

Possible Causes of Alzheimer's Disease Related Amyloid- β Plaques and Neurofibrillary Tangles

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Abstract

Alzheimer's disease is a major cause of dementia in the elderly and is a global health concern. However, researchers are not sure what causes the characteristic amyloid- β plaque accumulation and neurofibrillary tangles in the brain. Several model mechanisms have been proposed to answer this question. This paper examines three of these possibilities. Research suggests that a particular allele of the apoE gene is responsible for the neurodegeneration found in Alzheimer's disease. Another hypothesis is that the mechanism of Alzheimer's is related to prion-mediated protein misfolding. Other studies indicate that certain environmental factors can cause the neuropathology of Alzheimer's. Specifically, this paper will investigate the effects of a neurotoxin produced by cyanobacteria. Each of these possibilities is backed by supporting evidence, and there is probably not just one cause. Alzheimer's is a complex disease caused by a combination of interacting factors that may include these models, as well as others that have not been focused on in this paper. The more that is discovered about the multiple possible causes of Alzheimer's, the closer we are to developing ways of preventing these pathways in the hope of a cure.

Introduction

Alzheimer's disease is the most common cause of dementia in the elderly (Seeley, Miller 2015) and a devastating disease for those affected and their families. According to the Alzheimer's Association, Alzheimer's disease affected 5.4 million American people in 2016. Age is a major risk factor for developing Alzheimer's, and the risk increases the longer a person lives past age 60. A person over the age of 65 has a one in nine chance of having the disease. These numbers will only increase in the future years. Because of advancing science and better treatments, people are living longer, therefore increasing the chances of developing this disease. The average cost of caring for a person with Alzheimer's is over \$50,000 a year, creating an emotional and financial burden on caregivers and family members (Seeley, Miller 2015).

Alzheimer's disease progresses in stages, and the first symptoms noted are generally memory related. The disease is usually diagnosed in the "mild" stage, where memory loss becomes more apparent and the patient exhibits other cognitive impairments (NIH). It is important to note that these are not symptoms of normal aging; this is evidence of a disease state in the brain (CDC). As the disease progresses to moderate and severe Alzheimer's, the patient gradually loses language ability, reasoning, sensory processing and conscious thought. The disease culminates in the patient being completely uncommunicative and bedridden, wholly dependent on a caregiver (NIH). The disease usually lasts for 8-10 years and ends in death from secondary factors, such as malnutrition or pneumonia. This pattern of degeneration is patterned by the atrophy of brain tissue, which begins in the medial temporal lobes, then affecting the lateral parietal, medial parietal and temporal lobes before spreading to the lateral frontal cortex, as seen by brain imaging of Alzheimer patients (Seeley, Miller 2015).

The brain tissue of an Alzheimer patient exhibits significant shrinkage and characteristic amyloid plaques and neurofibrillary tangles (Seeley, Miller 2015). Amyloid plaques consist of beta-amyloid oligomers that stick together. These beta-amyloid fragments arise

from a transmembrane protein called amyloid precursor protein (APP). Different enzymes called alpha-secretase, beta-secretase, and gamma-secretase can cleave the APP protein in different places causing different results. In a healthy pathway, alpha-secretase will cleave off a fragment called sAPP α , which may be beneficial to the neuron. The rest of the APP fragment is cleaved with gamma-secretase and released. In the harmful pathway, APP is cleaved with beta-secretase which releases sAPP β . The residual fragment is cleaved with gamma-secretase and is released as amyloid- β . These amyloid- β fragments accumulate and become the damaging amyloid plaques found in Alzheimer patients (NIH).

Another feature of Alzheimer's disease is the neurofibrillary tangles caused by the protein tau, which normally helps support the internal structure of the neurons. Neurons contain microtubules, which support them and help in transporting nutrients. Attached to these microtubules are the tau proteins that aid in stabilization. In Alzheimer's the tau proteins are hyperphosphorylated, which causes the tau proteins to separate from the microtubules and tangle together with other tau threads. The microtubules break down which causes the neuron's transport system to fail, compromising the neuron's ability to communicate (NIH).

