A REVIEW OF CURRENT RESEARCH ON AMYLOID BETA AND ITS RELATION TO ALZHEIMER’S DISEASE
Alzheimer’s disease is a neurodegenerative disease that eradicates memory and hinders a person’s ability to think. The effects of Alzheimer’s is usually seen after the age of 60 and it is believed that at least five million Americans and over twenty-four million people around the world are affected by this disease (Genetics Home Reference 2012, Korolainen 2010).

Alzheimer’s disease is named for Dr. Alois Alzheimer who first described the disease in 1906, after noting significant brain changes during an autopsy of a patient with extreme memory loss (Alzheimer’s Association 2014). While significant progress in diagnosing and treating Alzheimer’s has been made, it is still unclear why age triggers the disease and what mechanisms cause the disease to occur. One theory is that, as an individual ages, his or her cells are not able to perform important processes that support cell repair and the production of energy (Korolainen 2010). One protein that is known to be associated with Alzheimer’s disease is the amyloid precursor protein (APP). Mutations in the APP gene, which is located on chromosome 21, can cause Alzheimer’s disease. One mutation causes valine 717 to be replaced by isoleucine (National Institute on Aging 2014). This protein is found in the synapses of neurons; when it undergoes proteolysis, the breakdown of a protein into peptides, it forms beta amyloid. The amyloid beta then aggregates into a plaque in the brain (Genetics Home Reference 2012). In this review, the role of amyloid beta in the progression of Alzheimer’s disease will be explored.

Amyloid beta is a byproduct of the catabolism of the amyloid precursor protein. There are two different pathways that the amyloid precursor protein (APP) can be broken down. APP goes through the non-amyloidogenic pathway in a normal brain (Roberts 2011). In this process,
APP is cleaved by α-secretase. This produces an ectodomain fragment sAPPα and a membrane bound C-terminal fragment. These fragments are again cleaved by γ-secretase into smaller fragments that can be safely degraded. The second way that APP can be degraded is by the amyloidogenic pathway. This is the path APP goes through in a diseased brain. APP is first cleaved by β-secretase and then it is cleaved again by γ-secretase. This method creates amyloid beta peptides of various lengths (Roberts 2011). The pathway that APP is degraded by depends on the levels of metals in the brain. It was found that copper, zinc and iron cause amyloid beta to form a precipitate. This supported the conclusion that amyloid beta is a metalloprotein. Enzyme kinetics were used to figure out that amyloid beta had two binding sites for either copper or zinc and that one site has a higher affinity for its substrate than the other site. The binding of these metals to amyloid beta increases its toxicity (Roberts 2011). Reactive oxygen species also play a role in the progression of Alzheimer’s disease. Oxidized forms of iron and copper bind to amyloid beta and become reduced. This produces hydrogen peroxide and hydroxyl radicals, which create lipid peroxidation products, protein carbonyl modifications, and nucleic acid adducts (Roberts 2011). All of these are characteristics of Alzheimer’s disease.

Amyloid beta has many different secondary structures including monomers, oligomers and insoluble fibrils. The researchers studied the oligomeric forms of AB using atomic force microscopy and neurotoxicity assays. Atomic force microscopy (AFM) uses a very sharp tip to survey the surface of the protein (Cert 2009). This provides precise images of the protein. The results showed that AB monomers had little structure but that the oligmers were situated in a beta sheet conformation. The results showed that amyloid beta peptides in the insoluble fibril conformation were the most stable form of amyloid beta (Ono 2009). It is widely believed that
soluble oligomers are more toxic than insoluble fibrils because memory loss and cognitive decline in Alzheimer’s disease comes before the formation of amyloid beta plaques. This suggests that the effects of Alzheimer’s disease are more related to the soluble form of amyloid beta than the insoluble fibrils. In order to compare the secondary structures of amyloid beta ATR-FTIR spectroscopy was used. The spectrum of the fibrils showed that there was a narrow peak at 1630cm\(^{-1}\) which indicated that there was an extremely stable parallel beta sheet (Cert 2009, Ono 2009). It was also discovered that the fibrils have beta sheets composed of two strands connected by either a turn or a loop (Cert 2009). The fibrils are made up of at most seventy-five percent of beta sheets. NMR revealed that there are two regions of amyloid beta fibrils that are protected from solvents. These regions account for seventy percent of the amino acids in the protein. They are also the reason why the beta sheets are formed in fibrils. The oligomers have anti-parallel beta sheets, which gives them a different conformation than the fibrils (Cert 2009). The results from the NMR and ATR-FTIR spectroscopy suggest that even though both secondary structures contain beta sheets, they do not share the same conformation.

