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Abstract

Alzheimer's disease is a neurodegenerative disorder that is the 6th leading cause of death in the United States. More than 5.5 million People over the age of 65 are currently diagnosed with Alzheimer's disease with predictions of 13.8 million to be diagnosed by the year 2050 (Sultana, et al., 2013) (Hebert, Weuve, Scherr, & Evans, 2013). With few treatments available, scientists are desperately looking for a solution to this growing epidemic. Creutzfeldt-Jakob disease is also a neurodegenerative disorder, but with a far less prevalence of only 4.6 persons per million per year. It was discovered that Alzheimer's and Creutzfeldt-Jakob disease share many pathophysiological mechanisms with each other. Being that both of these illnesses are currently incurable, a thorough critical analysis of mechanisms and potential treatments were preformed to ascertain if knowledge in one disorder can help find a cure for the other. With the strong relationship between these two disorders, it was found that many treatments intended for one illness had positive results for the other (some with slight modifications). The discovery of this correlation improved scientist's knowledge of the pathological mechanism of these ailments along with finding new and creative ways for treatment. Experiments geared towards the relationship between Alzheimer's and Creutzfeldt-Jakob disease has brought researchers closer to finding a cure for several neurodegenerative disorders.

Introduction

Alzheimer's Disease (AD) and Creutzfeldt-Jacob Disease (CJD) are two disorders characterized by their neurodegenerative symptoms. These ailments are both considered forms of dementia consisting of phenotypes portraying a patient's loss of memory, mood irregularities, paranoia, and several other neurological symptoms. Physiologically, AD is characterized by its Amyloid-β and Tau protein plaques while CJD is characterized by its prevalence of misfolded prion proteins throughout the brain. Albeit these two diseases are believed to have different modes of physiological symptoms, they share many similarities with each other and other neurodegenerative disorders causing many scientists to theorize a possible correlation between their mechanisms. It is partly due to these similarities that physicians often misdiagnose various dementia relating disorders as either CJD or AD. In a study of 304 autopsies that showed no prion disease prevalence, 71 (23%) of the patients had Sporadic CJD (a variant form of CJD characterized by unknown cause) as a possible diagnosis in their medical records (Chitravas, et al., 2011). Another study showed that "between 12% and 23% of patients diagnosed with AD do not have sufficient AD pathology at autopsy to account for the presence of dementia ("misdiagnosed") (Gaugler, et al., 2013)." Due to the vast likeness between many dementias, there has not been a definitive noninvasive procedure to precisely diagnose disorders such as CJD and AD (Mayo Clinic Staff, 2014).

Although AD and CJD share similarities, their prevalence in American society is far dissimilar. AD is the 6th leading cause of death with an estimated 5.5 million people over the age of 65 who are afflicted with this neurodegenerative disorder in the United States (Sultana, et al., 2013). CJD on the other hand, displays a prevalence of a mere 4.6 cases per million people over the age of 60 (Centers for Disease Control and Prevention , 2014). This is far fewer than the thousands of people who are diagnosed each year with AD.

Despite the rarity of CJD, numerous research endeavors have been conducted in understanding this prion disease. One explanation for this attention is due to the unique properties of a prion; a protein which acts as an infectious pathogen misfolding other proteins into additional prions (Wadsworth, et al., 2008). What is more surprising is that prions have been found in patients diagnosed with AD (Armstrong, et al., 2005). This would further suggest a possible correlation between pathogenic mechanisms of AD and CJD. Today various treatments for AD and CJD are currently in clinical trials to try to treat these incurable diseases. If there is a correlation between pathological mechanisms, further research into one of these neurodegenerative disorders can help scientists better understand and treat the other.

The purpose of this research article will be to define and explain the physical and physiological symptoms and mechanisms of AD and CJD, suggest possible correlations between the two, discuss current treatments, and lastly, the different forms of possible treatments will be compared to postulate a possible venue to determine if they would be effective to treat the other illness.

Methods

Several online databases were used such as: Google Scholar, PubMed, and Jstor which were accessed through Touro College's online library. Additional references were gleaned from papers found in these databases

Discussion

CJD Pathophysiology

CJD is quite unique due to its pathophysiological mechanism. While most infectious diseases are viral or bacterial based, CJD uses a prion to spread its illness. In actuality, every individual contains Prion Proteins (PrPc) which are believed to be necessary for normal synaptic function (Collinge, et al., 1994). It is when this human-coded PrPc is post-translated and converted into

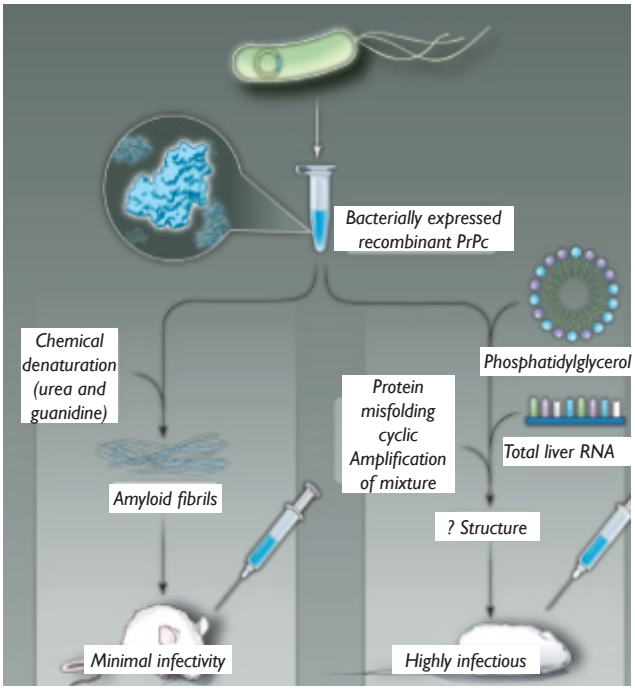
an abnormal isoform (PrPsc) that it starts to exhibit pathological tendencies. Data suggests that this abnormal protein is the main, if not the solitary, component of the transmissible disease (Wadsworth, et al., 2008). Once the PrPsc comes into contact with a normal PrPc, it causes a transmutation of residue 129 turning it into a pathological agent. This replaces the amino acid by residue 129 on the protein into either valine or methionine.

