Is Understanding Alzheimer's as Easy as (Aβ)C?: The Role of Amyloid Beta and APOE4 in Alzheimer's Disease

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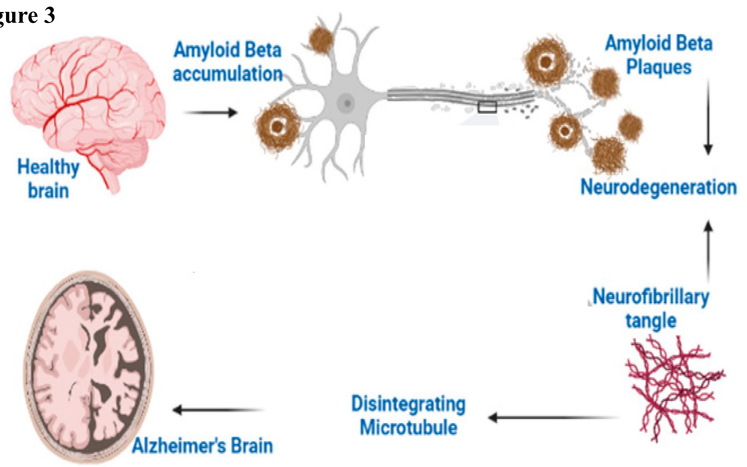
Abstract

Alzheimer's Disease (AD) is a chronic brain disorder that slowly destroys a person's memory and thinking skills. AD injures neurons, and throughout the brain they die, therefore shrinking memory-associated regions of the brain. Researchers have found a correlation between Brain Insulin Resistance (BIR) and AD, along with a major genetic risk for AD for a person with the apolipoprotein type 4 (APOE4) genotype. Insulin resistance is caused by impaired function of the GluT4 transporter. Insulin stimulates the exocytosis of GluT4, which enhances its redistribution, and consequently an increased glucose uptake. As the GluT4 attempts to reach the surface of the cell membrane of a neuron, Amyloid Beta proteins (Aβ) cluster in the synapses after binding with APOE4. GluT4 transports signals through the Phosphoinositide 3-kinase (PI3K) pathway, but is unable to reach the synaptic cleft due to Aβ clusters. In a brain unaffected by BIR, the glucose transported by the GluT4 allows neurons to transduce signals involved in memory processing and regulation, however, the clustering of Aβ inhibits GluT4 and causes BIR, as well as the neuron impairment seen in Alzheimer's Disease. We explored this connection to distinguish interactions at an intermolecular level. Our research and 3D modeling using Jmol suggest a binding site in APOE4 at hydrophobic amino side chains 137-138. We suggest that this corresponds with Aβ's hydrophobic amino acids 17-21, giving them a great affinity to bind with any of the corresponding hydrophobic amino acids in the APOE4 binding site I. Additionally, the hydrophilic amino side chain 145-147 of APOE4 is likely to bond to the hydrophilic amino side chain 22-23 of Aβ. We infer these binding sites have the strongest possibility of binding due to the compatible chemical properties of each site. Based on our findings, we propose further investigation into how Aβ binds with APOE4 in the brains of Alzheimer's patients in order to target these mechanisms in a possible treatment. The Mahtomedi Center for BioMolecular Modeling MAPS Team used 3D modeling and printing technology to structure-function relationships of APOE4 and Aβ in AD patients. This visual model will be a valuable tool in developing our story.examine

APOE4

Apolipoprotein (APOE) has three common isoforms, APOE2, APOE3, and APOE4. The presence of APOE4 in the brain has been associated with a heightened risk for neurodegenerative disorders such as late-onset Alzheimer's, making it the only gene that has consistently been associated with AD. The ε4 allele is carried by about 25% of the population. APOE is also responsible for the metabolism of Aβ, and the APOE4 protein in particular does not form bonds with Aβ strong enough to fulfill this purpose. This is because the APOE isoform 4 has an ARG112 mutation, which causes the salt bridges to be unstable. Unlike the other isoforms, APOE4 forms a salt bridge in the C-terminus, linking it to the N-terminal receptor binding domain, preventing effective bonding with Aβ.

Figure 3



Amyloid Beta (AB)

Amyloid Beta (Aβ) is a peptide found in the brain that is procured from the proteolysis of Amyloid Precursor Protein. In a healthy brain, Aβ plays an important role in memory consolidation and synaptic regulation as well as protecting the brain from infection, cancer, and recovery from Traumatic Brain Injury. However, the misfolding of Aβ can lead to over-deposition in the brain, which can be responsible for synaptic dysfunction, a key component of the cognitive deterioration found in AD patients.

