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Comparison of DHA Omega-3 Polyunsaturated Fatty Acids and
Curcumin in β -amyloid Clearance and Alzheimer's Deceleration

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Alzheimer's Disease at Large

Alzheimer's Disease (AD) is the most common form of dementia currently affecting over 50 million people worldwide, and over 5 million Americans (Alzheimer's Association). One third of Americans over the age of 85 are living with AD, and one in three seniors will die with some form of dementia (Alzheimer's Association). AD is a neurodegenerative disease characterized by the loss of memory, thinking, ability to reason, and ability to care for one self. Cognitive impairment is a hallmark sign of the disease which leads to the individual's gradual decline. Alzheimer's disease kills more people every year than breast cancer, prostate cancer and essential hypertension combined (Alzheimer's Disease Facts and Statistics). A disease of this caliber is not only devastating to the brain of the individual living with it, but the disease is also costly. In 2018, the estimated cost of dementia and Alzheimer's care in the U.S was \$277 billion dollars (Alzheimer's Association). Not only have the healthcare costs of managing the disease gone up, but the number of AD-associated deaths have increased by 89% between 2000 and 2014 (Alzheimers.Net).

Although the cause of AD is not fully understood yet, the disease process is associated with amyloid plaques and neurofibrillary tangles in the brain. One of the protein fragments that's most commonly associated with Alzheimer's is Beta-amyloid (β -amyloid). β -amyloid is a sticky protein fragment that disrupts communication between neurons (Alzheimer's Association). Recent evidence has shown that β -amyloid destroys synapses in the brain and causes the formation of the plaques that lead to the death of brain cells (Kim et al 2013). β -amyloid is largely responsible for widespread brain damage in AD causing loss of communication between neurons and eventually cell death. The accumulation of β -amyloid also induces the toxic form of tau to accumulate in the brain which causes neurofibrillary tangles to form and neuronal death to

take rise in AD (Deng et al. 2015). Tau is a protein that allows nutrients to be passed through the brain, and the toxic form of this protein creates twisted fibers called neurofibrillary tangles (Amyloid Plaques and Neurofibrillary Tangles). The formation of amyloid plaques and neurofibrillary tangles can be exacerbated by a poor diet which causes AD to progress at a faster rate (Hanson et. Al 2013).

A poor diet or a healthy diet can impact the body and also play a major role in brain health (Hanson et al. 2013). With the treatment options for AD being both limited and expensive, exploring the link between diet and AD is such a crucial endeavor to undertake in order to slow the progression of the disease. AD is the one condition in the top 10 leading causes of death in the U.S that can't be cured or prevented. But recent scientific research has showed that it's possible to alter the rate at which β -amyloid plaques are cleared from the brain through dietary substances (Alzheimers.net). The two natural dietary substances that will be investigated for the purposes of this research are DHA omega-3 polyunsaturated fatty acids (DHA O3PUFAs), and curcumin which have both been found to aid in clearing β -amyloid protein fragments from the brain (Hoppe et al. 2013, Yan et al. 2019).

O3PUFAs are acids found in the body and in food, they are known to lower the amount of triglycerides in the body (Docosahexaenoic Acid Healthline). Insofar as diet goes, O3PUFAs are primarily found in fish (Docosahexaenoic Acid Healthline). Docosahexaenoic acid (DHA) is the most common O3PUFA, and is found in in cold water fish more so than the other types of O3PUFAs. DHA is also found in the human body as it is a structural component of the brain, and the retina (Docosahexaenoic Acid Healthline). Humans primarily obtain DHA O3PUFAs from their diet, and DHA has been found to help clear β -Amyloid from the brain (Yan et al. 2019).

Curcumin is a natural substance derived from turmeric, a plant which is native to India where yellow curry is comes from. Curcumin is a powerful antioxidant, and also has anti-inflammatory effects in the body. Research surrounding this plant-based substance is popular on account of the fact that a large population of people that thrive on a plant-based diet often fail to obtain adequate levels of DHA in the brain since they don't eat fish (Wu et. Al 2015). It has been found that curcumin enhances the synthesis of DHA which contributes to the clearance of β -amyloid plaques (Wu et. Al 2015).

This literature review seeks to contribute information on what is already known about the neurological effects of DHA O3PUFAs and curcumin, and compare the two substances' abilities to clear β -amyloid and alleviate the pathophysiological burden posed by β -amyloid accumulation. Learning about what natural dietary substances increase β -amyloid clearance has possible implications for improving the conditions of the millions of people living with AD in terms of increasing life expectancy, creating a healthier way of life, and coming closer to eventually finding a cure.

History of Alzheimer's

Alzheimer's Disease was first identified by German psychiatrist, Dr. Alois Alzheimer, in 1906. Dr. Alzheimer. He described this disease after examining the brain of an older woman, Auguste Deter, after she died of what was thought to have been an unusual mental illness. Auguste Deter was only 50 when her increasing memory problems, paranoia, and aggression became evident to her husband making admission to a psychiatric hospital necessary (The History of Alzheimer's Disease). The woman had suffered symptoms such as memory loss, language problems, and behavior that was deemed unpredictable (Alzheimer's Disease Fact

Sheet). Before the neurological traits of AD were discovered, people displaying the signs and symptoms of AD were treated as if they were mentally ill, and often institutionalized. When her brain was thoroughly examined by Dr. Alzheimer following her death, abnormal clumps (now identified as amyloid plaques) and bundles of tangled fiber (now identified as tau/neurofibrillary tangles) were found in the deceased woman's brain (Alzheimer's Disease Fact Sheet). Plaques and tangles are the hallmark features of AD on the anatomical level of the brain.