Whereas many scientists agree that the prion protein is the main constituent of CJD, there is debate over the validity of this claim. Manuelidis, et al (2007), argue that the abnormal PrPsc form of the prion protein is a result, not the cause, of CJD. They claim that a 25 nm virus is the cause of the abnormal prion isoform. They discredit the long accepted hypothesis, that prions are the sole pathological constituents of CJD, for several reasons. Studies show, "high PrP-expressing transgenic brains, as well as abnormal recombinant PrPs, have failed to show significant or reproducible infectivity". Additionally, the authors claim that after several decades of research, scientists found no "infectious conformation" of PrPsc. Furthermore, sheep with scrapie showed signs of these 25 nm viruses while uninfected controls showed no prevalence of these particles. These facts caused many researches to share doubt on the prion-only hypothesis.

Another theory with tangible evidence suggests a different mode of pathological mechanism. Several studies suggest that non-proteinaceous cofactors are needed to facilitate the infectious properties of PrPsc, hypothesizing that prions work via multiple components in order to function (Deleault, et al., 2012). While there are studies that show that purified PrPcs which were folded chemically into amyloid fibrils showed little infectivity, a combination of PrPc, liver RNA, and synthetic 1-palmitoyl-2-oleoyl-phosphatidylglycerol (POPG) lipid molecules facilitated the production of authentic infectious prions. The contrasts between the infectivity of PrPc obtained from amyloid fibrils and from PrPc combined with lipids and RNA support this theory (see figure 1). However, further study should be conducted to determine whether the cofactors are required for pathology or are merely a catalyst for a slow progressive disorder (Supattapone, 2010). These experiments cast doubt on the viral hypothesis of prion disease. If viruses were the cause of prion pathology, why were scientists able to reproduce CJD symptoms with only PrPc and various cofactors?

There are several ways for an individual to contract CJD. Factors include ingestion of prion-infected tissue, contamination during a procedure (most commonly a contaminated tissue transplant or equipment), inheritance of a mutation in the PrPc gene (PRNP), or sporadically (no apparent cause). When tissue infected with abnormal prions is ingested, such as meat from a cow infected with Bovine Spongiform Encephalopathy (BSE, also known as Mad

Figure 1



Extra ingredients: Two different biochemical protocols yield recombinant PrPc with different infectivity. (Left) Minimally infectious amyloid fibrils are formed by incubating recombinant PrPc with chemical denaturants. (Right) Mixing recombinant PrPc with phospholipid and RNA produces highly infectious prions. (Supattapone, 2010)

Cow Disease), a variant form of CJD is contracted named variant CJD (vCJD). Contamination via a procedure causes a form of CJD termed Iatrogenic CJD while a genetic mutation that is inherited is called Genetic CJD. CJD that is acquired sporadically is referred to as Sporadic CJD (sCJD) (Wadsworth, et al., 2008).

According to Wadsworth et al (2008), approximately 85% of cases with CJD occur as the sporadic variant (sCJD) while 15% are associated with a pathogenic mutation in the PRNP gene (Genetic CJD). Wadsworth further explains that the rare iatrogenic form of CJD occurs most frequently due to the transmission of prions via contaminated growth hormones from cadavers or by implementation of contaminated dura mater grafts. Additionally, it has been speculated that iatrogenic CJD can be transmitted via blood transfusions although it is extremely rare (Ricketts, et al., 1997). Prion disease prevalence has been tied to vCJD in the United Kingdom by the consumption of cattle with BSE. Another unique variant of CJD, named Kuru, is found in the Eastern Highlands of Papua New Guinea where members of the community would feast on the deceased relatives as a sign of respect and grief. From the community in Papua, scientist discovered that the incubation period of individuals infected with PrPsc could exceed 50 years (Wadsworth, et al., 2008).

Individuals with CJD often exhibit phenotypical signs of dementia and various other neurodegenerative symptoms. The primary indication of CJD is the observation of sponge-like holes in a person's brain giving the appearance of a sponge; for this reason, many scientists refer to prion diseases as transmissible spongiform encephalopathies (TSEs). Additionally, patients have been known to portray feelings of anxiety, depression as well difficulties of cognition such as impaired thinking, memory loss, personality changes, insomnia and difficulty speaking. Blurred vision, difficulty swallowing and sudden jerky movements are also typical signs of CJD. As the progression of the illness takes its course, cognitive phenotypical symptoms worsen. A majority of individuals lapse into a coma and eventually die due to cardiac arrest, respiratory failure, or an infectious pathogen. The duration of duress is typically 7 months for classical CJD and 12-14 months for variant CJD; however, patients have been known to live up to 2 years after diagnosis (Mayo Clinic Staff, 2012).

Currently, the only way to verify the diagnosis of CJD is via an autopsy to confirm the presence of PrPsc plaques and to observe the formation of spongy-like holes and structures within the patient's brain; however, doctors can accurately identify this disease via several diagnostics. First, a physician might asses the patient to determine if he/she portrays any of the symptoms of CJD. Additionally, doctors may administer an Electroencephalogram (EEG) to measure the individual's brain's activity. People with CJD typically portray an abnormal pattern. Magnetic resonance imaging (MRI) may be used to produce a high resolution image of a person's brain in order to determine a signs of abnormality. Another known method of testing is a spinal tap where a physician withdraws a small amount of cerebral spinal fluid that surrounds an individual's brain and spinal cord. The presence of several proteins in the CSF may be an indication of illness (Mayo Clinic Staff, 2012). A simple blood test to detect trace amounts of PrPsc may be an additional venue to test for CJD, but further testing is needed to determine if this is a viable method of diagnosis (Castilla, Saa, & Soto, 2005). Furthermore, in a study conducted by Moda et al (2014), 13 out of 14 patients with vCJD showed signs of PrPsc in their urine samples suggesting a future possible diagnostic for vCJD.

AD Pathophysiology

AD is a form of dementia characterized by the formation of Amyloid-β protein (Aβ) plaques or the hyperphosphorylation of Tau proteins along with neuron degradation in the brain. This is accompanied with numerous cognitive relating symptoms. While the symptoms of AD are well documented, there is much debate over the exact mechanism in which the disease carriers out its pathology.

