The Cellular Biochemistry of Cholesterol and Statins: Insights into the Pathophysiology and Therapy of Alzheimer’s Disease

Benjamin Wolozin¹, James Brown III¹, Catherine Theisler¹ and Simone Silberman²

Depts. of ¹Pharmacology and ²Pathology, Loyola University Medical Center, Maywood, IL, USA

Keywords: Amyloid precursor protein — Apolipoprotein — Beta-amyloid — Cholesterol 24 hydroxylase — Cholesterol esters — Cyp46 — FXR — Hydroxycholesterol — LDL — LXR — Oxysterols.

ABSTRACT

The causes of late onset Alzheimer disease (AD) are poorly understood. Although β-amyloid (Aβ) is thought to play a critical role in the pathophysiology of AD, no genetic evidence directly ties Aβ to late onset AD. This suggests that the accumulation of Aβ and neurodegeneration associated with AD might result from an abnormality that indirectly affects Aβ production or accumulation. Increasing evidence suggests that abnormalities in the metabolism of cholesterol and related molecules, such as cholesterol esters and 24(S) hydroxycholesterol might contribute to the pathophysiology of late onset AD by increasing production of Aβ. 24(S) Hydroxycholesterol is a member of a family of oxidized cholesterol catabolites, termed oxysterols, which function to regulate export of cholesterol from the cell and transcription of genes related to cholesterol metabolism. Cholesterol esters are cholesterol derivatives used for cholesterol storage. Levels of 24(S) hydroxycholesterol increase with AD. Polymorphisms in several different genes important for cholesterol physiology are associated with an increased load or level of Aβ in AD. These genes include apolipoprotein E, cholesterol 24 hydroxylase (Cyp46), acyl-CoA:cholesterol acetyltransferase (ACAT), and the cholesterol transporter ABCA1. Other studies show that levels of cholesterol, or its precursors, are elevated in subjects early in the course of AD. Finally, studies of the processing of amyloid precursor protein show that cholesterol and its catabolites modulate amyloid precursor protein processing and Aβ pro-
duction. These lines of evidence raise the possibility that genetic abnormalities in cholesterol metabolism might contribute to the pathophysiology of AD.