Since Dr. Alzheimer's monumental discovery over one hundred years ago, many more scientific inventions have aided in further discoveries regarding the causation and treatment of AD creating milestones in AD understanding and treatment. Not too long after Dr. Alzheimer described AD for the first time, the electron microscope was invented in 1931 which allowed cell magnification up to 1 million times which aided scientists in understanding neurons (History of Alzheimer's 2013). Decades after that groundbreaking invention, the National Institute on Aging (NIA) was established and AD centers were funded by the NIA to establish a network for research on the disease between the 1970s and 1980s (History of Alzheimer's 2013). By the early 1990s, the first AD drug became FDA approved, and today there are five medications approved for use by the FDA (History of Alzheimer's 2013). Awareness for AD also became widespread when former President Ronald Reagan was diagnosed with it, and when the disease became the 6th leading cause of death in U.S in 2010 (History of Alzheimer's 2013). Despite the innovations and discoveries that have been made throughout the last century, there is still much that is unknown about this devastating disease, and much more to learn regarding its causation, pathology, and how to cure it.

Alzheimer's Pathology

Dementia is an umbrella term for “diseases and conditions characterized by a decline in memory, language, problem-solving, and other skills that affect a person’s ability to perform everyday activities” (Alzheimer’s Association). AD is a form of dementia defined as the “irreversible and incurable progressive neurodegenerative illness featuring cognitive and functional deficits as well as loss of functional independence and behavioral changes” (Zvěřová et al. 2019). Though there is no definitively known cause of AD, it’s speculated that a combination of genetic, lifestyle, dietary, and environmental factors play a role in its development.

Areas of the brain effected by AD are the hippocampus and the frontal lobe (National Institute on Aging). The hippocampus is important for memory storage and memory formation. As hippocampal cells degenerate as a result of AD, short-term memory begins to decline (The Progression of Alzheimer’s). AD spreads through the outer layer of the brain known as the cerebral cortex (The Progression of Alzheimer’s). Widespread neuronal death, then, causes the brain tissues of a person with AD to shrink over time as the disease progresses, especially in the frontal lobe (Kim et al 2013, National Institute on Aging). The frontal lobe is the brain region largely responsible for language, executive functioning, and higher order thinking, and it is part of the brain’s cerebral cortex (The Progression of Alzheimer’s). The spread of AD through the cerebral cortex and to the frontal lobe is responsible for the worsening of judgement, emotional outburst, and language impairment that are characteristics of AD in its later stages (The Progression of Alzheimer’s). Both the hippocampus and the frontal lobe are affected by AD when the plaques accumulate in these areas of the brain. AD spreads when plaques formed from β -amyloid accumulation and abnormal protein deposits accumulate in the brain which causes the

disruption of synapses between neurons, and causes those neurons to die off (Kokawa et al. 2015).

A recent study speculates that AD specifically originates in a part of the brain known as the “locus coeruleus” which is often the first place Alzheimer's-related pathology appears (Mather and Harley 2016). The locus coeruleus (LC) is a vulnerable part of the brain struck by AD, and may reveal damage decades before disease symptoms even become present. This part of the brain is the first to show the build-up of the tau protein aggregate which contributes to the tangles found in the brain that are characteristic of AD (Mather and Harley 2016). LC neurons are associated with cognitive decline in the later stages of life (Mather and Harley 2016). The LC is vulnerable to AD because of the long, unmyelinated axons of neurons coupled with its high exposure to blood flow and proximity to the 4th ventricle of the brain that make it extremely vulnerable to toxins (Mather and Harley 2016). LC neurons are affected by circulating toxicants more than neurons in other brain regions due to the high exposure to blood circulation which may expose the neurons to toxins that could cause AD. Norepineprine released by the LC helps to maintain the blood–brain barrier (BBB) by protecting the neurons from inflammation and neuronal damage (Mather and Harley 2016).

Beta Amyloid and the Amyloid Hypothesis

The phenomenon of β -amyloid aggregation forms one of the most common disease hypotheses for AD which is known as the “amyloid hypothesis”. The plaques associated with AD are formed from a sticky protein aggregate known as β -amyloid which disrupts communication between neurons and initiates cell death thus causing cognitive decline. In AD, brain cells that process, store and retrieve information degenerate and die. β -amyloid

accumulation destroys synapses and causes neuronal circuits to progressively dismantle in the brain which leads to the death of brain cells (Hoppe et al. 2013, Kim et al. 2013). The imbalance of β -amyloid production and β -amyloid clearance ultimately leads to the aggregation, or the clumping together of both β -amyloid protein fragments to form plaques. This causes plaques made from β -amyloid peptides to accumulate in the brain thus disrupting neural synapses, and causing cell death (Kokawa et al. 2015). The disruption of synapses as a result of β -amyloid accumulation is largely associated with the cognitive impairment aspect of AD.

The β -amyloid peptides come in 42 different forms when the protein responsible for cleaving or cutting β -amyloid, the amyloid precursor protein, is split. The numbers of β -amyloid 1-42 indicate isoforms, or protein variants, of different lengths that the peptide comes in (Schmidt et al. 2009). β -amyloid 1-40 are the most abundant β -amyloid isoforms in the brain, and β -amyloid 40 and 42 are the isoforms found in AD (Schmidt et al. 2009). The β -amyloid 40 and 42 peptides promote apoptosis or cell death more so than the other peptide isoforms (Lukiw et al. 2005). The average clearance rate for both β -amyloid 40 and β -amyloid 42 is slower in people with AD in comparison with healthy, normal brains without AD (Mawuenyega et al. 2010). β -amyloid clearance is impaired by about 30% in patients that have AD (Mawuenyega et al. 2010). Those with AD clear only 5.6% of β -amyloid from their brains per hour versus the 7.6% per hour that is cleared by healthy controls without the disease (Mawuenyega et al. 2010).

Not only does β -amyloid aggregation disrupt cell-to-cell communication, but it also activates immune cells which triggers an inflammatory response causing the brain cells to be destroyed (Beta-amyloid and the Amyloid Hypothesis). Although the exact causation of AD is unknown, the accumulation of β -amyloid is thought to be the primary cause of AD (Beta-amyloid and the Amyloid Hypothesis). Clearing β -amyloid, therefore, could be important to

healthy aging, and crucial in preventing AD from progressing at a faster rate (Mather and Harley 2016).

