

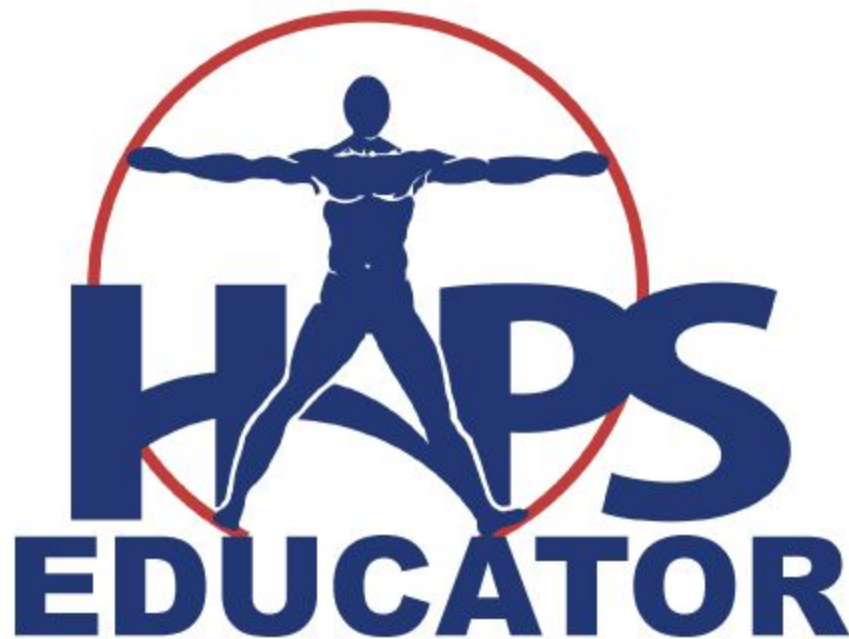
**Positive Feedback Relationship between Lipid Peroxidation  
and Amyloidogenesis Offers Insights Into the Pathogenesis of  
Alzheimer's Disease**

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# Positive Feedback Relationship between Lipid Peroxidation and Amyloidogenesis Offers Insights Into the Pathogenesis of Alzheimer's Disease

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## Abstract

Alzheimer's disease is a progressive neurodegenerative disorder characterized by amyloid plaques, synapse dysfunction, and memory loss. The production and accumulation of A $\beta$  peptides, a major component of the amyloid plaques, is sensitive to many genetic and environmental factors. Recently, research has focused on the role of oxidative stress in initiating or exacerbating the neurodegeneration associated with A $\beta$  production. Lipid peroxidation, a type of oxidative stress that results in damaging cellular products such as 4-hydroxynonenal (HNE), has been demonstrated to increase the concentration of A $\beta$  peptides through several mechanisms. In addition to their association with memory loss and synapse dysfunction, these A $\beta$  peptides cause lipid peroxidation. This positive feedback relationship between lipid peroxidation and A $\beta$  peptides may be the causative sequence of events initiating the pathogenic cascade of AD. This article examines the relationship between lipid peroxidation and amyloidogenesis in order to determine the sequence of events leading to A $\beta$ -plaque deposition and potential treatments with antioxidants targeting lipid peroxidation and its products. doi: 10.21692/haps.2017.049

**Key words:** A $\beta$ -plaque deposition, oxidative stress, lipid peroxidation, amyloidogenesis,

*The information contained in this article will enhance student comprehension of the nervous system and their appreciation for clinical applications and current research associated with the pedagogy of courses in Human Physiology, Advanced Physiology and Neurobiology.*

## Introduction

The pathology of the defining neuropathological characteristics of Alzheimer's disease (AD), synapse loss, neuronal tangles, and amyloid plaques is not yet known. Although familial early-onset AD (FAD) is known to be caused by autosomal dominant mutations in presenilin and the Amyloid Precursor Protein (APP) genes, sporadic late-onset AD (SAD) remains poorly understood.

SAD currently accounts for approximately 60-80% of all dementia cases (Alzheimer's Association 2016). Although memory loss varies among individuals, most people who suffer from SAD first lose their ability to recall recently stored information, as the neurons located in short-term memory areas are first to be damaged (Alzheimer's Association 2016). Later clinical symptoms include slurred speech, depression, severe confusion and other behavioral changes, and ultimately loss of functional capabilities. In addition to the progressive decline in both cognitive function and memory, psychiatric symptoms are often displayed (Yang *et al.* 2013).

