CAPSTONE

# Structural and functional prion malfunction as a catalyst for Alzheimer's disease

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## Introduction

Alzheimer's disease (AD) is a form of dementia which is described by memory loss and impaired cognitive behavior. Diagnosed by a mini mental status exam (mMSE) and detailed patient history to monitor changes in behavior and memory function.[1] AD is an idiopathic neurological disease which is only diagnosed from an array of signs and symptoms, then a final post-mortem autopsy to confirm the pathology. One study found that in AD autopsy brains, there was a severe and consistent loss of nicotinic receptors.[2] One experimental study found that Amyloid-β binds to α7-nAChRs and modulates their function. Aβ and amyloid plaques indicate that nicotinic receptors play a role in the pathogenesis of AD.[3]

Prions (PrPC) are genetic protein-like structures found in the central nervous system. PrPc manipulate transcription factors and proteins within neurons by conformational conversion of protein structures. PrPc function by activating or deactivating proteins and transcription factors through self-propagating actions.[4] PrPCs function in regular cell maintenance, like Amyloid-β and TIA-1 prions. They affect learning and memory in the hippocampus, "prion-like, self-templating mechanisms also underlie a variety of neurodegenerative disorders, including amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease."[5] PrPC have a rich α-helical structure and small β-sheet content, but the disease-causing isoform (PrPSc) have small α-helical structures and are rich in β-sheet content.[4] Functional prions are likely to have a distinctive regulatable structure. The prion domains are stacked together, exposed, and free to bind mRNA on the surface of the β-sheet. This structure can allow the coordinated translation of the population of interrelated mRNAs required for stabilization of synaptic growth.[6]

Memory storage and synaptic plasticity are regulated by prions assembling into aggregates. These aggregates form into functional prions which regulate memory storage.[7] It is through gene expression that AD is ultimately developed in the hippocampus. Cholinergic dysfunction in the hippocampus, including reductions in nicotinic acetylcholine receptors is a main killer of neurons in AD brains. Using immunohistochemistry, Teaktong found that nAChRs, when malfunctioning, they produce a cytotoxin which leads to astrocytes building up plaque in neurons, "Elevated α7 nAChRs on astrocytes in AD may contribute to alterations in calcium homeostasis and nitric oxide production, which in turn could affect β-amyloid–mediated inflammatory processes in AD."[8]

## AD in the hippocampus

Many studies show that AD initially starts in the hippocampus with onset memory impairment.[9] The disease causes damage by disrupting the regular cell function, one degenerating effect is damage to nAChRs. This damage is linked to regulation of nAChRs by functional prions like amyloid-β. Eventually, there is enough damage to trigger apoptotic function through TIA-1 prions activating P53 transcription factors, then neuroinflammation kicks on. The study published in the May, 2019 issue of Science Translational Medicine, found important data that the two leading proteins associated with AD, amyloid beta and tau were seen to act as prions, thus making it a

potential double-prion-initiated disease.[5] The early stages of AD are from the hippocampus and they propose multiple mechanisms to explain potentially why AD may originate from the hippocampus. The two main theories are, dysfunctional neurogenesis could increase neuronal vulnerability to AD and contribute to memory impairment. The second theory is that enhanced neurogenesis is a compensatory response, simply a repair mechanism for the brain.[10] Literature shows that Ad progression starts from the hippocampus. That it is why one early symptom of AD is impaired memory and memory loss. Due to a lack of synaptic plasticity, there is a clear loss of new memory formation and consolidation for other mechanisms of memory formation.

## Prion malfunction in the hippocampus

Prions play a critical cellular physiological role, specifically in the hippocampus, PrPc play a role in synaptic plasticity and memory formation. Healthy prion function in the hippocampus is critical for cell physiology. However, when a prion has a folding fault, it can spark a cellular cascade of pathogenesis. There is a study which focused on the genetic mechanisms of prion infection in the hippocampus, specifically CA1 neurons. They found that prion replication results from continual stimulation of a programmed response that is modulated by synaptic NMDA receptor activity that initially promotes cell survival and neurite remodeling.[11] Hippocampal learning and long-term memory retention occur from prion regulation. This study found that $PrP^{c}$ are needed for latent learning and long-term memory retention by knocking out prion genes in mice.[12] Prion disease in the hippocampus was studied and found to attack the mitochondria of the hippocampal cells which decreases synaptic plasticity and regular receptor function.[13] Flies with Orb2 deletion fail to show characteristics of long-term memory tasks and functions.[7]

## Conclusion

AD starts in the hippocampus, due to faulty nAChRs. Because of these faulty α7 nAChRs, amyloid β released binds to the receptor and causes a cellular cascade of damage leading cell death. That is why regulatory prions such as TIA-1, activate to start the process of programmed cell death in response to damaged receptors and transcription factors.PrPC like amyoid-beta have faulty conformational changes turning them into PrPSc. This now structurally changed prion, is no longer able to properly alter transcription factors, thus when it binds proteins, the neurocytochemistry is wrong and leads to a halt in synaptic plasticity. It takes only one PrPSc that can change proteins and lead to additional proteins becoming PrPSc through propagating mechanisms. Furthermore, this cascade is what leads to cell death in the hippocampus and ultimately AD. Further studies are needed to investigate the relationship between prion function and malfunction in the hippocampus which is a proposed mechanism of the etiology of AD. Such studies can look specifically at the role of Aβ and amyloid plaques and prion folding faults. There is little known about functional prions in the central nervous system and they can potentially cause many neurodegenerative diseases. Prion malfunctioning and starting disease is theory of neurodegenerative pathology and there is a wide array of research needed to be done in order to further the claims of prionopathophysiology. When more studies can investgate the prionpathic properties of regular functioning prions in the CNS, new treatments and cures of neurodegenerative diseases can be discovered.

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