A Cell Culture System For Studying the Role of ApoE in Alzheimer’s Disease

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Introduction

Apolipoprotein (apo-) E, a 34,000 molecular weight protein, exists in three major isoforms (apoE2, apoE3, and apoE4) that are produced by three alleles (e2, e3, and e4) at a single gene locus on chromosome 19. Through its function in transporting lipids among cells, apoE plays a critical role in lipid metabolism within the body, including the CNS. Recent findings demonstrate that inheritance of apoE4 allele increases the risk of Alzheimer’s disease (AD). As a first step towards understanding the role of apoE in the brain, we examined the effects of purified human apoE3 and apoE4 in regulating the growth of neurites. Neurons grown in the presence of apoE3 had enhanced neurite outgrowth, whereas neurons grown in the presence of apoE4 had stunted outgrowth. Further studies revealed that there are significant differences between apoE3 and apoE4 in regulating the growth of neurites. Neurons grown in the presence of apoE3 had enhanced neurite outgrowth, whereas neurons grown in the presence of apoE4 had stunted outgrowth. Further studies revealed that there are significant differences between apoE3 and apoE4 in the amount and cellular localization in AMC neurons. What cell surface protein regulates internalization of apoE3 and apoE4? Our studies revealed that LRP is the primary receptor that mediates the internalization of apoE in neurons.

Results

Apolipoprotein (apo-) E, a 34,000 molecular weight protein, exists in three major isoforms (apoE2, apoE3, and apoE4) that are produced by three alleles (e2, e3, and e4) at a single gene locus on chromosome 19. Through its function in transporting lipids among cells, apoE plays a critical role in lipid metabolism within the body, including the CNS. Recent findings demonstrate that inheritance of apoE4 allele increases the risk of Alzheimer’s disease (AD). As a first step towards understanding the role of apoE in the brain, we examined the effects of purified human apoE3 and apoE4 on the growth of cultured adult mouse cortical (AMC) neurons. We found major differences between apoE3 and apoE4 in regulating the growth of neurites. Neurons grown in the presence of apoE3 had enhanced neurite outgrowth, whereas neurons grown in the presence of apoE4 had stunted outgrowth. Further studies revealed that there are significant differences between apoE3 and apoE4 in the amount and cellular localization in AMC neurons. What cell surface protein regulates internalization of apoE3 and apoE4? Our studies revealed that LRP is the primary receptor that mediates the internalization of apoE in neurons.

Conclusions

- ApoE3 accumulates more than apoE4 in AMC neurons
- ApoE4 accumulates significantly less in neurites than apoE3
- Both apoE3 and apoE4 enter the neuron via the LRP