## Post-Translational Processing of APP generates soluble A $\beta$ peptides

Major neuropathological symptoms of AD include neurofibrillary tangles, amyloid plaque deposition, synapse loss, and neuronal death (Arimon *et al.* 2015). Accumulation of amyloid- $\beta$  (A $\beta$ ) within the brain occurs due to post-translation processing of Amyloid Precursor Protein (APP) and is associated with neurodegeneration (Yang *et al.* 2013). Non-amyloidogenic APP processing is mediated by  $\alpha$ - and  $\gamma$ -secretase and produces a soluble p3 fragment in addition to an APP intracellular fragment (AICD). Alternatively, amyloidogenic processing of APP can occur, mediated by  $\beta$ - and  $\gamma$ -secretase. In this pathway,  $\beta$ -secretase first cleaves APP closer to the N-terminus than  $\alpha$ -secretase, producing a soluble fragment (sAPP $\beta$ ) and a membrane bound fragment (CTF $\beta$ ). CTF $\beta$  is then cleaved by  $\gamma$ -secretase resulting in an AICD and a soluble A $\beta$  fragment (McDowall J 2006). The soluble A $\beta$  fragments vary in length and 38-42 residues, depending on the exact cleavage site of  $\gamma$ -secretase, but A $\beta$ 42 fragments are associated with greater neurotoxicity than other fragment lengths, (Klein *et al.* 1999, McDowall 2006). APP is a transmembrane protein and all of these processing events occur within lipid membranes, resulting in events that are susceptible to modification based on damage to those lipid membranes.

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## **A $\beta$ peptides, oligomers, and aggregates are associated with neuronal deficits and inflammation**

A $\beta$  plaques are a cellular hallmark of AD and result from the aggregation of A $\beta$  oligomers. A $\beta$ 42 is the A $\beta$  isoform most often associated with fibrillary plaque formation. Plaque formation takes place in stages, first forming small oligomers, then clusters, and finally the  $\beta$ -sheet structures, which compile to form plaques (McDowall J 2006). Plaques interfere with neuronal communication and activate immune cells, causing inflammation and posing a threat to neuronal signaling. In addition to playing an intermediary role in plaque formation, A $\beta$  oligomers have also shown the ability to inhibit hippocampal long-term potentiation (LTP), one of the main processes in learning and memory formation (Walsh DM *et al.* 2002). Much current research in AD focuses on mechanisms that result in increased A $\beta$  levels within the brain, either through increased amyloidogenic processing of APP or decreased clearance of the A $\beta$  fragments.

## **Polyunsaturated Fatty Acids within the brain are susceptible to lipid peroxidation, a form of oxidative stress**

A multitude of environmental and genetic factors influence the rate of A $\beta$  production within the nervous system, but oxidative stress is emerging as a key player in the increased production of A $\beta$ 42. Oxidative stress results from an imbalance of reactive chemicals generated during normal mitochondrial function, and the body's detoxification mechanisms. Oxidative stress on the brain can prove detrimental in a variety of ways. Oxidation of key cellular components such as proteins, DNA, and lipids, interrupts normal cellular processes and communication, which can lead to cell death. Oxidative damage is observed in both early and late stages of AD, but is generally well established before symptoms of AD are presented (Arimon *et al.* 2015).

Reactive oxygen species damage a number of targets within the brain, but their effect in AD may derive from their effect on the lipid molecules within the brain. Reactive oxygen species extract single electrons from the polyunsaturated fatty acids found in membranes, a type of oxidative damage called lipid peroxidation. Since the brain has high concentrations of these fatty acids, this organ is extremely susceptible to lipid peroxidation. The removal of an electron from these fatty acids rearranges the membrane lipid bilayer and can increase permeability and alter or inhibit activity of enzymes and membrane-bound receptors (Birben *et al.* 2012).