β -amyloid, although it has negative cognitive effects, has been found to protect the brain from microbial infection in mouse and worm models of AD (Kumar et al. 2016). It was speculated by a recent study that the accumulation of β -amyloid may take place as people age because amyloid plaques accumulate in response to microbes present in the body as a defense mechanism, and β -amyloid has been found to kill off microbes (Kumar et al. 2016). This suggests that microbial infection can be a triggering factor for the accumulation of β -amyloid (Kumar et al. 2016). When bacteria crosses the brain-to-blood barrier (BBB), the brain may be responding to it by accumulating β -amyloid to trap and kill bacteria. If the plaques aren't cleared away fast enough, they may lead to inflammation and tangles of tau protein to form, which causes neurodegeneration and apoptosis (Kumar et al. 2016).

Amyloid Precursor Protein

The amyloid precursor protein (APP) is the protein responsible for producing β -amyloid. APP is a type-1 transmembrane protein that causes the formation of β -amyloid protein fragments through proteolysis (Priller et. Al. 2006). Though the exact physiological function of APP is still unknown, it is thought to be a regulator of synapse formation and function, particularly synaptic scaling and synaptic vesicle release (Priller et. Al. 2006, O'Brien and Wong 2011). APP passes through a fatty membrane around the cell in order to extend from the inside of brain cells to the outside (Beta-amyloid and the Amyloid Hypothesis). When APP is activated, the protein is cut into separate, smaller protein fragments, such as β -amyloid (Beta-amyloid and the Amyloid Hypothesis). β -amyloid is chemically stickier when APP is cut in comparison to the other protein

fragments that are produced from the cleavage of APP (Beta-amyloid and the Amyloid Hypothesis). β -amyloid is speculated to be sticky because it undergoes a partial denaturation which means that the protein loses its structure and ceases to function properly (Beta-amyloid and the Amyloid Hypothesis).

When APP is cleaved by the α -secretase enzyme, β -amyloid aggregates are not formed which is the normal cleavage of APP (Patterson et al. 2008, O'Brien and Wong 2011). Soluble APP- α peptide, which is generated from APP via the α -secretase pathway, decreases the production of β -amyloid peptides while supporting neural growth and stronger synaptic effects (Lukiw et al. 2005). Though the β -amyloid peptide that derives from APP is neurologically destructive, the sAPP α peptide that comes from the α -secretase cleavage of APP enhances neural synapses and promotes neurogenesis (Vanden Dries et al. 2017). sAPP α has been found to decrease β -amyloid generation (Deng et al. 2015; Vanden Dries et al. 2017).

When APP is cleaved by β - and γ -secretase enzymes, however, neurotoxic β -amyloid peptides get released which causes the accumulation of β -amyloid and the subsequent formation of plaques (Patterson et al. 2008, O'Brien and Wong 2011). Proteolysis by β -secretase or γ -secretase is the abnormal cleavage of APP which is characteristic in AD. Mutations in the APP gene tend to inhibit the ability for α -secretase cleavage which enables β -secretase and γ -secretase cleavage (Patterson et al. 2008). Since large amounts of APP are metabolized into β -amyloid in the brain, β -amyloid accumulation is partially due to alterations to the cleavage of APP that result from AD risk factors (O'Brien and Wong 2011).

Tau Protein and Neurofibrillary Tangles

Though the plaques formed by β -amyloid are a prominent part of AD pathology, neurofibrillary tangles made of tau protein are also a major component of the AD. The “tau” hypothesis is thought by some people to be the main cause of AD. Tau protein forms the microtubules that transport nutrients and crucial substances from one neuron to another. In AD, tau proteins don’t stabilize microtubules properly. AD pathogenesis triggers the conversion of tau from a normal to a toxic state through hyperphosphorylation causing the microtubules to disintegrate (Castillo-Carranza et al. 2015). Hyperphosphorylation, the excessive addition of phosphate molecules, causes tau proteins to break down and stick to each other instead of supporting the microtubules (Beta-amyloid and Tau). Tau hyperphosphorylation occurs in response to elevated β -amyloid in the brain which causes tau aggregation and fibrillization into neurofibrillary tangles (Hoppe et al 2013). Tau hyperphosphorylation causes the microtubule structures to collapse which stops nutrients from going to brain and crossing the brain-to-blood barrier (BBB) thus causing neurodegeneration and eventually cell death (Beta-amyloid and Tau).

Neurofibrillary tangles are twisted fibers found inside of neurons (Progression of Alzheimer’s Disease). They are formed when tau proteins become misfolded and accumulate. In AD, tau proteins form a C-shape, and once a tangle has been started, more tau proteins attached to elongate the chain making a tangle (Amyloid Plaques and Neurofibrillary Tangles). The molecule responsible for shaping tau proteins into a form that creates neurofibrillary tangles is currently still unknown (Amyloid Plaques and Neurofibrillary Tangles). It has been found, however, that the destruction of sAPPa, an APP fragment that enhances neural synapses and promotes neurogenesis, helps to induce the formation of neurofibrillary tangles (Vanden Dries et al. 2017).

Interplay of β -amyloid and Tau Protein

Though the two main hypotheses of AD, the amyloid hypothesis and the tau hypothesis, suggest two different causes for which phenomenon is the main cause of AD pathogenesis, there is evidence to suggest that there is a mechanistic relationship between β -amyloid and tau pathology. (Castillo-Carranza et al. 2015). Recent evidence suggests that β -amyloid and tau do not act in isolation of each other, but rather synergize in order to impair neural activity in AD and drive neurons into the diseased state that indicates AD (Bloom 2014, Castillo-Carranza et al. 2015). It has been found that the signature, toxic properties of β -amyloid require tau protein (Bloom 2014). The accumulation of β -amyloid is a major influence in tau pathology in that β -amyloid aggregation sets the stage for neurofibrillary tangles that contain the altered, toxic form of tau protein to impair brain function (De Felice et al. 2008, Deng et al. 2015). An increase of β -amyloid levels in the brain induces tau hyperphosphorylation and thus propagates the rapid spread of the toxic form of tau protein throughout the brain (De Felice et al. 2008, Castillo-Carranza et al. 2015). The devastating neurological effects of β -amyloid are also partially controlled by tau pathology since evidence suggests that tau mediates the level of toxicity exhibited by β -amyloid (Bloom 2014, Castillo-Carranza et al. 2015).