One suggested mechanism is through the formation of Amyloid-β proteins which in turn form amyloid-β plaques. The Aβ is formed from a far larger protein called the β-Amyloid Protein Precursor (APP). The cleavage to the Aβ form is catalyzed by the enzyme β-CITE APP cleaving enzyme-1 (BACE1) (Small & Cappai, 2006). It is believed that when there is an overproduction of Aβ, either via a faulty Aβ production mechanism or a failure of the body's clearance of the protein, Amyloid plaques are formed (Verkhratsky, et al., 2014). These aggregations of Aβ are believed to be toxic and are the main cause of AD. The conclusion that Aβ is involved with the pathogenesis of AD is strongly supported by an experiment involving APP transgenic mice. These mice contained human APP and when induced with an amyloid disease, showed very similar pathophysiological symptoms as AD. However, within recent years, studies have shown that Aβ plaques are not the most toxic form of Aβ. Experiments have shown that a low molecular weight diffusable form (non-plaque forming) of Aβ is more toxic. This would explain why in APP transgenic mice, abnormal cognitive symptoms are seen before Aβ plaque formation (Small & Cappai, 2006).

Another well-known hypothesis to the pathological mechanism of AD is the formation of toxic hyperphosphorylated tau proteins. Normal or dephosphorylated microtubule-associated protein (MAP) tau aid in the assembly and stability of microtubule networks in neurons. If an abnormality in the MAP tau arises, there are two other MAPs (MAP1A/B and MAP2) that can compensate; however, when the dephosphorylated tau turns into the hyperphosphorylated form, it turns toxic. This pathological form of tau sequesters normal tau (MAP1A/B and MAP2) while inhibiting and disrupting microtubule structure. The neuron that has been afflicted with this pathogenic MAP tries to dispose of the toxic substance by synthesizing additional normal tau and by turning the hyperphosphorylated form into an inert polymer. Eventually, this afflicted neuron begins to degenerate at a progressively slow pace. Aggregation of this abnormally hyperphophorylated tau has been linked to dementia and neurofibrillary degradation. This abnormal MAP tau appears to be the main contributor to tau pathologies, or tauopathies, for dephosphorylation returns the protein back to its normal functioning state. One possible reason for this abnormality may be due to a conformational change in the MAP tau. This causes it to be a better substrate to be phosphorylated or a worse substrate for dephosphorylation. In either case, these conformational changes appear to cause the pathology of AD (Iqbal, et al., 2005).

AD is typically defined via 3 diverse categories: early-onset AD (EOAD), late-onset AD (LOAD), or early-onset familial AD (EOFAD). With increasing age as a known risk factor, patients who contract the disorder past the age of 65 are said to have LOAD which resembles the majority of all AD cases. People who are diagnosed with AD before the age of 65 is said to have EOAD

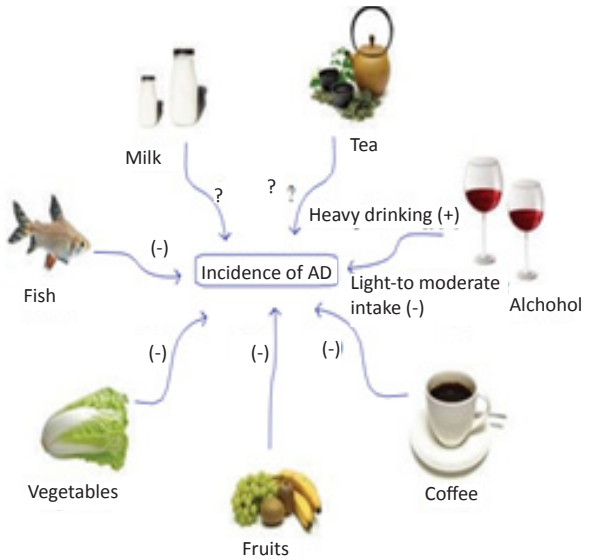
which encompasses up to 5 percent of all cases (WebMd, 2014). EOFAD is a form of the disorder where the onset of duress is under 65 years of age and where the individual has one or more of the genes associated with AD. These genes are believed to cause the person to attain a genetic disposition towards AD (Bird, 1999).

Genetic linkage studies have identified three different genes associated with EOFAD. The first gene identified was the APP gene (the gene that is responsible for APP production). It is believed that a missense mutation within this gene is a risk factor for EOFAD. Another gene found to be correlated with AD is PSEN1. Family studies have shown that mutations in this gene are pathogenic. The third gene found injunction with AD is PSEN2. Although it is far rarer than the PSEN1 mutation, it is believed that mutations in this strand of the gene are a precursor for pathogenesis of EOFAD. It is believed that the PSEN1 and PSEN2 genes are involved with γ-secretase, an enzyme involved with the cleavage of APP, and a mutation in these genes cause pathology via this pathway. The majority of EOFAD cases (81%) can be accounted for by a mutation in the PSEN1 gene, the second most (14%) by a mutation in the APP gene, and the least (6%) associated with the PSEN2 gene (Ertekin-Taner, 2007).

Similar to EOFAD, a gene has been found to be associated with LOAD. The Apolipoprotein (ApoE) gene codes for a protein that transports cholesterol in the bloodstream. It is found as different forms named ApoE ε2, ε3, and ε4. The ApoE ε3 form is the most common form of the gene while ApoE ε2 and ε4 are less prevalent. It is believed that ApoE ε2 reduces the risks of AD and ApoE ε4 has the contrasting effect of increasing AD pathogenesis. If an individual attains two sets of the ApoE ε4, it greatly increases his/her chances of AD. Unlike other known genetic mutations, inheriting both sets of the ApoE ε4 gene does not guarantee AD pathology (Alzheimer's Association, 2014).

While there is no definitive method of ascertaining if an individual will contract AD, there are several disease-modifying factors that decrease or risk factors which increase one's probabilities of pathology. Nam Hu et al (2013) characterizes a list of nutrients and their risks towards AD. Antioxidants obtained in an individual's diet were shown to reduce the risks of AD. Studies show that maintaining a healthy level of vitamin C in a person's diet can have a protective effect towards AD. In regards to metals, Iron is believed to be a risk factor for dementia while Zinc is believed to be a cause in the delay in AD pathology. In regards to fats and carbohydrates, while there is an assumption that these can pose as risk factors for AD, not enough reliable evidence is available to make a firm conclusion. Hu et al made a graph (figure 2) illustrating the effects of various everyday foods if whether or not they increase or decrease a person's risk towards AD.

