregation. Kohen et al. [42] have shown that carnosine and its homologs (homocarnosine and anserine) can react with the peroxyl radicals to scavange the sugar-induced β-A4-amyloidogenic peptide aggregation due to the presence of L-histidine. In another observation they have shown that the dietary histidine increases carnosine levels in rat muscle [67]. Though, Dunnet and Harris [68] during their study on the component amino acids (β-Alalnine and L-Histidine) of carnosine have revealed that the β-alalnine supplementation leads to increase the muscle carnosine concentration, this scenario was absent in L-histidine administration. Contradictory to this finding Chan et al. [69] have found that dietary carnosine did not increase the heart, liver or muscular carnosine concentration but the supplementation of carnosine together with α-tocoferol (Vitamine E) increases the liver and heart carnosine concentration. The exogenous supplementation of carnosine can prevent the protein carbonylation in the brain tissue against the ethanol-induced oxidative damage [70,71]. In mammalian brain homocarnosine is most prevalent dipeptide than carnosine [43]. The homocarnosine made up of the L-histidine and the inhibitory neurotransmitter GABA instead of β-alanine; whereas, carnosine is constituted with the β-alanine has the specific function depending on the molecular organization or combination [43]. In the physiological diseased condition carnosine has the beneficial role to attenuate the diseased oriented disorders [72-74]. In different diseased conditions, like aging-induced neurodegeneration, cancer, diabetic retinopathy carnosine plays a crucial role to overcome the physiological problem [72-74]. The growing number of evidences have indicated the protecting role of carnosine on the diabetes and diabetes related complications [75,76] like ocular diseases and neuropathy [74,77]. In ischemia and reperfusion oriented damage**,** carnosine also plays a protective role [78-80]. Carnosine due to its anti proliferative activity has generated its recent field of interest on cancer biology [73,81]. McFarland and Holliday [82] have given the breakthrough on the research of carnosine in the live cell model with the findings of protective role of carnosine on the senescence fibroblast cells to convert into the juvenile cells. After this breakthrough finding another feather was also added with the consecutive findings of longevity of fibroblast cells in presence of carnosine, providing a cross proof with the reverse phenotype withdrawing the carnosine [83]. Boldyrev et al. [84] and others [46,85] have shown that in the senescence accelerated mice carnosine prolonged the life span. These existing knowledge of carnosine as an antioxidant and the aging-induced deteriorations have inclined the mode of research for further studies regarding aging and involvement of neurotransmitter system during aging to explore the importance of carnosine. The metabolic instability of carnosine due to the prompt degradable property of carnosinase has made a great interest to find out the way of explanation to explain the mechanism of action of carnosine *in vivo* with the exogenous supplementation [86,87]. The current research with this thought has been progressed a step forward to achieve the goal in reality regarding attenuation and withdraw in aging-induced deterioration in brain monoamine neurotransmitter system and neurodegeneration. Recently it has been found that the treatment of carnosine directly to the central nervous system can attenuate the aging-induced (a) brain regional (cerebral cortex, hippocampus, hypothalamus and pons-medulla) (i) changes (increase or decrease in a brain region specific manner) in serotonergic activity [87], (ii) changes (decrease or increase) in steady state levels of 5-HT, its precursor tryptophan (Trp) and metabolites 5-HIAA [86], (iii) increase in 5-HT metabolizing rate limiting enzyme MAO-A activity [24] and its mRNA expression [88], (b) reduction in blood platelet MAO-A activity and its mRNA expression [88,89]. These observations also provide an evidence of greater attenuation in more aged rats than the less aged rats without affecting the young rats. This greater attenuating effect of carnosine on aging-induced (a) brain regional (i) decrease in serotonergic activity [87] and (b) increase in blood platelet serotonergic function [88,89] has been observed with the increase of age of the aged rats which is the most crucial and so far neglected scenario. This has been recently discussed mechanistically with the updated existing knowledge [86,87]. It is well known that during aging the tissue carnosinase (CN2) activity is increased and hence its (tissue) carnosine content is reduced with the increase of age of the aged rats [56]. The carnosine administration into the mammalian body provides carnosine into the different brain regions, muscle tissues as well as circulation where the carnosine content is reduced due to an enhancement in carnosinase activity during aging [56,87]. To explain the greater effect of carnosine in more aged rats than the less aged rats, in spite of aging-induced increase of carnosinase activity, it may be stated that in more aged rats the β-alanine content may be increased in the brain regions and blood and may attain a significant level which may stimulate the carnosine synthase enzyme to recycle the β-alanine to form carnosine further *in vivo*, as β-alanine is a rate-limiting precursor of carnosine [43] and carnosine synthase

has a much higher K_m for β-alanine [90]. Serena et al. [91] have also shown that the β-alanine supplementation in aged person increases the tissue carnosine content. In accordance with this concept, it has been hypothesized that the administration of carnosine may boost up the endogenous carnosine level with the β-alanine, a hydrolyzed product of carnosine and the resultant effect of this (boosted endogenous carnosine level) may act on the monoaminergic parameters as well as on aging-induced increase in ROS/RNS [92,93] to overcome the aging-induced increase in carnosinase activity with a greater percentage in more aged rats in comparison to the less aged rats [86,87], though further study is needed to confirm.

In conclusion, it may be stated that for the aging-induced neurodegenerative disorders (like Parkinsons' Disease) the treatment with carnosine as a combination with the traditional DOPA therapy may trail a new path of treatment [94] and carnosine being an endogenous biomolecule [42] may be used in near future as a molecular neuromedicine as neuroprotective/neuroregenerative agent by modulating cytoprotective enzymes such as SOD, HSPs, HO-1 etc [59-61] to overcome the aging-induced neural disorder-related phenomena in geriatric individuals and would help to live a normal healthy life, if not like young individuals at per (at the biochemical, molecular and behavioral levels) for better tomorrow.

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