These misfolded proteins cause the degradation of neurons in Alzheimer's and the subsequent brain atrophy. The causes and possible treatments for the accumulation of beta-amyloid and the neurofibrillary tangles are the subjects of ongoing research. This paper explores three different current ideas as to what causes these plaques and tangles to form, and by what mechanism they cause disease.

Methods

Articles and studies researched in this paper were obtained through the Ebsco and AccessMedicine databases with access provided by Touro College Library. Pubmed and Google Scholar were used to find other research articles. Several papers were obtained by use of the Touro College interlibrary loan system. Some of the research articles were kindly provided by Dr. Zev

Leifer, who has an interest in the topic. In addition, references in these articles were used as additional sources of information.

The Effect of apoE on the Development of Senile Plaques

Several possible causes of Alzheimer's disease are currently under investigation. Recent research has been done to study genetic factors of the disease. It has been found that the apolipoprotein E (apoE) gene exists in several alleles, and one, in particular, contributes to the biochemical mechanism of Alzheimer's disease (Liraz et al., 2013). Alzheimer's disease is characterized by the formation of senile plaques composed of amyloid- β , a 40-42 amino acid long peptide derived from amyloid precursor protein. Another feature is the neurofibrillary tangles that arise from the hyperphosphorylated protein tau, which leads to a compromised cytoskeleton and cell death. The apoE gene encodes for the apoE protein, which is produced by astrocytes in the brain. It is an important cholesterol carrier which is involved in the transport of lipids and injury repair. ApoE exists as three alleles: apoE2, apoE3, and apoE4. ApoE is a 299 amino acid protein, and the difference between the isoforms is at amino acid 112 and 158, where either a cysteine or arginine is present (Lui et al., 2013). This slight difference is enough to cause a change in the protein's tertiary structure, which affects its ability to bind lipids, receptors, and amyloid- β . ApoE3 is the most common allele, and apoE2 is associated with a decreased risk of AD (Simonovitch, et al., 2016). ApoE4 is a hypolipidated version of the protein, and it has been linked to an increased risk of developing Alzheimer's. A greater percentage of the apoE4 allele has been noted in families with late-onset and sporadic Alzheimer's. In sporadic AD, the frequency of apoE4 is greater than 50%, and each copy of the allele decreases the disease onset 7-9 years. Patients with a higher percentage of apoE4 have been found to have a higher level accumulated amyloid- β and hyperphosphorylated tau, as well as a decreased neural plasticity and neuropathology (Liraz et al., 2013). The fact that amyloid- β accumulation is increased in apoE4 positive patients led researchers to believe that the two pathways interact with each other, and cross-talk between them causes the pathological effects. The presence of the apoE4 allele adversely affects the binding of apoE4 to lipids, leading to the proposal that the disease is caused by lipid-related mechanisms (Liraz et al., 2013).

Impaired Autophagy in Alzheimer's Disease

Additional research on how apoE4 is related to Alzheimer's disease has shown how other factors can also play a role in the disease process. Besides causing the formation of senile plaques, the apoE4 protein can also impede the body's means of removing it. Amyloid plaques and neurofibrillary tangles are usually removed from the brain through the process of autophagy (Simonovitch et al., 2016, p. 917). Autophagy clears out cellular

