CARNOSINE PREVENTS Aβ-INDUCED OXIDATIVE STRESS AND INFLAMMATION IN MICROGLIAL CELLS: A KEY ROLE OF TGF-β1

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Introduction: Carnosine is a natural dipeptide widely distributed in mammalian tissues and exists at particularly high concentrations in muscles and brain. A growing body of evidence shows that carnosine is involved in cellular defense mechanisms against oxidative stress, including inhibition of amyloid-β aggregation, modulation of nitric oxide (NO) metabolism, and scavenging of reactive species. Microglia exert a dual role in the pathogenesis of Alzheimer's disease (AD); on one hand promoting the clearance of amyloid-β (Aβ) via phagocytosis, on the other hand increasing neuroinflammation through the secretion of inflammatory mediators and free radicals. The aim of this study was to investigate the protective effects of carnosine against amyloid-β-induced oxidative stress and neuroinflammation.

Materials and methods: A well-validated model of Aβ-induced stress along with a combination of methods including MTT assay, UV-Vis spectroscopy, high-throughput real-time PCR, and multi-Analyte ELISArray was used to assess the ability of carnosine to protect microglial cells as well as its ability to modulate the expression of genes related to oxidative stress and the secretion of pro-inflammatory and anti-inflammatory cytokines. We also tested by trypan blue exclusion assay the toxicity induced in rat primary mixed neuronal cultures (35-40% neurons, 60–65%glial cells) after Aβ oligomers treatment.

Results: Carnosine prevented cell death in BV-2cells challenged with Aβ oligomers through multiple mechanisms. Specifically, carnosine lowered oxidative stress decreasing the expression of amyloid-β-induced enzymes, nitric oxide synthase and NADPH oxidase, and the concentrations of both NO and superoxide anion. Carnosine also decreased the secretion of pro-inflammatory cytokines such as IL-1β simultaneously rescuing IL-10 levels and increasing the expression and the release of TGF-β1. Additionally, carnosine prevented Aβ-induced neurodegeneration in primary mixed neuronal cultures challenged with Aβ oligomers and these neuroprotective effects were completely abolished by the specific inhibitor of type-1TGF-β receptor, SB431542, suggesting that TGF-β1release and activation of TGF-β1signaling play a central role in mediating the neuroprotective effects of carnosine.

Discussion and conclusions: Our data suggest a novel multimodal mechanism of action of carnosine underlying its protective effects on neurons and microglial cells. Inhibition of Aβ oligomer-mediated inflammation and rescue of TGF-β1signaling have been recently considered as effective strategies for protecting against neurodegeneration and disease progression in AD. Carnosine, through its multipurpose activity, might represent a new pharmacological tool to yield neuroprotection in AD.