Figure 2



Foods and beverages that influence the incidence of AD. Fish, vegetables, fruits, coffee, and light-to-moderate alcohol intake are reported to reduce AD incidence. Milk and tea are reported to influence cognition, but their influence on AD is not clear. (Hu, et al., 2013)

Various other theories about the pathophysiology of AD contribute to our understanding of the disease. One proposed hypothesis is the degradation of the blood brain barrier (BBB). The BBB protects the brain from various pathogens and unwanted particles within the bloodstream. The deterioration of the BBB can cause various proteins in the blood to enter the cerebral spinal fluid and form plaques (Sardi, et al., 2011). Another theory involves the metal aluminum. While the correlation is not entirely known, it is believed that a high level of aluminum in the brain is a cause for AD (Shcherbatykh, 2007). Further research suggests, as mentioned by Moulton and Yang (2012), that air pollution too plays a role in AD. While the pathogenesis of AD is multifactorial, air pollution can accelerate "age-related oxidative changes observed in the brain", increasing one's risk of contracting the disorder.

Analogous to CJD, patients who suffer from AD share many similar phenotypical symptoms. Patients have been known to exhibit emotional symptoms such as depression, anxiety, and mood swings and cognitive symptoms such as loss of memory, difficulty speaking, and difficulty thinking. Additionally, those who contract AD are known to have delusions, such as paranoia, change in sleeping patterns, and loss of inhibitions. Towards the late progression of the disorder, important skills such as reading, hobbies, and reminiscing are lost (Mayo Clinic Staff, 2014).

Currently, there is no specific diagnostic to confirm the presence of AD. A physician determines whether you meet the criteria of

dementia and often they can determine if it is due to AD. Doctors have an arsenal of diagnostic tests that they can perform to assist in narrowing the diagnosis. One possible test is a neuropsychological test where they can identify cognitive changes. Different types of dementia can have different cognitive patterns. A blood test can be administered to rule out other causes of memory loss such as vitamin deficiencies. Frequently, brain imaging is used to identify any abnormalities within the brain. An MRI can be used to produce a high resolution image of the brain for further study. A computerized tomography (CT) scan uses x-rays and a computer to generate cross-sectional images of the brain. This can help rule out head injuries and tumors. A positron emission tomography (PET) scan is used in conjunction with an isotope tracer which is injected into an individual. With this machine, a doctor can track the movement of this tracer and determine which areas of the body are dysfunctional. All of these diagnostics aid in the identification of AD; however, similar to CJD, the only way to confirm illness is to perform an autopsy and to observe plaque buildup within the brain (Mayo Clinic Staff, 2014).

Pathophysiological Comparison of AD and CJD

AD and CJD are diagnosed via their dissimilar pathological mechanism and symptoms. AD is associated with Aβ plaques and Tau proteins and CJD with abnormal PrPsc. AD is a slow progressive disorder with an extremely high prevalence, afflicting a third of octogenarians, while CJD is rapidly progressing with an extremely low prevalence, afflicting one per million per year. However, no matter the dissimilar characteristics between the two disorders, there is evidence that there is an analogous mechanism between the two.

It was shown in a study that PrPc prevalence affects the function of BACE1. BACE1 is a cleaving enzyme which catalyzes the cleavage of APP to either Aβ-40 or Aβ-42, two versions of the Aβ differing in residue length. A high expression of PrPc reduces the severing of the APP into peptide fragments by more than 95. This in turn reduces the secretion of Aβ-40 by 92% and Aβ-42 to undetectable levels. The support for this conclusion arises from the study that showed that reduced PrPc prevalence showed an increase in Aβ-40 and Aβ-42 production. This provides strong evidence between the correlation between AD and CJD mechanisms (Hooper & Turner, 2008).

These findings increase the probability that a slight reduction in PrPc at a young age could cause an inconsequential accumulation of Aβ-40 and Aβ-42 over many years, furthering the accumulation of Aβ plaques and the onset of AD. Patients with AD showed lower levels of PrPc in their occipital lobes with an increased activity of BACE1. Additionally, studies show that a polymorphism in codon 129 of the PrPc gene is a risk factor for early-onset AD. This polymorphism changes the peptide coded in that location to a valine or methionine causing the transconformational alteration to the PrPsc pathogenic form. This is consistent with our assumed PrPc-BACE1 relationship. Hooper and Turner (2008) suggest that if PrPc affects Aβ production, we can assume that the absence of PrPc would lead to early-onset AD.

If prion proteins regulate Aβ accumulation thus preventing AD, does Aβ regulate and/or prevent prion pathology? In an experiment involving mice infected with scrapie, a form of prion disease in animals, it was found that in the terminal stages of the disease there was a considerable increase in the concentration of Aβ. Hooper and Turner comments on this that, "[i]nterestingly, the amounts of Aβ peptides were high in scrapie-infected mice, with a shorter disease incubation time raising the possibility that the higher levels of Aβ might exacerbate the disease process." If this theory is correct that high Aβ levels contribute to the rate of prion pathology, then this can be used as a way to slow down the progression of these ailments. However, they point out that we cannot rule out that the increased levels of Aβ are perhaps a result of the scrapie pathology, as stated before, and that further study is necessary to confirm this hypothesis (Hooper & Turner, 2008). Furthermore, Debatin et al (2008) point out that the increased levels of Aβ could be the result of the saturation of clearance mechanisms; since the body is preoccupied with PrPsc maintenance, the same mechanism that also deals with Aβ accumulation becomes saturated leading to a buildup of the AD associated protein. This theory is supported by evidence that suggests a common pathway for protein degradation of PrPsc and Aβ.

Alternatively, there are those that argue that overexpression of PrPc increase Aβ plaque production. Lara Ordonez-Gutierrez et al (2013) disregard the evidence that suggest that PrPc directly inhibits Aβ production by altering the activity of BACE1. They state that most of these tests were performed in cell cultures while studies involving older animals showed no change in the expression of BACE1 in regards to PrPc concentrations. Furthermore, in vivo experimentation conducted by Ordonez-Gutierrez et al (2013) discovered that older animals that expressed a high level of PrPc expression also illustrated a high level of Aβ deposits with no significant consequence on BACE1 levels. They speculate that since BACE1 levels stay the same while Aβ deposit levels increase, perhaps this surge in plaque formation is a result of increased protein degradation and/or production via an alternate pathway involving PrPc.