debris such as dysfunctional organelles, old proteins, and aggregated proteins. Normally astrocytes produce apoE in the central nervous system, which protects the brain from harmful protein buildup. However, the mechanism becomes faulty as the disease progresses, and impaired autophagy may become harmful because the accumulated protein can cause synaptic degeneration in hippocampal neurons. In 2016, an experiment was done to connect the presence of the apoE4 gene to the accumulation of amyloid- β buildup by the process of decreased autophagy. This experiment used knock-in mice with either apoE3 or apoE4 human cell lines and 5XFAD mice to replicate the disease process. 5XFAD mice have a phenotype similar to Alzheimer disease and exhibit many comparable characteristics such as amyloid plaques (Alzforum). Astrocytes were isolated from the apoE3 and apoE4 mice and cultured with frozen coronal brain sections from the 5XFAD mice. The experimental results were based on the ability of the astrocytes to clear the amyloid- β plaques from the brain slices. Brain slices with no astrocytes were used as a control. Amino acid deprivation was used to induce autophagy, and results were measured at the first, second and fourth hours of starvation. Results were calculated by means of the LC3 and p62/SQSTM1 proteins. LC3-I becomes a lipidated form, LC3-II, during autophagy and becomes associated with the autophagosomal membrane. P62 is a protein that is associated with LC3 and is degraded during autophagy. By looking at the LC3-II/LC3-I ratio, the rate of activation of autophagy can be monitored and measured. A higher ratio indicates greater autophagic activation, which in turn indicates more autophagy and more clearing of the amyloid plaques. This ratio was significantly higher in the apoE3 astrocytes compared to the apoE4 astrocytes. In addition, the levels of p62 decreased more rapidly in the apoE3 astrocytes compared to the apoE4 astrocytes following starvation. This evidence suggests that the initiation of autophagy in apoE4 astrocytes is somehow impaired in Alzheimer's disease (Simonovitch et al., 2016).

To test this hypothesis, the researchers examined the autophagy levels of the astrocytes when an autophagy inducer and inhibitor were added in separate experiments. Rapamycin was used as an autophagy inducer, and chloroquine was used as an inhibitor. In these sets of experiments, the apoE3 and apoE4 astrocytes were treated with rapamycin and chloroquine in separate trials. The results were measured with the LC3-II/LC3-I ratio and the rate of p62 degradation. The results showed that with treatment with rapamycin, the apoE3 cells were even more effective at clearing the amyloid- β plaques, and while it was more effective than the apoE4, the apoE4 was still more effective than the non-treated apoE4 cells. In contrast, treatment with chloroquine entirely prevented autophagy in both apoE3 and apoE4 cells (Simonovitch et al., 2016). This research highlights how the apoE gene can be connected to the buildup of the amyloid- β

plaques in Alzheimer's disease. It demonstrates that the presence of the apoE4 allele affects the body's mechanisms of naturally clearing protein buildup through the process of autophagy and that the problem is probably at the beginning of the process when autophagy is first induced. This research shows that not only is Alzheimer's disease caused by the buildup of misfolded proteins but also that the body's normal mechanism of clearing it away is also adversely affected.

ABCA1 Lipidates ApoE

Knowing how the function of apoE4 is different from apoE3 is valuable for possible therapeutic strategies. If apoE4 can be made to function like apoE3, many of the symptoms and pathologies of Alzheimer's disease can potentially be reversed. Although the full pathological process of apoE4 is not yet fully understood, evidence suggests that it is connected to lipid-related mechanisms (Boehm-Cagan et al., 2016). ApoE lipidation is controlled by the ATP-binding cassette transporters ABCA1 and ABCG1. ABCA1 triggers the efflux of cholesterol and phospholipids onto the apoE acceptor, and ABCG1 has a similar function. Studies have shown that apoE4 is less lipidated than apoE3 and is less effective at stimulating the efflux of cholesterol and phospholipids in a cell culture. These proteins are regulated by the retinoid X receptor transcription regulating system. If this system can be activated by some means, the pathological effects of apoE4 may be alleviated.