Acetylcholine Levels and AD

One of the harmful effects of AD induced by β -amyloid accumulation is cholinergic dysfunction (Minami et al. 1997). Acetylcholine levels are also crucial modulators of AD pathology, specifically in regard to synapses, because cholinergic disruption is increased in patients with AD (Minami et al. 1997). Acetylcholine is a neurotransmitter, or chemical messenger released by neurons to convey information. Cholinergic function underlies a great

deal of the short-term memory loss observed in AD (Liu et al. 2016). Acetylcholine plays a crucial role in learning, memory and attention. Disruption of acetylcholine to the neocortex of the brain impairs the learning of simple discrimination tasks, and disruption acetylcholine to the hippocampus causes memory issues similar to anterograde amnesia in which one is unable to recall the recent events while retaining long term memories (Easton et al. 2002). Acetylcholine levels decrease in those experiencing memory impairment such as in AD largely because β -amyloid aggregation reduces acetylcholine levels in the hippocampus (Minami et al. 1997, Hashimoto et al. 2005). Acetylcholine is created by the enzyme choline acetyltransferase (ChAT) from the compounds choline and acetyl-coenzyme A (Puglielli et al. 2001). AD causes a cholinergic deficiency as a result of reduced ChAT activity in the hippocampus which causes the amount of acetylcholine in the hippocampus to also be reduced (Ishrat et al. 2009, Liu et al. 2016).

Acetylcholine deficiency in AD not only comes from a low amount of ChAT in the brain needed to create acetylcholine, but also comes from the over activity of AChE in cleaving the existing acetylcholine too rapidly (Chacón et al. 2003). When acetylcholine is released by neurons, it is cleaved by acetylcholinesterase (AChE) to terminate its effects in the synaptic cleft (Chacón et al. 2003). The breakdown of acetylcholine via the over activity of AChE is detrimental to the AD brain which is needed for synapses because AChE inactivates acetylcholine at synapses (Ahmed et al. 2009). Acetylcholine being cleaved too quickly by AChE means that the neurotransmitter, acetylcholine, does not have time to exhibit its complete effect (Chacón et al. 2003). β -amyloid decreases acetylcholine levels in the brain and β -amyloid also increases AChE activity (García-Ayllón et al. 2008). AChE promotes the assembly of toxic β -amyloid peptides and also increases the neurotoxicity of the β -amyloid along with inducing

neuronal death (Chacón et al. 2003, García-Ayllón et al. 2008, Syamima et al. 2019). AChE can be found in senile plaques in AD that are made from β -amyloid demonstrating the enzyme's role in AD pathology (Chacón et al. 2003, Syamima et al. 2019).

Cholesterol also modulates the rate and mechanism by which acetylcholine receptors draw acetylcholine into the cell or internalizes (Borroni and Barrantes 2011). Not only is β -amyloid production and aggregation modulated by cholesterol, but cholesterol is also necessary in order for the homeostasis of acetylcholine receptor levels to be maintained (Borroni and Barrantes 2011, Di Paolo and Kim 2011). Dysregulation of cholesterol metabolism can play a potent role in the pathology of AD in relation to cholinergic degeneration because high levels of cholesterol cause an increase in AChE activity which contributes to the cognitive impairment seen in AD (Moreira et al. 2012, Moreira et al. 2014). Cholesterol homeostasis, therefore, is important in acetylcholine level maintenance (Moreira et al. 2012, Moreira et al. 2014). Preserving acetylcholine levels in AD is important because cholinergic neurons play an indispensable role in memory function, and the progressive disruption of cholinergic function seen in AD pathology underlies much the short-term memory loss observed in AD (Liu et al. 2016). Memory loss in AD correlates more so with synapse loss than with plaques or tangles which is why improving the acetylcholine levels at the synapse is crucial (Calon et al. 2004).

Inflammation Caused by Oxidative Stress in AD

Oxidative stress is one of the pathological hallmarks of AD induced by β -amyloid aggregation. Free radicals are unstable atoms that damage cells which can cause illness and accelerate aging and apoptosis (Reddy 2006). When oxygen molecules split into single atoms with unpaired electrons, they become unstable, free atoms (hence "free radicals") that try to bond

to other molecules (Pham-Huy et al. 2008). Free radicals derived from oxygen are known collectively as reactive oxygen species, and the accumulation of free radicals is known as oxidative stress (Pham-Huy et al. 2008). β -amyloid impacts the AD brain by inducing the production of free radicals and increasing oxidative stress in AD which causes inflammation (Reddy 2006).

As neurodegenerative diseases like AD progress, the brain it loses its ability to fight the effects of free radicals, and undergoes oxidative stress as a result (Pham-Huy et al. 2008). β -amyloid entering the mitochondria is what leads to the development of excessive free radicals and subsequent oxidative stress and inflammation (Reddy 2006). β -amyloid inducing the generation of free radicals is what causes the neuronal damage and loss of synaptic function hallmark in AD (Reddy 2006). More free radicals cause more oxidative stress, which causes more damage to cells thus contributing to the neurodegenerative pathology of AD (Reddy 2006, Pham-Huy et al. 2008). Oxidative stress and inflammation also impacts the integrity of the BBB because the BBB becomes more permeable during inflammation thus allowing more β -amyloid to get through (Pan et al. 2018).