Its been suggested that a divergent reasoning for the accumulation of Aβ deposits in patients with a high PrPc expression. They explain, given the fact an unaltered expression of PrPc is observed during the pathology of prion disease, it is unlikely prions are the cause for Aβ accumulation in specific sCJD patients. Being that the aggregation of misprocessed proteins is caused by

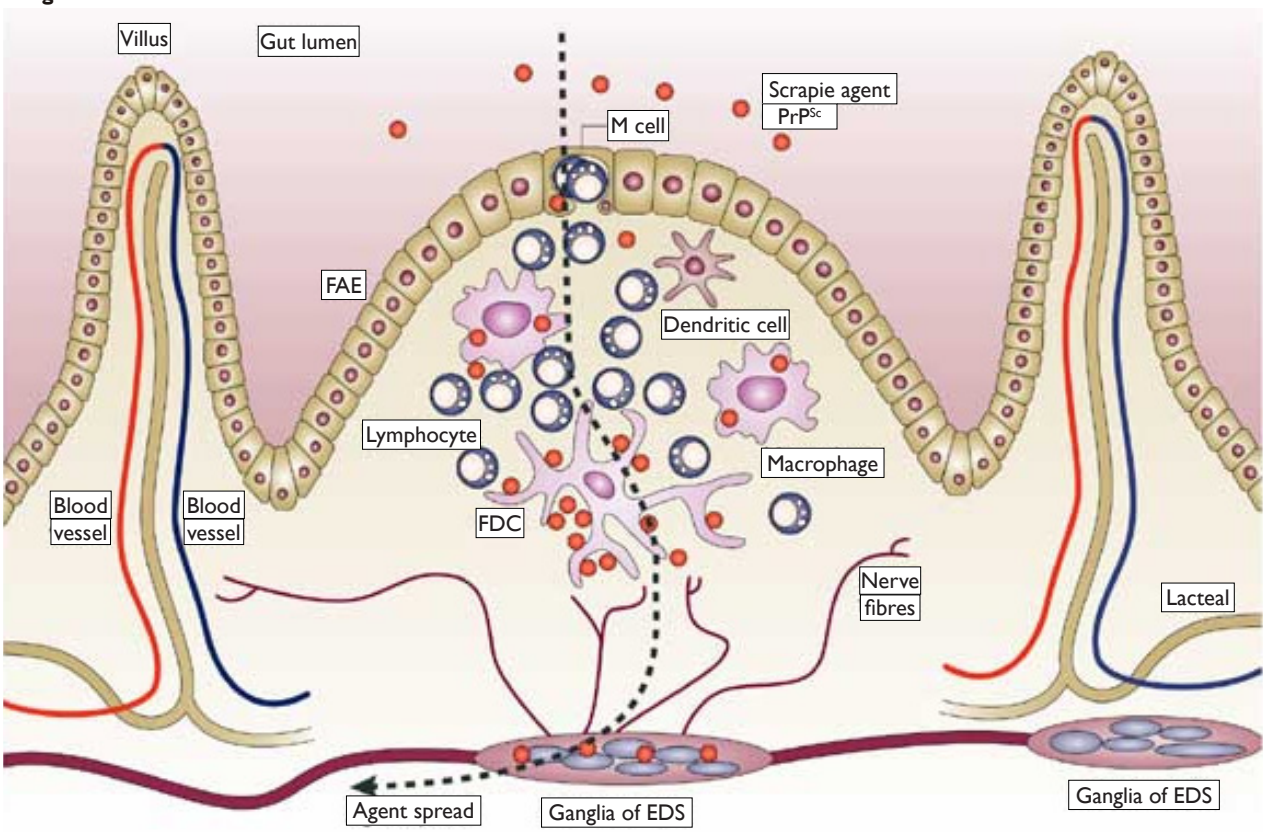
the differences between de novo generation and its elimination, it is a possibility that the increased levels of Aβ deposits in sCJD are a result of a saturation of common clearance mechanisms. This is validated by studies that show a similar clearance mechanism is in place for both PrPsc and Aβ. Furthermore, in a group study of sCJD patients, individuals who exhibited high levels of Aβ-42 showed little deposits of PrPsc while individuals with high levels of PrPsc had low amounts of Aβ-42. The correlation between Aβ-42 and PrPsc concentrations clearly indicates a shared mechanism between the two (Debatin, et al., 2008).

There are also reports discussing a few intriguing similarities between AD and CJD. Both AD and CJD are characterized by their peptide aggregations resulting in plaques; Aβ in AD and PrPsc in CJD. Additionally, the authors explain how AD and CJD can coexist in the same individual and that the Aβ and PrPsc plaques in sporadic AD and sCJD share a similar spatial distribution throughout the brain, "suggesting a consistent pattern of cortical degradation of the two disorders (Armstrong, Lantos, & Cairns, 2005)." With all of these similarities, including the ones mentioned earlier, it is hard to deny the correlation between these two neurodegenerative diseases.

Possible Treatments for CJD

In persons with vCJD, it was observed that when ingested orally, infectious prions aggregated towards gut-assisted lymphatic tissue and the spleen (Cashman & Caughey, 2004). From this location, the prions are transported via splanchnic innervation to the spinal cord and brain (Figure 3). Cashman and Caughey point out that replication of these prions occur in locations accessible to immunotherapy and antibody neutralization. Due to the pathogenic pathway observed in vCJD, it is a possibility to artificially induce an autoimmune response against prions affecting its replication. This can effectively slow down or block pathogenesis of the disease. It has been illustrated in studies that

Figure 3



Possible spread of scrapie infectivity from the gut lumen to the nervous system following oral infection (route indicated by dotted line). Soon after ingestion, the abnormal prion isoform (PrPSc) is detected readily within Peyer's patches on follicular dendritic cells (FDCs), within macrophages, within cells with morphology consistent with that of M cells and within ganglia of the enteric nervous system (ENS). These observations indicate that, following uptake of scrapie infectivity from the gut lumen, infectivity accumulates on FDCs in Peyer's patches and subsequently spreads via the ENS to the central nervous system. FAE, follicle-associated epithelium. © Elsevier Ltd (2000). (Cashman & Caughey, 2004)

antibodies targeted against PrPc, cleared cells that were scrapie-infected with PrPsc in vitro. However, in vivo, antibodies targeted against normal PrPc can have adverse effects since these cells in their non-pathogenic configuration are detrimental to normal neurological function. The autoimmune response to PrPc can prompt complement-dependent lysis in many cells disrupting normal function leading to apoptosis in the brain. It is entirely possible for an induced antibody response to reduce the immunological tolerance of PrPc with the subsequent induction of an autoimmune disease (Cashman & Caughey, 2004).