It was originally believed that amyloid beta had no function and was just a byproduct of the catabolism of APP. More current research suggests that amyloid beta actually has a normal physiological function. Amyloid beta is the main component of deposits in the brain in person’s affected in Alzheimer’s disease and it also may be an antimicrobial peptide. An antimicrobial peptide (AMP) is a peptide that functions in the innate immune system. The antimicrobial activity of amyloid beta was measure in vitro by its minimal inhibitory concentration (MIC). A peptide’s MIC is defined as the lowest concentration able to visibly inhibit the growth of a
pathogen overnight (Sosica 2010). The antimicrobial activity of amyloid beta was compared to the activity of LL-37, an archetypical human antimicrobial peptide. Both amyloid beta and LL-37 were tested against eight pathogens, two of which were *S. pneumoniae* (bacterial meningitis) and *C. albicans* (neurocandidiasis). Of the eight microorganisms tested, the antimicrobial activity of amyloid beta was either equivalent to or greater than that of LL-37 for seven of the microorganisms (Sosica 2010). This supports the hypothesis that amyloid beta is an AMP.

An important aspect of antimicrobial peptides is that they interact with bacterial membranes. In order for amyloid beta to be considered an AMP, the researchers must also show that amyloid beta associates with bacterial membranes. The researchers confirmed this by showing that amyloid beta disrupts the lipid bilayer in cell membranes but more research was needed to confirm the hypothesis.

If amyloid beta is an AMP and its normal function is to help the immune system, then it follows that a person who is deficient in amyloid beta will have an increased vulnerability to diseases. An example of this is morbus Kostmann disease, which results when a person is deficient in LL-37 and hinders a person’s ability to create an effective defense against pathogens (Sosica 2010). To test whether a deficiency in amyloid beta disrupted the immune system, the researchers created knockout mice, which had low levels of amyloid beta. The results showed that the mice had a mortality rate of forty percent. This confirmed the hypothesis that amyloid beta normally functions as an antimicrobial peptide in the innate immune system. The researchers believe that Alzheimer’s disease is some sort of response to a perceived infection by the innate immune system. Since problems arise when amyloid beta
aggregates in the form of plaques in the brain, it is important to understand what pathways cause amyloid beta to accumulate.

Amyloid beta accumulates in the brain because of the central nervous system clearance and a deficient efflux rate across the blood brain barrier (Bell 2007). The clearance of amyloid beta across the blood brain barrier is related to the aggregation of amyloid beta plaques in the brain. There are different transport pathways that amyloid beta can go through. These two pathways are affected by apolipoproteins. Apolipoproteins are proteins that bind lipids. Researchers needed to figure out how the clearance of amyloid beta across the blood brain barrier is affected by the apolipoproteins associated with the amyloid beta peptide. The blood brain barrier is a collection of cells that prevent certain substances in the blood from being able to pass into the brain (Nelson 2008). The blood brain barrier allows some substances to flow freely while others are blocked from entering the brain.

![Figure 1](image)