BInding and Clustering

In our abstract, we described the binding affinities of APOE4's amino side chain residues 137-138 (Binding Site I) and 145-147 (Binding Site II) (figure 2). We suggest that these sites bind with Amyloid Beta's amino side chains 17-21 (Binding Site III) and 22-23 (Binding Site IV) (figure 1). The binding site between regions I & III consists of Leucine and Alanine, which are both hydrophobic. The binding site between regions II & IV consists of Glutamine and Asparagine which are both hydrophilic. The corresponding affinities suggest a strong attraction between these two sites. However, there are slight complexities surrounding the bonding of APOE4 and Aβ. As we previously mentioned, APOE4 differs from the other APOE isoforms in residue 112, where APOE4 has Arginine, while the other isotopes have Cysteine, which causes differing salt bridge structures within the protein. This difference in salt-bridges between the N-terminal and C-terminus domains hinders the APOE4's ability to form a stable complex with Aβ. The instability of the bond prevents the metabolism of Aβ by APOE4. Additionally, when APOE4 bonds with Aβ, the Aβ misfolds. The misfolded Aβ allows the protein to form clusters within neuron synapses. GluT4 transports glucose through the PI3K pathway, but once the Aβ clusters, the GluT4 is blocked, and its ability to respond to insulin is hindered, therefore causing the Brain Insulin Resistance commonly associated with Late-onset Alzheimer's (figure 3).

Figure 1: Amyloid Beta

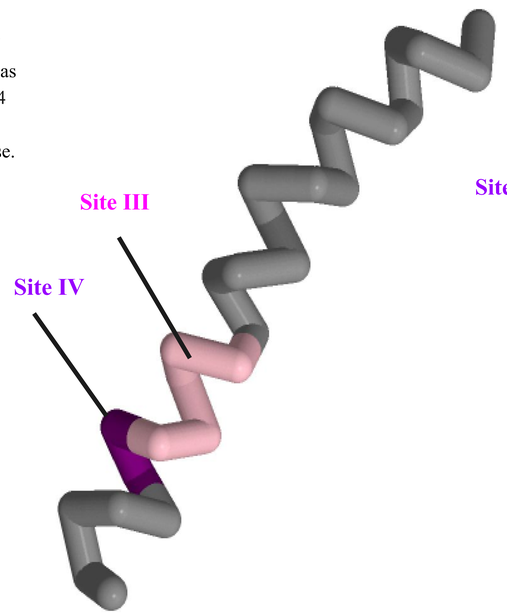
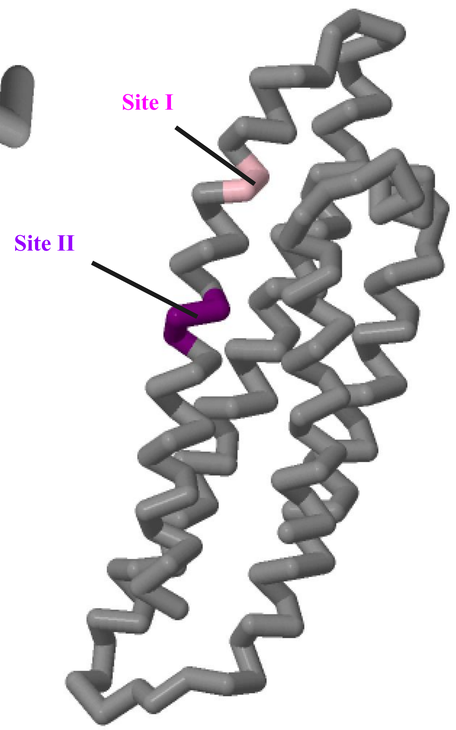


Figure 2: APOE4



Brain Insulin Resistance

Brain Insulin Resistance (BIR) is defined as "the failure of brain cells to respond to insulin" (Arnold et. al) leading to cognitive decline and memory impairment. In a non-neurodegenerative brain, insulin is able to regulate the uptake of Glucose Transporter Type 4 (GluT4), which redistributes glucose in the brain. Aβ prevents GluT4 from carrying glucose through the PI3K pathway in order to redistribute it and support the neuron-firing, thus impacting memory processing. Without GluT4 increasing the upregulation of glucose, it is likely that the metabolic needs of neurons aren't met. This means that the GluT4 is unable to successfully respond to the insulin, which is a form of BIR.

Conclusion

Late-onset Alzheimer's Disease (AD) is a neurodegenerative brain disease that affects memory and cognitive processing, and it currently has no known cure. Looking at Amyloid Beta and APOE4, we found that their binding has the potential to lead to Brain Insulin Resistance (BIR). Upon further investigation, we have noticed conflicting perspectives amongst scholarly articles about whether BIR or Aβ clustering leads to the other's occurrence. To account for this, we inferred the function of APOE4 and the process of BIR. We concluded that the clustering of Aβ and BIR form a cycle: both can influence and aggravate the process of the other. We recommend future studies to focus on the processes of this proposed cycle. Additionally, further research on the binding regions of Aβ and APOE4, in the search for conclusive answers on how their individual functions in the brain can lead to the over-accumulation of Aβ (after binding with APOE4) and the connection to BIR, along with the potential pathway to Late-onset Alzheimer's Disease. To find a cure for Alzheimer's, we propose additional research on the modification of the APOE4 genotype using gene editing, to attempt the correction of the DNA that causes the salt bridge differentiations in APOE4 compared to the other, non-risk factor isotypes.

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