Often when a protein misfolds causing pathology, a sidechain of peptides that originally was sequestered within the molecule becomes exposed providing a means of distinguishing between pathogenic and non-pathogenic conformational isotopes. This specificity can aid in devising a means of targeting PrPsc alone without affecting the normal PrPc. The therapeutic potential of this approach is immense with the benefit of leaving non-pathogenic proteins unharmed (Paramithiotis, et al., 2003).

There are several chemical inhibitors of CJD progression in vitro. Cyclic tetrapyrroles have been shown to slow the progression of scrapie in mice; however, this was only if treatment began immediately after infection due to its inability to cross the BBB. Other tetrapyrroles that do cross the BBB could prove to be efficacious further in the stages of infection. It is believed that cyclic tetrapyrroles inhibit PrPsc by direct interaction with the protein. Polyene antibiotics and dimethlysulphoxide are also thought to inhibit PrPsc pathology. Polyene antibiotics target prions while dimethlysulphoxide helps reduce accumulations and excretion of PrPsc. Unfortunately, no chemotherapeutic drug has been shown to significantly alleviate the pathology of CJD once clinical symptoms are present (Cashman & Caughey, 2004).

Several other therapies have been suggested for CJD treatment. One is through gene therapy via a lentiviral vector-mediated RNA interference (RNAi). A lentivirus is a genus of viruses that can be modified to implement specific genes within a host's genome or silence others. This is achieved through short hairpin RNAs (shRNAs) that can silence select genes. A study conducted with scrapie-infected neuronal cells that involved shRNAs that suppressed the PrPc gene, PRNP, showed an efficient suppression of PrPsc aggregation. Mice infected with lentivirues with shRNAs showed a reduced expression of PrPc and an extended lifespan of those infected with scrapie. Although further testing needs to be done, a lentiviral vector-mediated RNAi appears to be a valid approach for the treatment of CJD (Pfeifer, et al., 2006). However, reducing PrPc expression may hinder CJD pathogenesis but it may also contribute to various adverse effects. additional research will need to be conducted to attain a viable solution to these concerns.

Another suggested therapy is by the use of antihistamines, specifically astemizole. Experiments involving astemizole indicated that it prolonged the lifespan of scrapie-infected mice. Additionally, astemizole has the capabilities of crossing the BBB making it a favorable drug for the treatment of CJD. Except for a rare case of heart arrhythmia, astemizole is an over-the-counter drug that is relatively safe in recommended doses. It is theorized that astemizole's antiprion properties arises from its activity on autophagy, which is the degradation and recycling of cells and proteins. It is suggested that individuals containing mutations in the PRNP gene and who are genetically susceptible to CJD should take astemizole regularly as a preventative measure against disease. The effects of astemizole on autophagy could provide new methods for treating other neurodegenerative diseases (Karapetyan, et al., 2013).

CJD treatments vs AD pathology

Can several potential treatments for CJD be administered or modified to treat AD? AD is associated with the accumulation of abnormal proteins (Aβ and/or Tau proteins). It is possible to target these molecules via an induced autoimmune response such as that observed in CJD treatments (Cashman & Caughey, 2004). However, this can initiate a negative cascade in which the body targets normal functioning Aβ or Tau proteins resulting in cell lysis and the reduced immunological tolerance towards normal cells causing autoimmune disease.

Abnormal proteins are often accompanied by the exposure of a previously sequestered side chain. This side chain can be used to target pathogenic proteins alone without interfering with normal function. These findings can be applied to AD in treating Aβ and Tau fibril accumulations. Although further experimentation is needed to produce a safe autoimmune induced treatment, this can be a viable method to combat AD pathology (Paramithiotis, et al., 2003).

Lentivector-mediated RNAi can be used to treat AD as well. ShRNAs that repress specific gene expression could be used to suppress a faulty gene that causes pathology. For instance, if an individual has two genes coding for a molecule involved in the pathogenic AD pathway with one of the genes corrupted and the other in its normal function, shRNAs can be utilized to silence the faulty gene's expression without affecting the normal one. However, Lentivector-mediated RNAis can suppress the function of both normal and faulty genes causing unwanted adverse effects (Pfeifer, et al., 2006). This prototype treatment for CJD can ultimately be utilized to treat other disorders such as AD.

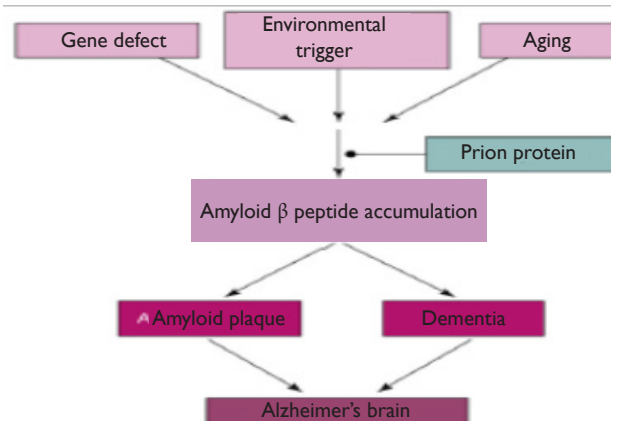
Direct modification of PrPsc/PrPc levels is another option for AD treatment. With a theorized mechanism correlation between PrPc and Aβ proteins, it is possible to indirectly treat AD by

inducing prion production. For instance, Hooper and Turner believe that PrPc regulates Aβ levels by inhibiting enzyme catalyzed cleavage of APP to Aβ-40 and Aβ-42. The greater the PrPc levels, the lower the levels of Aβ in the body. If a patient has AD due to high levels of Aβ, according to Hooper and Turner (2008), it should be possible to reduce these levels by increasing expression of PrPc production (see figure 4). Ordonez-Gutierrez et al (2013) argue that increased levels of PrPc increase Aβ plaque formation. This suggests that reducing PrPc concentrations is the viable method in treating Aβ aggregations in AD. More data has to be obtained to procure the exact mechanism between PrPc and Aβ. It seems that both Hooper and Turner and Ordonez-Guiterrez et al agree that a related mechanism exists between the two proteins, it is the effect one has on the either that is in question. Either way, understanding how these two molecules interact can be important in treating either of these two neurodegenerative disorders. Prion diseases can offer scientists a prototype on the processes of other neurological disorders such as AD (Cashman & Caughey, 2004).