CS-6253 Can Activate ABCA1

CS-6253 is a non-toxic peptide derived from the carboxyl terminal of apoE (Boehm-Cagan et al., 2016). It has been shown to interact with and stimulate ABCA1 to activate cholesterol and phospholipid efflux. A study was done to see what effect CS-6253 has in vivo on the neuropathology and cognitive decline in apoE4 mice. ApoE3 and apoE4 mice were injected intraperitoneally with CS-6253 every 48 hours for 6 weeks. A control group was injected with saline. They were then subjected to a series of cognitive tests to measure learning and memory. During the novel object recognition test, mice were placed in an arena with no objects. Then, two objects were introduced. 24 hours later the mice were replaced in the arena with one familiar object, and one new one. Their behavior and interactions with the objects were monitored and measured. During the Morris maze test, the mice were placed in a circular pool of cloudy water with a submerged hidden platform. The test examined the mice's memory by measuring the time it took the mice to reach the platform after being placed in the pool previously. After the experiment, the mice were euthanized and the brains were removed to be stained and studied (Boehm-Cagan et al., 2016).

The results of this experiment showed many important findings on the effect of CS-6253. Treatment with CS-6253 significantly lowered the buildup of amyloid- β in the test apoE4 mice compared to the untreated mice. The levels of amyloid- β in the treated apoE4 mice brains became similar to the untreated apoE3 mice, who were unaffected by the treatment. Treatment with CS-6253 also had an effect on the buildup of phosphorylated tau. The tested apoE4 mice showed a marked decrease of phosphorylated tau compared to the untreated apoE4 mice. Injections of CS-6253 also affected the results of the cognitive tests. Before treatment, apoE4 mice took a significantly longer time to reach the platform in the Morris maze test compared to the apoE3 mice. After treatment, the performance of the treated apoE4 mice was similar to the apoE3 mice. The treated apoE4 mice also scored similarly to the apoE3 mice during the novel item recognition test after they were treated with CS-6253. The experimental findings show that CS-6253 can successfully activate ABCA1 to reverse the hypolipidation of apoE4, decrease the levels of accumulated amyloid- β and phosphorylated tau, and reverse the cognitive deficiencies of apoE4 mice. These results indicate that ABCA1 can be an important therapeutic target in treating Alzheimer's disease (Boehm-Cagan et al., 2016).

Alzheimer's May be Linked to Prion Diseases

Many characteristics of Alzheimer's disease are similar to prion diseases, suggesting that there may be a connection between the two (Castellani et al., 2004). Prion diseases are characterized by the buildup of misfolded prion proteins (PrP) that can propagate themselves by causing other healthy protein to misfold in the same way (Prion Alliance). Prion diseases can affect humans and animals. The five human prion diseases are Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, fatal familial and sporadic insomnia, kuru, and new variant Creutzfeldt-Jakob disease. Alzheimer's disease is similar to these prion diseases in that both have an age requirement for the symptoms to become apparent, both usually occur sporadically although there is a genetic component in some cases. Most prion diseases appear in middle age to older patients, and that is the age demographic that is affected by Alzheimer's. There is significant overlap between the two diseases' characteristics. In both diseases, there is allelic segregation, with an allele that makes a person susceptible to getting the disease. In prion disease, this gene is the PRNP gene, and in Alzheimer's disease, it is ApoE and presenilin 1 genes. Furthermore, in a certain type of Gerstmann-Straussler-Scheinker syndrome, prion plaques in the gray matter also have tau protein with neurofibrillary tangles, amyloid- β accumulation, and gradual memory loss over a longer span of time than typical prion diseases, more similar to the pattern seen in Alzheimer's disease (Castellani et al., 2004).

