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Tackling the Amyloid Beta-Sheet Peptide with Autochthonous Epitopes: Beta-Sheet Breaker Peptides

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Letter to the Editor

The extracellular β-amyloid deposits in brain parenchyma in the form of plaques are one of the pathological hallmarks of Alzheimer's disease (AD). In order the Aβ in the plaques to become pathogenic, it should be oligomerized and fibrillized. It has been reported that the central hydrophobic cluster of amino acids 17-21 (LVFFA) is important in both amyloid fibril formation and stability. The residues 16-27 and 30-36 of Aβ42 also display β-structures [1], whereas other hydrophobic domains containing amino acids 16-20 (KLVFF) of Aβ have also been reported to be fundamental for Aβ protein–protein interaction [2]. The efficacy of the depends on their binding affinity: the stronger the ligand binding, the slower the oligomerization process [3].

The therapeutic agents used in treatment of AD neither target Aβ, nor cure the pathological changes that it induces. Accordingly, a therapeutic strategy that could either prevent formation and/or facilitate dissolution of the misfolded Aβ aggregates, decrease its neurotoxicity and memory impairing activity could be of great value in treatment of AD. Aβ fragment(s) containing the central core of the main Aβ, with a less propensity to adopt β sheet conformation, but able to bind to the full length Aβ and prevent its assembly into amyloid fibrils are known as beta sheet breaker peptide (βSBP). The BSBP 17-21 (LVFFA) [4], LPFFD [5,6], RVVIA [7], 16-20 [4] interfere with fibril formation and increase neuronal survival. Moreover, eight-residue Aβ-derived fragments Aβ1-8, Aβ9-16 and Aβ1-16 had been reported to inhibit caspases pathways activation and protect against Aβ40-induced apoptosis of neuronal cells [8].

We [9] have previously found that the eight-residue βSBPs (especially the βSBP 15–22), without any substitution of the original amino acids, could decrease Aβ40 burden, Aβ-induced cellular changes in amygdala and hippocampus, and Aβ-induced memory impairment. The octapeptide βSBPs we used also improved the Aβ-impaired vascular responses to vasodilators [10]. βSBPs increase Aβ removal by at least two possible mechanisms [11]. The first is that βSBPs may act as an immune complex that activates microglia to a greater extent than Aβ fibrils alone. This scenario may then result in enhanced phagocytosis and subsequent removal of Aβ. However, we do not think that all βSBPs follow this way because in an *in vitro* study we have found that βSBPs 15-22 decreased, the βSBP 16-23 did not change, whereas only the βSBP 17-24 increased microglial activity (our unpublished data). The second mechanism by which βSBPs produce their effects is that βSBPs can bind to the central hydrophobic cluster, via hydrogen bridges in a manner rendering the βSBP sitting in the central hydrophobic region of Aβ on the plane of amyloid dimmer [6], and thereby destabilizing the interaction between Aβ monomers and/or oligomers that is necessary for fibril stability. Aβ develops resistance to protease degradation when polymerized into fibrils *in vivo* [11] and *in vitro* [12]. The subsequent loss of fibril integrity may then lead to exposure of cleavage sites facilitating proteolytic processing and removal of Aβ. βSBPs could also induce their effects via increasing digestion of the Aβ40 by protease K, because we have found that βSBPs 16-23 and 17-24 increased Aβ40 digestion by protease K at temperatures 35°C to 42°C, and βSBPs 15-22 increased Aβ40 digestion only at high temperatures, 41°C to 42°C [13].

Further extensive researches are needed to disclose the efficacy of the βSBPs as one of the candidates for prevention of amyloid aggregation, and therapy of AD.

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