Possible treatments for AD

Currently, AD patients are treated with two different types of drugs, either acetylcholinesterase inhibitors or memantine. Acetylcholinesterase inhibitors act by increasing cell-to-cell communication chemical levels that were diminished during AD onset. This is accomplished by inhibiting enzymes that facilitate the breakdown of acetylcholine, a neurotransmitter found within the brain. Progression of symptoms is usually maintained for a time before AD pathology continues to worsen. Memantine works via a different pathway within the brain, slowing the development of symptoms relating to AD. The mode of action for memantine is to target and inhibit NMDA receptors which has shown to improve cognitive function compared to a placebo. Unfortunately, medication only forestalls pathology since there is no cure for AD (Gotz, Ittner, & Ittner, 2012) (Eubanks, et al., 2006) (Mayo Clinic Staff, 2014).

Figure 4



The role of the prion protein in Alzheimer's disease prevention: In the amyloid cascade hypothesis of AD, a genetic mutation (for example, in the genes encoding APP or the presenilins), ageing or some other environmental trigger (e.g. oxidative stress) causes an accumulation of the neurotoxic Ab peptide, which aggregates to form the characteristic amyloid (senile) plaques found post-mortem in the brains of AD patients. Through mechanisms that are poorly understood, the increased levels of Ab peptides, particularly oligomeric and fibrillar forms, cause neuronal cell death and dementia. The normal cellular form of the prion protein, through inhibiting the production of the Ab peptide, might help to prevent the development of AD (Hooper & Turner, 2008).

Research into the immunization against Aβ showed promising results. Mice immunized with Aβ-42 showed reduced Aβ burden and preserved cognitive function. In an interrupted clinical trial, patients who were injected with one, two, or three immunizations of Aβ-42 showed decreased levels of tau proteins with postmortem reports of diminished Aβ in the neocortex. The trial was interrupted because 6% of the patients developed meningoencephalitis (Gilman, et al., 2005). Using natural anti- Aβ antibodies derived from healthy humans may provide a better method in reducing adverse effects such as encephalitis in patients (Sardi, et al., 2011). Although the clinical trial was suspended, immunotherapy seems to be a viable method in treating AD (Gilman, et al., 2005).

In a recent pharmaceutical study, a monoclonal antibody aimed at Aβ named Bapineuzumab was intravenously administered for 78 weeks. It was found that there was a diminished phosphorylated tau along with a reduced accumulation of Aβ in the brain of AD individuals carrying the pro-pathological gene, ApoE ε4. These findings show promise in the treatment of AD through reductions of plaque buildup. Interestingly, these reductions of the disease-inducing molecules were not able to forestall the rate of pathological progression in the disorder. One suggested hypothesis is that Bapineuzumab was administered too far along in the AD pathology. To remedy this concern, the drug would have to be administered before the appearance of clinical symptoms. This poses an issue since it is extremely difficult to diagnose a patient before symptoms appear; however, it may be able aid those who are high risk for AD. Another hypothesis is the actual pharmaceutical mechanism of the drug. As of yet, Bapineuzumab does not target phosphorylated tau that aggregated into neurofibrillary tangles, another hallmark of AD (Cedernaes, et al., 2014). While further study is needed to improve the efficaciousness of antibodies against AD, immunotherapies are strong contenders in discovering a feasible treatment for neurodegenerative diseases.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be a preventative measure for AD. There are reports that suggest that BBB degradation plays a central role in AD. As the BBB degrades, many previously unwanted molecules cross into the fluid surrounding the brain possibly eliciting a response of inflammation. Inflammation can further increase the

permeability of the BBB allowing circulating Aβ to enter the brain where it can start a degenerative and inflammatory process. NSAIDs are drugs that reduce pro-inflammatory responses in the body. Studies have shown that patients who were medicated with NSAIDs over a long period of time exhibited a reduced incidence of AD. This indicates the presence of pro-inflammatory molecules in the pathology of AD (Sardi, et al., 2011).

Many therapies for AD focus on ameliorating Aβ levels in the brain without much focus on tau proteins concentrations. Treatments aimed at pathogenic tau proteins produced reasonable results. Abnormal tau proteins are phosphorylated versions of the normal tau form. One method of treatment is to inhibit this phosphorylation. Administered lithium chloride inhibited glycogen synthase kinase-3, an enzyme that catalyzes the transfer of a phosphate group onto other molecules, and reduces the levels of hyperphosphorylated tau, insoluble tau, and behavioral impairment in various mice models. Inhibition of other kinases also showed promising results. Furthermore, immunization with a tau phospho-peptide prevented pathology in tau transgenic models with no apparent adverse effects (Gotz, et al,, 2012). With the promise of tau directed therapies, it is worthwhile to formulate treatments involving both Aβ in conjunction with tau proteins.

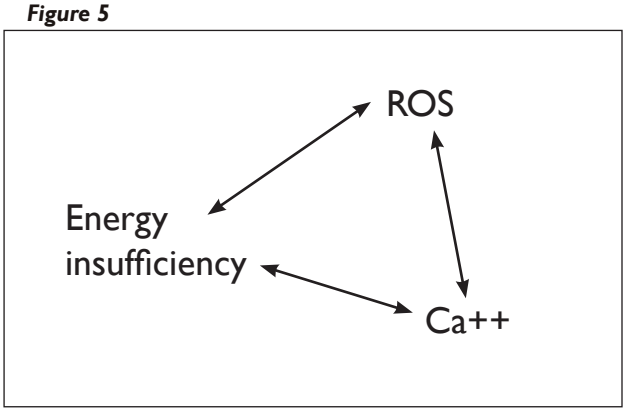
The active component of marijuana, Δ9-tetrahydrocannabinol (THC), appears to also be an efficacious and viable method in the treatment of AD. THC competitively inhibits the enzymatic protein acetylcholinesterase which catalyses the breakdown of acetylcholine. It is believed that acetylcholinesterase is a key component in the pathological progression of AD by inducing Aβ plaque formation. THC effectively inhibits this enzyme, reducing the degradation of acetylcholine transmitters in the brain while simultaneously diminishing Aβ plaque formation. This treats both the progression and the symptoms of the disease. THC is a superior inhibitor of acetylcholinesterase as opposed to other acetylcholinesterase inhibiters that are currently used to treat AD. Additionally, THC appeared more effective with only half the dosage compared to these other medications. (Eubanks, et al., 2006).

