



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

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## Letter to the Editor

The extracellular  $\beta$ -amyloid deposits in brain parenchyma in the form of plaques are one of the pathological hallmarks of Alzheimer's disease (AD). In order the A $\beta$  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 A $\beta$ 42 also display  $\beta$ -structures [1], whereas other hydrophobic domains containing amino acids 16-20 (KLVFF) of A $\beta$  have also been reported to be fundamental for A $\beta$  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 A $\beta$ , nor cure the pathological changes that it induces. Accordingly, a therapeutic strategy that could either prevent formation and/or facilitate dissolution of the misfolded A $\beta$  aggregates, decrease its neurotoxicity and memory impairing activity could be of great value in treatment of AD. A $\beta$  fragment(s) containing the central core of the main A $\beta$ , with a less propensity to adopt  $\beta$  sheet conformation, but able to bind to the full length A $\beta$  and prevent its assembly into amyloid fibrils are known as beta sheet breaker peptide ( $\beta$ SBP). The  $\beta$ SBP 17-21 (LVFFA) [4], LPFFD [5,6], RLVIA [7], 16-20 [4] interfere with fibril formation and increase neuronal survival. Moreover, eight-residue A $\beta$ -derived fragments A $\beta$ 1-8, A $\beta$ 9-16 and A $\beta$ 1-16 had been reported to inhibit caspases pathways activation and protect against A $\beta$ 40-induced apoptosis of neuronal cells [8].

We [9] have previously found that the eight-residue  $\beta$ SBPs (especially the  $\beta$ SBP 15-22), without any substitution of the original amino acids, could decrease A $\beta$ 40 burden, A $\beta$ -induced cellular changes in amygdala and hippocampus, and A $\beta$ -induced memory impairment. The octapeptide  $\beta$ SBPs we used also improved the A $\beta$ -impaired vascular responses to vasodilators [10].  $\beta$ SBPs increase A $\beta$  removal by at least two possible mechanisms [11]. The first is that  $\beta$ SBPs may act as an immune complex that activates microglia to a greater extent than A $\beta$  fibrils alone. This scenario may then result in enhanced phagocytosis and subsequent removal of A $\beta$ . However, we do not think that all  $\beta$ SBPs follow this way because in an *in vitro* study we have found that  $\beta$ SBPs 15-22 decreased, the  $\beta$ SBP 16-23 did not change, whereas only the  $\beta$ SBP 17-24 increased microglial activity (our unpublished data). The second mechanism by which  $\beta$ SBPs produce their effects is that  $\beta$ SBPs can bind to the central hydrophobic cluster, via hydrogen bridges in a manner rendering the  $\beta$ SBP sitting in the central hydrophobic region of A $\beta$  on the plane of amyloid dimmer [6], and thereby destabilizing the interaction between A $\beta$  monomers and/or oligomers that is necessary for fibril stability. A $\beta$  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 A $\beta$ .  $\beta$ SBPs could also induce their effects via increasing digestion of the A $\beta$ 40 by protease K, because we have found that  $\beta$ SBPs 16-23 and 17-24 increased A $\beta$ 40 digestion by protease K at temperatures 35°C to 42°C, and  $\beta$ SBPs 15-22 increased A $\beta$ 40 digestion only at high temperatures, 41°C to 42°C [13].

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

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