Chapter 27

The Important Role of Lipids in Cognitive Impairment

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DOI: 10.4018/978-1-60960-559-9.ch027
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ABSTRACT

The current knowledge base on circulating serum and plasma risk factors of the cognitive decline of degenerative Alzheimer’s Disease is linked to cholesterol homeostasis and lipoprotein disturbances (i.e., total cholesterol, 24S-hydroxy-cholesterol, lipoprotein(a), or apolipoprotein E). Lipoprotein lipase (LPL) is also expressed in the brain, with the highest levels found in the pyramidal cells of the hippocampus, suggesting a possible role for LPL in the regulation of cognitive function. Little is currently known, however, about the specific role of LPL in the brain. The authors of this chapter have generated an LPL-deficient mouse model that was rescued from neonatal lethality by somatic gene transfer. The levels of the presynaptic marker synaptophysin were reduced in the hippocampus while the levels of the post-synaptic marker PSD-95 remained unchanged in the LPL-deficient mice. The decreased frequency of mEPSC in LPL-deficient neurons indicated that the number of presynaptic vesicles was decreased, which was consistent with the decreases observed in the numbers of total vesicles and docking vesicles. These findings indicate that LPL plays an important role in learning and memory function, possibly by influencing presynaptic function.

I. INTRODUCTION

While a number of genetic and environmental factors have been demonstrated to be linked with the development of Alzheimer’s Disease (AD), the single greatest risk factor is aging. Several lines of evidence suggest a role for age-related increases in neuropathology in the development of AD and that the age-related accrual of AD pathology promotes the progression of AD. Most studies linking pathology with the onset of AD have focused solely on the role of AD-related pathology.

The principle indication that lipids may play an important role in amyloid precursor protein (APP) processing and β-amyloid peptide (Aβ) production was provided by a common feature shared by the proteins involved in APP processing, which is that they are all integral membrane proteins. Moreover, Aβ cleavage by γ-secretase occurs in the middle of the membrane, suggesting that the lipid environment influences Aβ production and hence AD pathogenesis. The current knowledge base on circulating serum and plasma risk factors of cognitive decline of degenerative AD is linked to cholesterol homeostasis and lipoprotein disturbances (i.e., total cholesterol (TC), 24S-hydroxy-cholesterol, lipoprotein(a) (Lp(a)), or apolipoprotein E (APOE)). Lipoprotein lipase (LPL) is predominantly expressed in adipose and muscle, where it plays a crucial role in the metabolism of triglyceride-rich plasma lipoproteins. LPL is also expressed in the brain, with its highest levels found in the pyramidal cells of the hippocampus, suggesting a possible role for LPL in the regulation of cognitive function. Little is currently known, however, about the specific role of LPL in the brain. We sought to investigate the role of LPL in the brain, specifically with respect to learning and memory. Behavioral studies have not been performed in adult LPL gene targeted mice because of neonatal lethality. Viable adult LPL-deficient mice were generated by rescue through the somatic gene transfer of a beneficial mutant form of LPL. In the present study, we report a significant impairment in learning and memory in LPL-deficient animals and demonstrate alterations in presynaptic morphology. Our findings demonstrate that LPL plays a role in cognitive function in the central nervous system (CNS).
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