



Office of Technology Management

Per-6-Substituted Cyclodextrins Inhibit Beta Amyloid Peptides and Treat Alzheimer's Disease (AD)

Technology Reference

CW079

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Field

Alzheimer's disease

Key Words

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Beta-amyloid peptide

Cyclodextrins

License Status

Seeking licensing partners

Patent Status

US and PCT patent applications filed

Overview

A prominent feature of AD is the presence of extracellular neuritic plaques, which have lengthy fibrils, constructed from amyloid β peptide ($A\beta$) monomers at their core. Therefore, increasing concentrations of $A\beta$ can contribute to AD pathology. It has been proposed that neurodegeneration in AD is caused by deposition of $A\beta$ in the plaques found in the brain tissue. However, a frequent objection to this hypothesis is that the number of amyloid deposits in the brain does not correlate well with the degree of cognitive impairment in transgenic mice or humans.

Recent research based on transgenic models of AD has cast doubt on both the fibril dependence and irreversibility of memory loss. In one model, despite accelerated formation of detergent-insoluble aggregates of amyloid β peptide ($A\beta$) and early onset of memory decline, no correspondence could be shown between memory and $A\beta$.

More remarkably, recovery of memory function recently was reported for transgenic mice vaccinated with antibodies against $A\beta$. Such recovery, which occurred within a day of injection and without impact on insoluble amyloid fibrils, had been predicted by an alternative hypothesis for the structure and pathogenic role of $A\beta$ -derived toxins.

Recent studies also indicate that the most important role of $A\beta$ in the progression of AD may not be beta-amyloid plaque formation, but the formation of intermediate, soluble oligomers.

Technical Summary

The present invention discloses per-6-substituted-cyclodextrins (CDs) that inhibit the formation of ADDLs, and are useful in the treatment and prevention of AD and related diseases and conditions.

Alterations in brain amyloid activity are modulated by passage of the active agent across the blood brain barrier. The present per-6-substituted-cyclodextrins can be improved by modification to increase transport across the blood brain barrier. These compounds can be modified in a fashion that retains the anti-ADDL activity, while being capable of transport across the blood brain barrier.

Also, per-6-substituted-CDs that do not appreciably penetrate into the brain can provide clearance of neurotoxic aggregates from the brain by providing a peripheral link across the blood brain barrier. It has been shown that antibodies against $A\beta$, induced by active immunization with $A\beta$ peptides, reduce brain $A\beta$ burden in amyloid-forming mice. Although enhanced microglial phagocytosis via Fc receptors might represent one plausible explanation, it has been suggested that antibodies present in the peripheral blood may alter the central nervous system/peripheral $A\beta$ equilibrium.

Benefits

- Treatment for AD
- Inhibit the formation and/or activity of ADDLs

Areas of Application

- Drug discovery
- Drug Development

Stage of Development

- *In vitro* data