The oxidation of lipids is known as lipid peroxidation, and it is the degradation of lipids that results from the destructive process of oxidation (Pham-Huy et al. 2008). The production of toxic β -amyloid peptides is accelerated by lipid peroxidation (Pham-Huy et al. 2008). β -amyloid facilitating the generation of free radicals causes lipid peroxidation and increases the amount of reactive oxidative species present (Hensley et al. 1994, Reddy 2006). This is because the production of free radicals in excess alters the structures or cell membranes and lipids (Pham-Huy et al. 2008). The body's defense mechanism against oxidative stress is the production of anti-oxidants which are substances in the body that prevent or slow the damage to cells caused

by free radicals and reduce inflammatory responses (Reddy 2006, Pham-Huy et al. 2008). The overwhelming amount of oxidative stress producing more free radicals than can be eliminated with anti-oxidants poses a problem in the AD pathogenesis (Pham-Huy et al. 2008).

Oxidative stress also enhances the activity of AChE thus preventing adequate acetylcholine synaptic levels and causing cholinergic dysfunction which leads to induces β -amyloid production (Minami et al. 1997, Melo et al. 2003, Ishrat et al. 2009). The hippocampus and cortical regions of the brain are the areas primarily involved in cholinergic transmission since they modulating memory processing and learning and these brain areas in particular are also more prone to oxidative damage in the AD pathogenesis (Ishrat et al. 2009). Oxidative damage to lipids progresses AD by disrupting the cell membranes of neurons, inactivating enzymes such as AChE, and causing cells to die (Melo et al. 2003, Ishrat et al. 2009).

Role of the Brain-to Blood Barrier in AD

The brain-to-blood barrier (BBB) is a semipermeable border that separates the circulating blood from the brain and extracellular fluid in the central nervous system (Daneman and Prat 2015). The BBB is comprised of a network of blood vessels that blocks harmful substances and pathogens from going into the brain, while allowing essential nutrients to enter (Daneman and Prat 2015). The BBB has endothelial cells are connected by tight junctions that that line blood vessels in the central nervous system and prevent most molecules from passing between them (Andreone et al. 2017). β -amyloid and the toxic form of tau proteins, however, are able to cross the barrier which is why the clearance of β -amyloid and other toxins is indispensable to maintaining brain health (Yan et al. 2019). The BBB becomes compromised when inflammation from oxidative stress weakens the BBB by increasing its permeability to the destructive amyloid

which causes neurodegeneration and cell apoptosis (Magaki et al. 2018). In AD, blood plasma containing β -amyloid enters the brain via the BBB and adheres to astrocytes which are the star-shaped glial cells that regulate neuronal synapses and provide support for the neurons (Hooijmans et al. 2007, Zipser et. al 2007). β -amyloid adhering to the glial cells (astrocytes) that provide structural support to the neurons weakens the BBB.

Though the specific relationship between cerebral capillaries and amyloid plaques is not completely understood, recent evidence has suggested that plaques may result from leaky capillaries that allow β -amyloid into the BBB (Zipser et. al 2007). This suggests that vascular damage plays a role in the pathogenesis of AD, specifically in the micro-vascular structure of the BBB since the disease is aggravated by the gradual breakdown of the BBB due to β -amyloid (Zipser et. al 2007). The BBB may also be compromised by the accumulation of amyloid plaques in the wall of arteries and capillaries which is known as cerebral amyloid angiopathy (CAA) (Magaki et al. 2018). Cerebral amyloid angiopathy is another major hallmark often occurring in AD pathology (Liu et al. 2013). About 85% of people with AD also have CAA which accounts for the integrity of the BBB becoming weakened as a result of β -amyloid in the blood vessels (Magaki et al. 2018). The phenomenon of β -amyloid being inside of blood vessels like capillaries and arteries in AD makes a high percent of AD cases fall under the umbrella of vascular dementia which is when the brain and cells undergoes neurodegenerative damage as a result of issues with the BBB (Magaki et al. 2018). AD and CAA represent two sides of a single condition which is cerebral amyloidosis caused by β -amyloid (Yamada 2012). CAA is capable of exacerbating BBB dysfunction related to AD which is why vascular dementia and AD often occur together (Magaki et al. 2018). The BBB and its structural integrity becomes compromised

when inflammation weakens the BBB by increasing its permeability to the destructive β -amyloid thus causing neurodegeneration and cell apoptosis (Magaki et al. 2018).

The primary receptors used for the transport of β -amyloid peptides and tau protein across the BBB are known as low-density lipoprotein receptor related protein-1 (LRP-1) (Deane et al. 2015, Yan et. al 2019). LRP-1 is responsible for bringing nutrients to the BBB, but since the BBB is permeable to β -amyloid and tau protein, those are also transported by LRP-1 (Deane et al. 2015, Yan et. al 2019). The decline of LRP-1 levels in the brain as a part of aging contributes to the imbalance of β -Amyloid that is characteristic of AD (Deane et al. 2015, Yan et. al 2019). The BBB is dependent on LRP-1 to clear β -Amyloid from the brain, therefore, greater LRP-1 production means that more β -Amyloid can be cleared by the brain-blood barrier which helps to mediate the imbalance of β -Amyloid in the brain. (Yan et. al 2019).

Cholesterol and AD

Defects in cholesterol homeostasis in the adult brain are linked to AD in that β -amyloid production and clearance is regulated by cholesterol, and high cholesterol is neurotoxic (Yao and Papadopoulos 2002, Di Paolo and Kim 2011). The human brain is the most cholesterol-rich organ in the body containing 25–30% of the total body cholesterol (Di Paolo and Kim 2011). Lipids control many aspects of the AD pathogenesis in that lipids, like cholesterol, control the processing of amyloid precursor protein, the synaptotoxic signaling of both β -amyloid formation and tau pathology formation (Hashimoto et al. 2005). Because cholesterol plays an important role in β -amyloid formation, one of the physiological functions of APP is to control cholesterol transport as well as homeostasis (Yao and Papadopoulos 2002).