The treatment of metabolic deficiency is another suggested alternative in treating AD. An abnormality in the energy metabolism, calcium metabolism, or free radical pathways showed to contribute to deficiency within the other two metabolic routes creating a "mitochondrial spiral". This spiral forms a negative cascade effect where the defects of one metabolic pathway continue to degrade other pathways which in turn further damage the original faulty pathway (see figure 5). It is thought that mitochondrial spiral causes abnormities in the metabolism of the APP and the segments of Aβ it produces. It may also be a proximate reason for clinical debilities found in AD. Ameliorating the spiral may be an alternative route in AD treatment. Studies involving an induced increase in metabolic activity by administering a concoction of glucose and several Krebs cycle intermediates into patients showed an increase in cognitive function with less neurodegeneration. Improving a deficient mitochondrial spiral may prove to be effective in treating AD (Blass, 2001).

AD treatments vs CJD pathology

With AD and CJD sharing many pathological pathways, it seems it may be possible to treat CJD via techniques previously reserved for AD. Acetylcholinesterase inhibitors that reduce the enzymatic degradation of acetylcholine perhaps can be used to alleviate symptoms of dementia found in patients with CJD (Cummings, 2000). With the increased levels of the neurotransmitter acetylcholine in vivo, there can be an increased level of cell-to-cell communications within the brain possibly easing several cognitive symptoms. However, inhibition of this enzyme is most likely not a viable method of treatment for there is little research conducted on the effects of acetylcholinesterase inhibitors on CJD. There is some evidence that memamtine, another drug used to treat AD, has some inhibitory effects towards PrPsc (Muller, et al., 1993).

Figure 5



The mitochondrial spiral. Impairments of energy metabolism, alterations in cellular calcium homeostasis, and excess free radicals (ROS) interact with each other in mitochondria; inducing any one of them leads to abnormalities in the other two. The interaction can set up a deleterious, downward cycle (Blass, 2001).

Immunizations for CJD have been thought of as a method of treatment as well. Similar to AD, antibodies targeted against proteins associated with CJD have showed some promising results. However, being that adverse effects were found with immunizations, research has to be done before it is safe for public use as a treatment for CJD (Cashman & Caughey, 2004). NSIADs have been suggested as a treatment for CJD. Inflammation has been associated with both AD and CJD. In contrast to AD, there is little data available on the effectiveness of NSAIDs on CJD. In vivo studies showed that NSAIDs may have some effect on prion pathology, nevertheless, experiments using patients showed

disappointing results. It is possible that the NSAIDs were given too late in the disease pathogenesis. Further study is needed to determine if antiinflammatory drugs are a suitable treatment for CJD (Eikelenboom, et al., 2002).

Treatment of the "mitochondrial spiral" may play a role with individuals with CJD. In regards to AD, it was found that a deficiency in one of three different metabolic pathways can cause deficits in the other two creating a mitochondrial spiral. Attempts to alleviate the stress on this spiral showed to improve cognitive symptoms in patients (Blass, 2001). In CJD, some studies show oxidative abnormalities plays a role in pathogenesis (Petersen, et al.). This can cause defects in one of the three metabolic pathways mentioned earlier. Alleviating these deficiencies may be a viable venue of treatment. It should be mentioned that other studies found no role of oxidative stress in CJD (Bleich, et al., 2000). Further study is needed on the topic to fully understand the effects of the mitochondrial spiral on disease pathogenesis.

It was suggested that it is possible that Aβ contributes to CJD pathology. It has been hypothesized that Aβ exacerbated the disease process by possibly accelerating the pathology (Hooper & Turner, 2008). If this hypothesis proved to be correct, any treatment formulated towards AD can in turn be prescribed for the mitigation and delaying of symptoms in CJD. Additionally, it was found that the other protein linked with AD, tau proteins, were associated with prion pathology (Han, et al., 2006). As additional experimentation is required to determine the exact impact of one protein on the other, treatments made to diminish tau pathology may ameliorate symptoms of CJD. These hypothesized venues of remedy will not cure prion pathology but can most likely hinder CJD neurodegenerative impacts on the brain. The correlation between these two diseases is too strong to suggest otherwise. Furthering research into understanding CJD is a viable method of ascertaining a feasible treatment for the growing epidemic that is AD.

Conclusion

AD and CJD are both neurodegenerative disorders that share a common pathophysiological mechanism. PrPc and Aβ, proteins associated with pathology in CJD and AD respectively, are believed to interact with each other. There is a slight debate whether they interact directly by contact or indirectly by affecting enzymatic proteins, such as BACE1. Additionally, there is an argument how they influence each other in regards to inhibiting/promoting pathology; for example, does PrPc induce or inhibit Aβ aggregations that cause pathology? Either way, there is a strong correlation of pathologies that most scientists agree with. It is this connection that helped researchers discover new and creative treatments for AD and CJD. Treatments that were previously reserved for either disease are now being tested against the other. This is enhancing the understanding of the mechanisms of each ailment, bringing researchers one step closer to discovering a cure for both neurodegenerative diseases. Perhaps, discovering the means of pathologies for AD and CJD will lead to cures for many other forms of dementia.

Abbreviations

AD – Alzheimer's Disease
ApoE - Apolipoprotein
APP – β-Amyloid precursor protein
Aβ – Amyloid-β protein found in excess amounts in patients with AD
BACE1 - β-CITE APP Cleaving Enzyme-1
BBB - Blood Brain Barrier
CJD – Creutzfeldt – Jakob Disease
EOFAD – Early-Onset Familial Alzheimer's Disease
LOAD – Late-Onset Alzheimer's Disease
MAP - Microtubule-Associated Protein
NSAIDs - Non-steroidal anti-inflammatory drugs
POPG - 1-Palmitoyl-2-oleoyl-phosphatidylglycerol
PrPc – The normal form of a prion protein
PrPsc – the abnormal variant of a prion protein associated with CJD
RNAi - RNA interference
sCJD – Sporadic Creutzfeldt-Jakob Disease
shRNAs - Short Hairpin RNAs
THC - Δ9-Tetrahydrocannabinol, the active component in marijuana
TSE - Transmissible spongiform encephalopathies
vCJD – Variant Creutzfeldt-Jakob Disease

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