The word prion comes from “proteinaceous infectious particle” (Jeffrey 2013). These particles are neither bacteria nor virus, but they cause transmissible diseases. Prion diseases are also known as “transmissible spongiform encephalopathies” because they are neurodegenerative and ultimately fatal. Amyloid plaques are frequently present in these diseases, which leads to the possibility that Alzheimer's disease may be related. Prions are caused by a pathogenic form of cellular prion proteins (PrP^c), which are encoded by the host's PRNP/prnp gene (Jeffrey 2013). PrP^c is an endogenous, cell surface glycoprotein of unknown function (Elezgarei, Biasini 2016). In prion diseases, this normal protein undergoes a conformational change and is called a “scrapie form of PrP” or PrP^{Sc}. This misfolded isomer accumulates in the central nervous system of affected individuals. PrP^{Sc}, or prions, are capable of propagating themselves by binding to normal PrP^c proteins and forcing their conformational change to new PrP^{Sc}, thereby perpetuating a cycle that leads to a buildup of misfolded proteins, which causes neurodegeneration and cell death (Elezgarei, Biasini 2016). PrP^{Sc} changes PrP^c into prions by affecting the tertiary structure of the protein. Normal PrP is made up of 209 amino acids and the tertiary structure is 40% alpha helix with minimal beta sheet. PrP^{Sc} however, is made of 40% beta sheet and 30% alpha helix (Castellani et al., 2004). Research shows that the prions are formed when alpha helices are converted into beta sheets. This change causes PrP^{Sc} to be insoluble and resistant to proteolytic enzymes (Castenelli et al., 2004).

Similarities Between Amyloid- β and Prions

Amyloid- β oligomers in Alzheimer's disease have similarities to prions. Soluble amyloid- β oligomers affect the neuronal synapse in Alzheimer's disease, causing synaptic abnormalities and neurodegeneration (Elezgarei, Biasini 2016). These oligomers are different from the insoluble amyloid- β that builds up in the brain. There is evidence that the amyloid- β oligomers bind to PrP^c in a similar manner to prions, and cause a cascade that leads to cell death (Laurén et al., 2009). PrP^c can act as a receptor site on the cell membrane of neurons, which have been shown to bind amyloid- β and mediate the pathological effect. Suppression of these receptors may, in fact, have therapeutic benefit for people suffering from the disease (Laurén et al., 2009). PrP^c-amyloid- β complexes occur in the brains of Alzheimer patients, which is further evidence that this prion-like mechanism is implicated in Alzheimer's disease. PrP^c is not necessarily involved in all cases of Alzheimer's; Amyloid- β can cause neural damage without PrP^c (Elezgarei, Biasini 2016). This fact demonstrates the complexity of the disease and that the cause may be due to several factors. There are several similarities between amyloid- β precursor protein (A β PP) in Alzheimer's disease and PRNP in

prion diseases (Castenelli et al., 2004). Mutations in both of these genes can cause a buildup of their respective proteins with increased beta sheet structure.

Disease Transmission

Classic prion diseases are transmissible from one affected individual to another. They are able to be passed from person to person, from animal to person, and from person to animal. PrP^{Sc} initially forms in sporadic diseases by nucleation. The initial formation of the protein is kinetically less favorable; however, once it overcomes the activation barrier it is able to propagate, changing PrP^c to PrP^{Sc} very easily (Beekes et al., 2014). Once you have an initial prion “seed,” it can quickly proliferate and corrupt other proteins (Figure 1). However, prions are not infectious in the typical sense; you cannot “catch” a prion disease through direct contact (Weissmann et al., 2002). Transmission of prions occurs perorally and perenterally. The kuru epidemic that occurred in Papua New Guinea in the 1900's was spread through cannibalism. A greater concern is the spread of prions to humans iatrogenically. Prion contaminated cadaver-derived human growth hormone gonadotrophin has caused Creutzfeldt-Jakob disease in people in the past, and surgical instruments that have been used on affected people have caused the disease in others, even after being properly sterilized. If Alzheimer disease is so similar to prion diseases, can Alzheimer's be spread through such means? Studies were done where amyloid- β taken from the brain tissue of Alzheimer's patients was injected into mice (Kane et al., 2000). This resulted in the stimulation of amyloid- β deposition in mice that were genetically predisposed to the formation of such plaques. Amyloid- β deposition was recovered past the site of injection, similar to prion spreading. Inoculation of amyloid- β in wild-type mice initiated amyloid- β build up in brain tissue at the site of injection, and in certain species, in distant areas of the brain as well. However, none of the mice developed cerebral neurodegeneration or cognitive decline (Beekes et al., 2014). Similar experiments were done with the protein tau (Sanders et al., 2014). The protein was able to replicate itself with high fidelity in a prion-like manner and cause an increase of hyperphosphorylated tau in the mouse brain tissue. Nevertheless, this buildup of tau did not cause cognitive decline or severe disease in these mice. Epidemiological studies investigated the transmission of Alzheimer's disease between humans in real life (Beekes et al., 2014). Available data indicates that Alzheimer's disease is not likely to be spread between people. Blood transfusions do not cause a risk of Alzheimer's in the recipient, and neither does plasma protein therapy for hemophilia. Another study examined the risk associated with receiving cadaveric human growth hormone, derived from the pituitary gland of the deceased. Such growth hormone has caused over 200 cases of iatrogenic Creutzfeldt-Jakob disease because of