Low-density lipoprotein (LDL) cholesterol is the “bad” form of cholesterol which leads to β -amyloid accumulation (Yao and Papadopoulos 2002, Di Paolo and Kim 2011). High levels of LDL cholesterol induce the processing of APP and increase APP cleaving β -amyloid eventually leading to the formation of β -amyloid plaques (Yao and Papadopoulos 2002). High levels of LDL cholesterol cause the LDL cholesterol to bind to the α -secretase site of APP thus blocking the action of the enzyme which generates the toxic form of β -amyloid (Yao and Papadopoulos 2002). Low levels of LDL cholesterol, conversely, cause APP to be cleaved in a way that does not generate β -amyloid (Yao and Papadopoulos 2002). When there is a low amount of LDL cholesterol, APP is cleaved by α -secretase which overrides the amount of toxic β -amyloid 40-42 peptides formed (Yao and Papadopoulos 2002). Changes in cholesterol transport and homeostasis, therefore, lead to neurotoxicity mediated by β -amyloid.

Hypercholesterolemia, or high LDL cholesterol in the blood, is a risk factor for AD and vascular dementia because it impairs the integrity of the BBB and induces β -amyloid overproduction (Hooijmans et al. 2007). CAA, the phenomenon of β -amyloid in the blood vessels, is exacerbated by high cholesterol levels since the formation of β -amyloid is modulated by LDL cholesterol (Di Paolo and Kim 2011, Reed et al. 2014). An increase of cholesterol in the cerebral vasculature causes vulnerable areas of the brain to experience hypoperfusion, or reduced blood flow (Hooijmans et al. 2007). The removal of LDL cholesterol from the brain is important because high levels of LDL cholesterol accelerate the formation of β -amyloid plaques (Zuliani et al. 2010, Di Paolo and Kim 2011).

High-density lipoprotein (HDL) cholesterol, on the other hand, is respectively known as the “good” form of cholesterol, and it helps to remove LDL cholesterol from the blood (Zuliani et al. 2010, Di Paolo and Kim 2011). HDL cholesterol is also crucial for synapse generation,

maturation, and synaptic plasticity in that it increases the number of synaptic vesicles which have high cholesterol levels (Mauch et al. 2001, Zuliani et al. 2010, McGrowder et al. 2011). HDL cholesterol is important to AD pathology because along with helping to remove LDL cholesterol, it is also involved in helping to clear the β -amyloid from the brain and even plays a role in maintaining the integrity of the BBB (Ole and Lone 2000, Zuliani et al. 2010, McGrowder et al. 2011).

The apolipoprotein E (ApoE) gene is the major cholesterol carrier that transports lipids like cholesterol, supports injury repair in the brain, and is a genetic determinant of AD pathogenesis (Liu et al. 2013, Devassy et al. 2016) While ApoE mainly regulates homeostasis by acting as a lipid transporter in the brain, it also regulates β -amyloid formation and aggregation (Liu et al. 2013, Devassy et al. 2016). ApoE exists in three major isoforms which are ApoE ϵ 2, ApoE ϵ 3, and ApoE ϵ 4 (Devassy et al. 2016). ApoE ϵ 4 is the isoform that stimulates AD pathology the most being the greatest genetic risk factor for AD since people with this genetic trait have an increase level of a particular cholesterol transport and thus have a greater risk of late-onset Alzheimer's (Di Paolo and Kim 2011, Devassy et al. 2016). While 40–65% of people with AD patients have at least one copy of the ϵ 4 allele, *APOE4* is not a surefire determinant of the disease despite it being the largest predisposing genetic risk factor (Ryan 2013). About one third of those with AD negative for the *APOE4* allele and some *APOE4* homozygotes (two identical alleles) never develop (Ryan 2013). People who are homozygotic for ϵ 4 alleles, however, have up to 20 times the risk of developing AD (Ryan 2013). ApoE ϵ 4 is a transporter with a high affinity for LDL cholesterol which causes the accumulation of more β -amyloid peptides (Devassy et al. 2016). The ApoE ϵ 4 genotype strongly affects the deposition of β -amyloid into amyloid plaques (Liu et al. 2013). ApoE ϵ 2 and ϵ 3 have a higher affinity for HDL

cholesterol and thus have little involvement in AD pathology (Devassy et al. 2016). People carrying the $\epsilon 4$ ApoE allele have an increased risk of AD in comparison with those carrying the less dangerous $\epsilon 2$ and $\epsilon 3$ alleles because LDL cholesterol accelerates β -amyloid formation, and the $\epsilon 4$ ApoE allele carries LDL to the brain which causes more β -amyloid build-up (Liu et al. 2013).

The $\epsilon 4$ ApoE allele also increases the risk for cerebral amyloid angiopathy, and the $\epsilon 4$ ApoE allele impairs the BBB by making it more permeable to β -amyloid (Liu et al. 2013). The prevalence of dyslipidemia, or high levels of lipids in the blood, caused by LDL cholesterol weakens the BBB and is associated with its impairment in AD (Bowman et al. 2012). Conversely, HDL cholesterol strengthens the integrity of the BBB by removing excess LDL cholesterol (Bowman et al. 2012). The effects of LDL and HDL cholesterol on the BBB and β -amyloid clearance implicate the role of cholesterol in AD pathogenesis (Di Paolo and Kim 2011, Bowman et al. 2012).

