IN VITRO AND IN VIVO PHARMACOLOGICAL EFFECTS OF PROTOFIBRIL AB-SELECTIVE MONOCLONAL ANTIBODIES

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Introduction: Alzheimer's disease (AD) is characterized histologically by accumulation of Aβ-containing plaques and tau-containing neurofibrillary tangles in the brain, although the pathophysiology of the disease is not fully understood. Recently, soluble Aβ oligomers and protofibrils (PFs) have been implicated in mediating neurotoxicity, altering synaptic function, and inhibiting hippocampal long-term potentiation. Reducing these pathogenic assemblies of Aβ may provide an effective treatment approach to AD.

Aims: Two kinds of monoclonal antibody (mAb) were used in this study. mAb158 is a mouse mAb selective to PFAβ, and BAN2401 is the humanized mAb of mAb158. The effect of BAN2401 on PFAβ-binding to synaptic spines of rat primary neurons was studied. Also the effect of mAb158 on brain PFAβ and monomeric Aβ levels in Tg2576 was investigated.

Methods: Primary hippocampal neurons were incubated with PFAβ in the presence or the absence of BAN2401. Bound PFAβ was visualized by immunofluorescence procedure after labeling with anti-Aβ antibody. Tg2576 mice received weekly i.p. injections of mAb158 for 18 weeks. Brains were collected at 5 days after the last injection, and PFAβ, Aβ(40) and (X-42) levels were measured with ELISA. Plaque burden was analyzed after immunohistochemical staining.

Results: BAN2401 concentration-dependently decreased the postsynaptic PFAβ binding. Significant decreases in brain PFAβ and soluble and insoluble Aβ(x-42) levels were observed after 18 weeks treatment with mAb158. Decrease in brain 6E10-positive Aβ plaques was also observed after this treatment.

Conclusion: Anti-PFAβ mAbs inhibited PFAβ binding to postsynaptic spines, and also decreased brain PFAβ and Aβ(x-42) levels in Tg2576 after long-term treatment.