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Commentary

Preservation of the blood brain barrier integrity may underlie neuroprotective effects of statins in Alzheimer's disease

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Alzheimer's disease is a complex disorder for which there is currently no cure. While the pathogenesis of Alzheimer's disease is still unknown, identification of risk factors and mechanisms by which these factors contribute to the pathology of Alzheimer's disease may help lead to the development of interventional strategies that prevent the onset or slow the progression of this devastating disorder. Epidemiological and laboratory studies suggest that abnormalities in cholesterol metabolism are risk factors for Alzheimer's disease. However, plasma cholesterol levels do not correlate with the severity of Alzheimer's disease, and this raises the possibility that abnormalities in cholesterol metabolism earlier in life might trigger the ultimate development of Alzheimer's disease. Accordingly, reducing cholesterol levels before the clinical manifestations of Alzheimer's disease begin might represent a therapeutic strategy to decrease the incidence and/or the severity of Alzheimer's disease.

In this issue of the Journal of Alzheimer's Disease, Robert G. Riekse and co-authors present a study on the use of simvastatin, a lipophilic statin that readily enters into the brain, and pravastatin, a hydrophilic statin with a low propensity to enter the brain, on Alzheimer's disease biomarkers in CSF of hypercholesterolemic non-demented human subjects. The authors found that simvastatin reduced CSF levels of phospho-tau-181 (p-tau$_{181}$) in all subjects, whereas only 54% of subjects who took pravastatin had reductions in CSF p-tau$_{181}$. Neither simvastatin nor pravastatin influenced CSF levels of Aβ, the peptide that form the basis of the amyloid hypothesis, or F_2-isoprostanes, a marker of oxidative stress, the alternate hypothesis for Alzheimer's disease. Taken together, the authors suggest modulation of the phosphorylation of tau as a new mechanism for statins.

Previous retrospective epidemiological studies have suggested that individuals treated with statins are at a low risk of developing Alzheimer's disease [1–4]. However, the mechanisms by which statins reduce the risk of Alzheimer's disease have not been identified. In addition to lowering cholesterol levels, statins have immunomodulatory, anti-oxidant and anti-inflammatory effects [5–9]. Results of various clinical studies, as well as the current study, suggest that statins have no significant effects on Aβ levels (see for review [10]. Rieske and colleagues suggest that the ability of simvastatin, but not pravastatin, to reduce levels of phosphorylated tau in hypercholesterolemic non-demented patients may be link to the degree of penetrability of statins into the brain. Simavastatin reduced phosphorylation of tau in all subjects while pravastatin reduced phosphorylation of tau in 50% and increased the tau phosphorylation in the remaining 50% of subjects. There are many possible reasons that might help

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explain these variable results with pravastatin including random variations in CSF p-tau$_{181}$ concentrations in the pravastatin-treated subjects. Gender (20% male and 80% female in the simvastatin; 46% male and 54% female in the pravastatin group) and age (34–77 in the pravastatin group and 46–87 in the simvastatin group) differences may account for the differences in the degree of phosphorylation of tau obtained with the two statins in the study by Riekse and colleagues.

Two major issues need to be resolved in order to link hypercholesterolemia to Alzheimer's disease and to propose statins as a therapeutic avenue for this disorder. *First*, the mechanisms by which hypercholesterolemia affects the brain and causes damage characteristic of AD are difficult to understand because brain cholesterol homeostasis is regulated through *de novo* synthesis, with little or with no transfer from the peripheral circulation due to the impermeability of the BBB to plasma lipoproteins [11]. Of relevance, hypercholesterolemia has been shown to compromise the BBB in rabbits fed cholesterol-enriched diets [12,13], and in contrast to cholesterol, its oxidized derivative, 27-hydroxycholesterol, has the ability to cross the BBB and to reach the brain [14]. Disruption of the BBB by hypercholesterolemia may therefore increase the entrance of oxidized cholesterol metabolites or lipoproteins into the brain, thus causing brain damage. *Second*, although a small number of case reports suggest no adverse effects on cognition, however, given the importance of cholesterol to brain function, it is important to know the extent to which chronic statin treatment might affect cholesterol homeostasis.

This study conducted in hypercholesterolemic non-demented patients provides important new data supporting a potential link between AD and high levels of cholesterol, and suggests a possible therapeutic intervention. A placebo-controlled study in a large group of mid-age hypercholesterolemic non-demented subjects is now warranted to determine the long-term effects of statins on Alzheimer's disease biomarkers.

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