Alzheimer’s Disease: The Effect of Neuregulin1/ErbB4 Back Signaling on Gamma Secretase Production

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Alzheimer’s disease (AD) is a neurodegenerative disorder resulting from the buildup of neuritic plaques and neurofibrillary tangles. Those with AD exhibit worsening memory and language function, and AD is the most common cause of dementia in the US. There is currently no treatment, prevention, or cure for AD, primarily because there are no factors proven to increase or decrease accumulation of amyloid-beta plaques associated with AD. Neuregulin1, Nrg1, is a protein substrate of gamma secretase, a protease responsible for production of amyloid-beta plaques. Previous studies attempted to reduce amyloid-beta buildup through inhibition of gamma secretase activity but were unsuccessful. This study tested whether presence of Nrg1 and ErbB4 could induce changes in transcription of gamma secretase subunit encoding genes through the back signaling pathway. After RNA extraction from N2a cells, RT-PCR, GSP PCR, and gel electrophoresis, relative expressions of Psen1, Ncstn, and Aph1b were quantified through ImageJ analysis of band intensity. Nrg1/ErbB4 back signaling led to a statistically significant increase in expression of the genes studied, yet Nrg1 or ErbB4 alone did not have this effect. This study is the first to test the effect of back signaling on transcript levels of gamma secretase subunits and demonstrate that Nrg1/ErbB4 back signaling is linked to AD pathogenesis via its upregulation of gamma secretase. The research provides a molecular interaction which can potentially be regulated to lessen gamma secretase production levels as a novel approach to reduce amyloid-beta plaque accumulation. The investigation highlights promising directions for development of treatments, preventions, or cures for AD.