PcPSc seeds that contaminated the hormone and caused the prion disease in the recipient. In this study, researchers found small amounts of amyloid- β in the pituitary glands of the recipient. Yet, none of the recipients studied developed Alzheimer's disease. Based on these studies, as similar as Alzheimer's disease is to prion diseases, there is an essential difference when it comes to disease transmission. Although seeding effects of Amyloid- β can somewhat cause neurotoxicity, it does not cause the neurodegenerative cognitive impairment characteristic of Alzheimer's (Beekes et al., 2014).

Environmental Effects on Neurodegenerative Disease: Mystery Disease in Guam is Similar to Alzheimer's

The environment can have a role in the development of neurodegenerative diseases such as Alzheimer's. On the Island of Guam, many of the native villagers, known as Chamorros, suffer from a debilitating neurodegenerative disease with symptoms similar to Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease (Cox et al., 2016). The illness caused paralysis, shaking, and dementia at 50-100 times the incidence of ALS worldwide (Holtcamp 2012). This disease was first described in the 1950's by US Army physicians, who called it amyotrophic lateral sclerosis/Parkinsonism dementia complex (ALS/PDC). Amyloid- β plaques and neurofibrillary tangles were present in the brains of Chamorros who developed this mystery disease. Although in some villages a quarter of adults died from this disease, no distinct pattern of heredity was apparent. Because outsiders who adopted the Chamorro lifestyle were also affected, the cause of this disease seemed likely to be an environmental toxin (Cox et al., 2016).

The BMAA Hypothesis

There was difficulty in determining the exact nature of the toxin because symptoms could appear years after the exposure. However, researchers were able to isolate the neurotoxin-

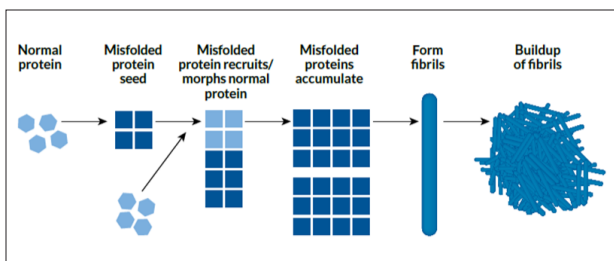


Figure 1: Mechanism of prion mediated misfolding of protein. (Sanders 2015)

in β -N-methylamino-L-alanine (BMAA) from the cycad seed, which the Chamorros use to make flour, a staple in their diet. In the 1980's, BMAA was fed to macaques which caused acute neurological symptoms. However, these results were disregarded