The products of these lipid peroxidation events have a number of roles throughout the brain that are associated with decreased neuronal function, making this process a putative causative agent for neurodegeneration in AD. Specifically, the lipid peroxidation product 4-hydroxynonenal (HNE) accumulates in the brain during aging and is increased in AD

patients when compared with healthy controls (Butterfield *et al.* 2006, Perluigi *et al.* 2012). Several lines of evidence indicate that the lipid peroxidation product HNE may be a causative agent in increasing A $\beta$  levels within the brain.

## **A $\beta$ peptides exhibit a positive feedback relationship with reactive oxygen species**

The progressive, sporadic, age-related nature of AD makes a positive feedback relationship a likely causative event as such a relationship would lead to slow accumulations of toxic chemicals. Evidence suggests that the increase of A $\beta$  production by oxidative stress and the subsequent oxidative stress resulting from an increase in A $\beta$  levels may be such a relationship. Lipid peroxidation has been demonstrated to increase the activity and number of the two enzymes responsible for amyloidogenic processing of APP.

The amyloidogenic processing of APP via  $\beta$ -secretase and  $\gamma$ -secretase that results in A $\beta$  species occurs within neuronal membranes and the rate of production is sensitive to the environment of those membranes. A mouse model of high lipid peroxidation has resulted in the increased expression of  $\beta$ -secretase, a transmembrane enzyme responsible for a key step in amyloidogenic processing of APP and subsequent A $\beta$  production (Chen *et al.* 2008). Additionally, HNE has been shown to cause an increase the activity of  $\gamma$ -secretase, leading to increased production of A $\beta$  both *in vitro* and in a mouse model of AD (Gwon *et al.* 2012). Presenilin-1 is the catalytic component of  $\gamma$ -secretase and more than 150 mutations in the gene encoding presenilin-1 have been identified in early onset, familial AD (Kelleher and Shen 2017). Environmental factors, rather than the genetic factors associated with familial AD, can cause presenilin-1 to achieve a pathogenic conformation (Zoltowska *et al.* 2016). Lipid peroxidation leads to such a pathogenic change in presenilin-1, leading to increased amyloidogenic processing of APP without the mutations associated with familial AD, but as a result of oxidative stress. Together, these changes result in increased A $\beta$  load within brains experiencing extensive lipid peroxidation.

## **A $\beta$ fragments induce lipid peroxidation**

A $\beta$  fragments have long been associated with increased oxidative stress within the brain (Butterfield *et al.* 2002). The exact mechanism has long remained unclear due to the number and dynamic nature of A $\beta$  fragments within the brain, as well as the ability of A $\beta$  fragments to bind with pro-oxidant metals. Much work elucidating the ability of A $\beta$  peptides to induce oxidative stress *in vivo* has focused on the role of A $\beta$  conjugated with copper or zinc ions, but recent work has demonstrated that A $\beta$  alone is capable of inducing lipid peroxidation.

Once formed by post-translation processing by  $\beta$ - and  $\gamma$ -secretase, A $\beta$  peptides can experience further modifications, including truncations at the amino terminal of the peptide

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that result in a cyclic peptide (Mori et al 1992). These amino-truncated, cyclic, modified A $\beta$  isoforms (pE-A $\beta$ ) are highly amyloidogenic and can rapidly aggregate at low concentrations, marking them as a considerable concern for plaque deposition. Isomers of pE-A $\beta$  have a dominant presence in the central core of the amyloid plaques in AD brains (Sullivan *et al.* 2011). Treatment of cultured mouse neurons with an n-truncated pE- A $\beta$  fragment increased lipid peroxidation (Gunn et al 2015). In addition to this direct role, pE-A $\beta$  42 also increases the ability of A $\beta$ 42 to induce lipid peroxidation of neuronal membranes (Gunn *et al.* 2015).

### **pE-A $\beta$ inhibits clearance of A $\beta$ 42 and increases lipid peroxidation**

In addition to being an intermediate of enhanced oxidative stress, cyclic A $\beta$  peptides have the ability to quickly oligomerize within the brain (Gunn *et al.* 2015). Although the brain has processes to clear these oligomers, an increased load of cyclic A $\beta$  peptides resulting from oxidative stress may saturate these clearance mechanisms and allow the cyclic A $\beta$  peptides to begin aggregating (Enya *et al.* 1999).