Western Diet and Neurodegeneration

Risk factors for AD include moderate to severe brain traumas in a person's history, age, smoking, hypertension, hypercholesteremia, insulin resistance/diabetes, alcohol abuse, and obesity (Zvěřová M. 2019, Alzheimer Society of Canada). One of the greatest risk factors for AD, however, is an unhealthy diet since a bad diet can prime the brain for AD (Zvěřová M. 2019). Not only does an unhealthy diet put one at greater risk for developing AD, but an unhealthy diet may also hasten the development of cognitive decline in someone that already has it (Dandona et al. 2007, Hanson et al. 2013). Recent studies have shown that diets high in fat, sugar, and cholesterol, a staple of the average American diet, rob the brain of substances, such as

DHA, that help to clear β -amyloid which contributes the buildup of plaques that is a hallmark of AD (Hanson et. Al 2013). Although oxidative stress is part of the AD disease pathology due to the increased presence of β -amyloid, high amounts of LDL cholesterol from diet can trigger oxidative stress and cause inflammation (Moreira et al. 2012, Moreira et al. 2014, Farnaghi et al. 2017).

An unhealthy diet results in malnourishment meaning that a person's diet does not contain the right amount of nutrients. Though people tend to associate malnourishment with being thin and frail, that is not always the case as malnourishment stems from lack of nutrients and a lack of a healthy diet, but not necessarily whether a person is thin or obese. Preventing malnourishment is indispensable for good brain health. Studies have established that a correlation exists between frailty and AD, but there is also a correlation between malnutrition and AD (Buchman et al. 2008, Meijers et al. 2014). This is a crucial distinction to make because AD patients do not always experience weight loss or frailty, but still may not be getting the right nutrition in their diets making them malnourished. This malnourishment could exacerbate the production of β -amyloid if the person is eating the wrong type of diet, such as one high in fat or sugar (Hanson et. Al 2013). β -amyloid plaques accumulating leads to neurodegeneration in terms the loss of connections between neurons and cell death (Kim et al 2013).

It's no secret that the western diet that is a primary part of many people's lives is far from healthy. The western diet refers to the standard American diet that is characterized by large intakes of LDL cholesterol, sugar, high-fructose corn syrup, red meat, processed and pre-packaged foods, fried foods, fast food, and high fat dairy products (Guerin et. al 2005). The average American diet is ill-proportioned in that people tend to overeat, and meals often lacks the correct amounts of unprocessed fruits and vegetables, whole grains, fish, and poultry needed

to sustain a healthy lifestyle (Guerin et. al 2005). In fact, an unhealthy diet directly ties in with some of the leading causes of death in the U.S such as cardiovascular disease and diabetes (Guerin et. al 2005). Typical American diets far exceed the recommended daily intake of calories, and many foods contain a superfluous amount of LDL cholesterol, sugar, sodium, fat, and processed chemicals. Unhealthy dietary habits that lead to hypertension, insulin resistance, inflammatory processes, metabolic syndrome, midlife obesity, and excessive free radicals also increase the risk of AD (Zvěřová et al. 2019). Vascular risk factors and vascular disease closely correlate with the neurodegenerative aspect of AD in that an unhealthy diet impacts the vascular system which disrupts the BBB causing blood plasma containing β -amyloid to enter the brain and accelerate the formation of plaques (Zipser et al. 2007).

Need for More AD Treatment Options Using Dietary Substances

Exploring dietary substances as potential tools to improve the AD prognosis is an important endeavor to undertake because according to the CDC, AD is in the top ten list of most expensive chronic diseases to treat in the U.S (Health and Economic Costs of Chronic Disease). In 2018, the estimated cost of Dementia and Alzheimer's care in the U.S was \$277 billion dollars and by 2040, the costs of treating AD is projected rise between \$379 billion and \$500 billion annually (Alzheimer's Association, Health and Economic Costs of Chronic Disease). Not only have the healthcare costs of managing the disease gone up, but the number of deaths caused by it have increased exponentially in the last decade. Finding alternative treatment options that are cost effective and efficient in slowing the progression of the disease is no easy task, but one that must be undertaken in order to eventually improve the quality of life for those living with AD and their caretakers who also share in the heartache and financial burden.

Changing one's diet and eating healthy to slow the progression of AD or dementia or try to prevent it all together (within the limits of genetics) is one of the easier and more cost-effective ways of helping and protecting oneself. Though a change in diet is more easily accessible and less costly than medications, this is in no way to discourage the use of medication to treat AD. Diet alone cannot replace AD treatment with medication, but eating healthier goes a long for promoting brain health, and slowing the progression of AD. Diet can not only improve one's overall health and cognition, but many dietary substances, such as DHA and curcumin, can combat the effects of β -amyloid and the other slew of factors that hasten neurodegeneration in AD.

Docosahexaenoic Omega-3 Fatty Acids and Neural Development

Neurodegeneration is impacted when one's diet is deficient of Docosahexaenoic acid (DHA) (Lukiw et al. 2005). DHA is the omega-3 polyunsaturated fatty acid (O3PUFA) most abundantly found in the brain tissues accounting for one third of the polyunsaturated fatty acids in the brain (Wu et al. 2015). DHA is one of the main structural component of the brain, and is essential for the development of the brain itself as well as also helping to form the retina and the liver (Anderson et al. 1990). The dietary intake of DHA supports properties of the cell membranes found in gray matter (Wu et al. 2015). DHA is transported from blood in the circulatory system, and it crosses the BBB to get to the brain (Zhao and Zlokovic 2014). DHA is associated with cognitive decline as the amount of brain DHA is decreased in those with AD (Moriguchi and Salem 2003, Lukiw et al. 2005). This is because DHA attenuates, or reduces, the secretion of β -amyloid thus participating in the pathophysiology of AD (Lukiw et al. 2005). DHA not only reduces the β -amyloid burden but also alleviates the other aspects of the AD

induced by excessive β -amyloid. DHA also reduces neuronal degeneration and rescues learning ability as experimentally demonstrated through rodent models with an accumulation of β -amyloid in their brains (Lukiw et al. 2005). DHA is typically obtained through dietary means, particularly with the consumption of fish and fish oils which are rich in DHA omega-3 polyunsaturated acids. DHA deficiency can be mediated by a healthy dietary intake of foods containing DHA O3PUFAs (Lukiw et al. 2005). Studies have showed that dietary DHA is efficient in increasing brain DHA content and improving brain function which has implications for the prevention and treatment of diseases like AD that are associated with DHA deficiency (Sugasini et al. 2017).