when it was shown that a human would have to consume an inordinate amount of cycad seed flour to ingest a comparable dose (Cox et al., 2016). Paul Alan Cox, an ethnobotanist, arrived in Guam in the 1990's and revived the hypothesis that BMAA causes ALS/PDC seen in the natives (Holtcamp 2012). With his colleague Sandra Banack, he was able to show that BMAA was produced by a symbiotic cyanobacteria living in specialized cycad roots. BMAA accumulates in the gametophytes of the cycad seeds that are ground and eaten by the villagers. Cox then showed that animals such as flying foxes, feral deer, and pigs all feed on the cycad seeds, which are then eaten by the Chamorro people. BMAA is biomagnified in these mammals 10,000 times that which is produced by the cyanobacteria. This process of biomagnification allows a sufficiently toxic amount of BMAA to accumulate in the food chain that it can cause neurological symptoms in the Chamorro people. This problem is not limited to Guam. BMAA producing cyanobacteria live in many marine ecosystems that biomagnify BMAA up the food chain, accumulating in sharks, bottom-dwelling fish, and shellfish (Cox et al., 2016). People who eat these organisms are at risk of BMAA ending up in their brain tissue.

Mechanism of Toxicity of BMAA

BMAA is readily able to cross the blood-brain barrier into the brain and central nervous system. It is mistaken for L-serine by the cellular mechanism and misincorporated into proteins, leading to misfolding, aggregation, and apoptosis of the cell (Cox et al., 2016). In normal proteins, the hydrophilic part is on the outside of the structure and the hydrophobic part is on the inside. However, because of protein misfolding due to the incorporation of BMAA, the hydrophobic part can end up on the outside, exposed. These hydrophobic areas are sticky and tend to clump together forming the characteristic aggregates of neurodegenerative plaques. These small aggregates end up forming larger ones that prevent the cells from functioning properly (Holtcamp 2012). A misincorporation rate of even 1 in 10,000 has been shown to have a neurodegenerative effect in laboratory animals. BMAA can also result in phosphorylated tau by activating mGluR5, a metabotropic glutamate receptor, which decreases the activity of protein phosphatase 2A (PP2A). PP2A is significantly decreased in Chamorro ALS/PDC brains, resulting in an increase of phosphorylated tau (Cox et al., 2015).

Neuropathology Caused by BMAA in an Animal Model

To further prove that BMAA is responsible for the neurodegenerative disease, Cox and his colleagues conducted an experiment in which they attempted to show that chronic exposure to BMAA causes neuropathology and that BMAA can be re-isolated from the induced organisms. Vervets, a type

of non-human primate, were the subject of this study. The vervets in this experiment were exposed to L-BMAA in their diets for 140 days, and then the brain tissue was examined for tau and amyloid deposition. Sixteen juvenile vervets divided into 4 cohorts of 4 were used in this experiment. The first cohort of vervets was given a piece of fruit dosed with 651 mg of L-BMAA. Because L-serine has been shown to prevent misincorporation of BMAA into proteins, a cohort was given 651 mg of L-BMAA and 651 mg of L-serine. A third cohort was given just 651 mg of L-serine. Finally, a control group was given a piece of fruit with 651 mg of rice flour as a placebo. A second experiment was done using adult vervets, also using four cohorts. The first cohort was given 987 mg of L-BMAA. The second was given 98.7 mg of L-BMAA, a tenfold reduction. The third was given 987 mg of L-BMAA, and 987 mg of L-serine. The fourth, a control, had 987 mg of rice flour as a placebo (Cox et al., 2016).

In the first experiment, the vervets that received L-BMAA had neurofibrillary tangles and sparse amyloid- β plaque buildup in many areas of the brain. In contrast, the cohort that received L-serine and the control cohort did not show signs of amyloid- β or tau inclusions. The cohort that received an equal amount of L-BMAA and L-serine showed an 80-90% reduction in amyloid- β plaques and neurofibrillary tangles. In the second experiment, all BMAA exposed vervets developed hyperphosphorylated tau proteins and neurofibrillary tangles. The density of the neurofibrillary tangles in the brain was clearly related to the dose of BMAA administered. Besides for the control cohort, the low dose cohort had the lowest median count of neurofibrillary tangle density; the median density of the high dose cohort was more than twice the levels of the low dose cohort. The cohort that received both high dose BMAA and L-serine had a 50% decrease of neurofibrillary tangles compared to the high dose cohort. Exposure to BMAA also increased the chances of developing amyloid- β deposits, which were not found in any of the control vervets (Cox et al., 2016).