Figure 1 which is recreated from Bell et. al., shows the brain clearance of unlabeled AB and apolipoproteins and their Iodine-125 labeled counterparts. The AB and apolipoproteins
were infused with C-14 inulin into brain cells in the caudate nucleus (Bell 2007). Inulin is used as a reference marker to aid in determining percent recovery. Percent recovery’s were used to compare the amount of protein that passed through the blood brain barrier. To figure out the levels of unlabeled AB and apoE, enzyme-linked immunosorbent assay (ELISA) was used. In an ELISA, proteins are absorbed to an inert surface. Multiple antibodies are used bind to the protein of interest. One of the antibodies used is liked to an enzyme that reacts to form a colored product. The intensity of the color change is related to concentration of the protein of interest (Nelson 2008). To figure out the levels of labeled counterparts, gamma counting was used to measure radioactivity. The percentage recovery was calculated and compared. The lipodated apoE had the highest percentage recovery, almost of 100 percent, followed by the non-lipodated apo, which had a percent recovery of 90 percent. The AB had significantly lowered percent recovery, ranging from 37% to about 70%. The researchers also compared the clearance of labeled apoJ in the absence and presence of the lipopeptide acceptor proteins anti-LRP1 and anti-LRP2. The labeled apoJ was recovered about 50%. With the addition of a receptor associated protein (RAP), the percent recovery increased to 70%. Anti-LRP2 increased to percent recovery of apoJ and anti-LRP1 barely increased to percent recovery. This suggests that apoJ clearance is inhibited to RAP and anti-LRP1, but not by anti-LRP2. The figure also shows that amyloid beta bound to apoJ was cleared faster than amyloid beta alone and that the clearance of the AB+apoJ was blocked completely by the anti-LRP2 antibody. Based on this information, the researchers concluded that apoJ is a carrier protein for amyloid beta in biological fluids and its receptor protein LRP2 is expressed at the blood brain barrier (Bell 2007). ApoJ also increases the clearance of amyloid beta across the blood brain barrier. The main
conclusion was that lipoprotein receptors play a key role in determining the rate of amyloid beta efflux in the brain.

From the current research on amyloid beta and related proteins, it has been found that even though amyloid beta has a normal function in the innate immune system, aggregation of amyloid beta plays a role in the progression of Alzheimer’s disease. Amyloid beta aggregates in plaques in the brain due to central nervous system clearance. The related proteins apolipoprotein E and apolipoprotein J play a key role in the clearance of amyloid beta across the blood brain barrier. While the exact cause and triggers of Alzheimer’s disease are still unclear, the research reviewed in this article have helped to understand the function of amyloid beta and its relationship to the progression of Alzheimer’s disease. The results from these experiments have the potential to be developed into methods for treating Alzheimer’s disease. For example, if the aggregation of amyloid beta is a response from the innate immune system, one treatment strategy is to target pathogens create a negative response from the innate immune system. While there has been significant progress in treating Alzheimer’s disease, more research is needed to fully understand how amyloid beta interacts with the brain and how it effects the progression of Alzheimer’s diseases.

In order to understand the progression and causes of AD, the role of metallobiology was explored. Zinc, copper and iron levels in the brain play a role in determining which process the amyloid precursor protein is degraded. It can go through the amyloidogenic or nonamyloidogenic pathways. The amyloidogenic pathway creates amyloid beta.

The researchers used precipitation reactions to figure out that amyloid beta was a metalloprotein and that it had two binding sites for metals. Enzyme kinetics were then used to figure out that one of the sites was a low affinity binding site and the other had high affinity for its substrate. The binding of the metals to amyloid beta increases its toxicity.


The goal of the article was to understand the different transport pathways of amyloid beta (AB) and the related apolipoproteins apoJ and apoE. The researchers tracked the brain clearance of amyloid beta and the apolipoproteins across the blood brain barrier. Enzyme-linked immunosorbent assays were used to figure out the final concentrations of the apolipoproteins and amyloid beta. The results suggested that the clearance of amyloid beta was related to the clearance of apolipoprotein J.

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The researchers used in vitro assays to show that the amyloid beta peptide has antimicrobial activity against eight microorganisms. This supports their hypothesis that the amyloid beta peptide is not just a by-product of catabolic processes and that it may be an antimicrobial peptide that plays a role in the immune system.
If amyloid beta is an AMP and its normal function is to help the immune system, then it follows that a person who is deficient in amyloid beta will have an increased vulnerability to diseases. To test whether a deficiency in amyloid beta disrupted the immune system, the researchers created knockout mice, which had low levels of amyloid beta. The results showed that the mice had a mortality rate of forty percent. This confirmed the hypothesis that amyloid beta normally functions as an antimicrobial peptide in the innate immune system.


Alzheimer’s disease is related to the misfolding of the amyloid beta peptide. The researchers compare the fibrillar form of AB in the parallel b-sheet conformation to oligomeric AB in the antiparallel b-sheet conformation using ATR-FTIR (attenuated total reflection-fourier transform infrared spectroscopy).

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