In addition to mediating accumulation of A $\beta$ 42 by inhibiting clearance mechanisms, A $\beta$ 3pE- Because of this attribute, it can be deduced that A $\beta$ 3pE-42 may increase both the cytotoxicity of A $\beta$ 42 to neuronal membranes and the deposition of amyloid plaques. As stated above, increased A $\beta$ 42 levels are cause for concern. In addition to the ability of 42-residue peptide to upregulate inflammatory cytokines and interfere with glutamate transport, it has also been known to modulate the structural integrity of the bilayer (Poojari and Strodel 2013). Further studies need to be done to indicate what role pE-A $\beta$  peptides, specifically A $\beta$ 3pE-42, play in increasing lipid peroxidation levels and promoting A $\beta$ -accumulation.

### **HNE as a therapeutic target**

Several antioxidants, including GM-1 ganglioside (GM-1) and N-acetylcysteine amide (NACA) have been suggested as treatments for the initiation and progression of AD. GM-1 is a ganglioside lipid found in all tissues and plentiful in the brain, with essential roles in neuroprotection and cell-cell communication (Ledeer and Wu 2015). An important mediator of synaptic transmission, the antioxidant-like ganglioside can decrease the build-up of lipid peroxidation products such as HNE while promoting nerve growth (Yang *et al.* 2013). Mice treated with GM-1 also exhibited improvement of spatial learning and memory, which correlated with a decrease of HNE levels in the hippocampus (Yang *et al.* 2013). Additionally, GM-1 was able to prevent accumulation of malondialdehyde (MDA), a lipid peroxidation product, and hydrogen peroxides, both highly reactive oxidative agents (Sokolova *et al.* 2007). These data suggest that GM-1 may be

valuable in targeting multiple pathogenic targets associated with neurodegeneration. Because GM-1 displays multiple neuroprotective properties it presents promise for being a possible participant in future therapies for diseases such as SAD.

Other antioxidants have also been shown to negate oxidative stress induced by amyloidogenic peptides. NACA is a thiol antioxidant that is a precursor to glutathione (GSH), an abundant endogenous antioxidant (De Flora *et al.* 1991). NACA treatment is demonstrating positive outcomes in many pathologies associated with oxidative stress, including spinal trauma and radiation-induced toxicity (Patel *et al.* 2014, Wu *et al.* 2008). Although NACA does not inhibit lipid peroxidation reactions from occurring, it does neutralize reactive aldehyde products via Michael Addition, decreasing the damaging effects of oxidative stress (Rauniyar and Prokai 2009). Pretreatment of mice with NACA completely suppressed the oxidative stress induced by HNE (Arimon *et al.* 2015). Specifically, this treatment decreased the pathogenic conformational changes in PS1 resulting from HNE, allowing and A $\beta$ 42 levels to remain constant after the HNE treatment (Arimon *et al.* 2015).

### **Conclusion**

Although current studies have observed lipid peroxidation upstream of amyloid pathology, a cause-and-effect relationship has yet to be established (Arimon *et al.* 2015). The lipid peroxidation product HNE induced a pathogenic conformational change to PS1, in turn amplifying the rate of amyloidogenesis. The generation of this same HNE product is escalated when toxic A $\beta$ 42 and pE-A $\beta$  peptides accumulate and attack the lipid bilayer, resulting in increased HNE production. The question that remains is whether HNE and other naturally occurring products of lipid peroxidation are the primary initiators of the amyloid cascade, or if these products are intermediates of the cascade that just amplify its progression. Determining the exact sequence of events resulting in A $\beta$  accumulation will be key in developing therapeutic agents and preventative strategies for Alzheimer's Disease. Currently, several chemical antioxidants show promise in decreasing the A $\beta$  load associated with the progressive neurodegeneration of AD.

### **About the Authors**

Brie Paddock, PhD is an assistant professor of Biology at Arcadia University. Her research lab investigates the pathogenesis of Alzheimer's Disease using a *Drosophila* model. She teaches Comparative Anatomy and Physiology, Human Physiology and Advanced Physiology and she serves as the Chair of the Biology department Curriculum Committee.

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Caty Davenport is currently employed as a medical scribe at Wilkes-Barre General Hospital in Wilkes-Barre, PA. She anticipates completion of an Master of Science in Nursing degree with the goal of becoming a Nurse Practitioner.

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