This study shows that dietary exposure to BMAA can cause the formation of neurofibrillary tangles and deposition of amyloid- β (Figure 2). BMAA-producing cyanobacteria live worldwide and can have an important effect on human health. BMAA may possibly act as an initiator for sporadic Alzheimer's disease by triggering the formation of amyloid plaques and neurofibrillary tangles. This study also indicates that L-serine is able to reduce the risk of formation of the characteristic plaques and tangles in the brains tissue of affected individuals, and that L-serine may have a possible therapeutic role in the treatment of mild cognitive impairment and early Alzheimer's disease (Cox et al., 2016).

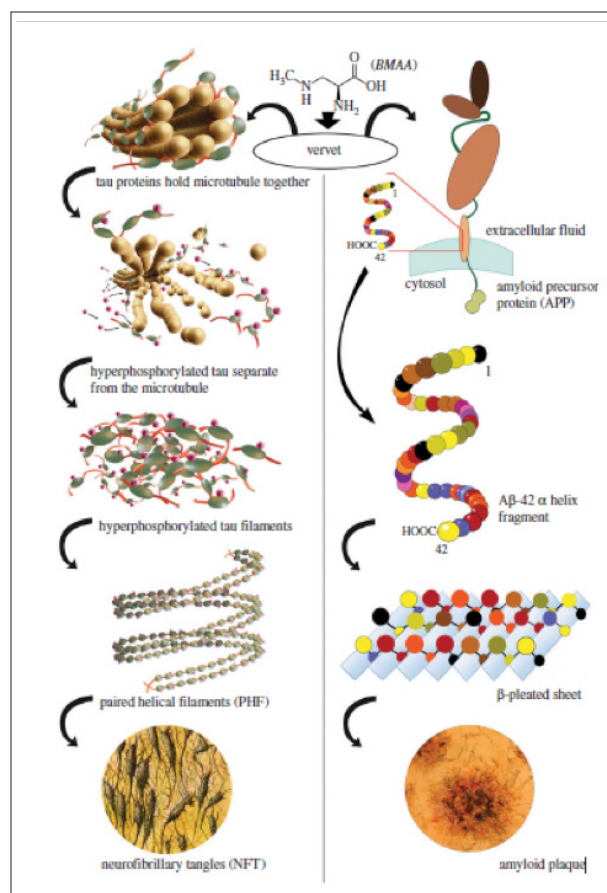


Figure 2: Theoretical pathways of development of ALS/PDC and Alzheimer's disease neuropathology from dietary BMAA exposure causing neurofibrillary tangles and amyloid- β plaques. (Cox et al., 2016)

Conclusion

This paper investigated three seemingly unrelated mechanisms that have been proposed to cause the neuropathology seen in Alzheimer's disease. Although the means of each method reviewed are very different, they have all been studied as a potential cause of the buildup of the characteristic plaques and tangles present in the disease. Alzheimer's disease is a public health problem; it is the sixth-leading cause of death in the United States, and fifth among people 65 and older (Alzheimer's Association). Therefore it is important to study various models of the mechanism of the disease in the hope of gaining a better understanding of it, and eventually finding a cure. These three models may seem disconnected from each other, but in reality, Alzheimer's disease is a complex disease. There are multiple factors involved that cause a person to develop Alzheimer's related neurodegeneration; there is no one "correct" model. The three mechanisms discussed are only part of the multipart picture, and yet they are important to understand to get a complete understanding of the various pathways that lead to this disease.

By examining different routes, hopefully some light will be shed on questions like; why, if two people have a genetic predisposition, does one develop Alzheimer's and one does not? Only by studying the causes will we ever discover a cure to the disease that affects so many.

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