Curcumin and Neural Development

Curcumin, a natural substance derived from the turmeric plant, is a powerful antioxidant that has been found to cross the BBB and clear β -amyloid from the brain. Curcumin derivatives are capable of acting as potent β -amyloid inhibitors, especially with the β -amyloid 42 peptide. Curcumin can bind to β -amyloid itself, and some curcumin derivatives also bind to APP (Shinzato et al. 2020). The use of curcumin also increases brain DHA and has beneficial effects on neuroplasticity which is the ability of the brain to form synaptic connections (Wu et. Al 2015). Curcumin not only reduces the β -amyloid burden but also alleviates the other aspects of the AD induced by excessive β -amyloid. Curcumin not only has the capacity to modulate neuronal death by slowing the rate at which neurons die which aids in improving the AD prognosis (Wu et. Al 2015). This is especially pertinent given that the highest curry consumption is in India, and India has the lowest incidence of AD compared to every other country in the

world (Lim et al. 2001). The prevalence of AD in India between ages 70-79 is 4.4-fold less than the AD rate of occurrence in the United States (Lim et al. 2001).

Methodology for Composing the Thesis

Although both β -amyloid and tau are important aspects of the AD pathogenesis, for the purposes of this literature review, β -amyloid will be focused on as β -amyloid accumulation and deposition can be primarily credited to triggering the cascade of events that lead to the progression of AD and the neurodegenerative pathology (Syamima et al. 2019). β -amyloid is responsible for inducing many of the other pathological hallmarks of AD including tau hyperphosphorylation and neurofibrillary tangles which is why β -amyloid clearance will be the focus. DHA O3PUFAs and Curcumin will not only be compared based on their ability to clear β -amyloid and prevent its aggregation, but will also be evaluated on their abilities to promote DHA development in the brain, improve cholesterol levels, improve acetylcholine levels in the AD brain, improve synapses, alleviate inflammation and oxidative stress, preserve the BBB, promote neurogenesis, improve memory and learning, and prevent cell death. DHA O3PUFAs and curcumin will be compared as dietary substances that slow the pathology of the AD by clearing β -amyloid and decelerating the aforementioned slew of factors that modulate and accelerate the progression of AD as a result of β -amyloid accumulation.

Clearing β -amyloid and preventing β -amyloid aggregation in AD

DHA O3PUFAs

Dietary DHA has the potential to improve AD prognosis on account of the fact that it has the ability to clear β -amyloid and prevent it from aggregating to form plaques.

β -amyloid plaques are characteristically linked to AD because these sticky plaques disrupt the connections between neurons. DHA has been found to promote brain-to-blood clearance of β -Amyloid which could effectively prevent the progression of Alzheimer's Disease (Yan et al. 2019). In various AD mice models with an accumulation of β -amyloid that were fed a DHA-rich diet and compared to a control group, the hippocampus and cortex of the mice fed the DHA-rich diet displayed reduced β -amyloid levels and β -amyloid toxicity (Lim et al. 2005, Lukiw et al. 2005, Yan et al. 2019). DHA also resulted in a decrease of senile amyloid plaques in the hippocampus (Yan et al. 2019). In a mouse model where the mice are 17-19 months old, DHA-enriched diets have been shown to significantly reduce total β -amyloid in the brain by over 70% in comparison to low-DHA diets or control diets (Lim et al. 2005). A DHA-enriched diet resulted in a 40–50% reduction in the deposition of β -amyloid in the cortex and hippocampus (Calon et al. 2004, Lim et al. 2005, Hashimoto et al. 2005). This demonstrates the role of DHA O3PUFAs in reducing the amyloid plaque burden in AD.

DHA also aids in β -amyloid clearance by acting as a precursor to neuroprotection D1 (NPD1) which is a specific molecule derived from DHA that represses β -amyloid 42-triggered activation of inflammatory genes (Lukiw et al. 2005). NPD1 also upregulates the genes that prevent apoptosis and reduces the neurotoxicity of β -amyloid 42 (Lukiw et al. 2005). NPD1, which has DHA as a precursor, has its biosynthesis stimulated by α -secretase of APP which reduces β -amyloid in the hippocampus (Lukiw et al. 2005). Soluble APP- α peptide, which is generated from APP via the α -secretase pathway, decreases the production of β -amyloid peptides while supporting neural growth and stronger synaptic effects (Lukiw et al. 2005). DHA aids in clearing β -amyloid because a larger presence of DHA means a greater amount of NPD1 that can

be biosynthesized by the APP- α peptide which acts to attenuate β -amyloid, reduce its toxicity, and promote survival of hippocampal and cortical neurons (Lukiw et al. 2005).

Curcumin

Curcumin also has the potential to improve AD prognosis by clearing β -amyloid and preventing it from aggregating to form plaques. Curcumin was recently reported to decrease the attenuation of β -amyloid in the brain (Hoppe et al. 2013a). The neuroprotective effects of curcumin have been examined using hippocampal slices of rats exposed to β -amyloid through spectral analysis of multi-electrode array (MEA) recordings of spontaneous neuronal activity (Hoppe et al. 2013a). Studies using hippocampal rat slices have revealed that curcumin reverses the tendency for β -amyloid to attenuate prevents cellular death induced by β -amyloid (Hoppe et al. 2013a). This demonstrates curcumin's ability to modulate β -amyloid-induced neuronal death (Hoppe et al. 2013a). Curcumin is most effective in clearing β -amyloid in low doses of curcumin in mice models rather than in high doses (Lim et al. 2001, Ye and Zhang 2012). It has been found from comparing a low-dose curcumin diet, high-dose diet, and control diet that the amyloid plaque burden decreases in the greatest amount with a low-dose curcumin treatment which inhibits β -amyloid toxicity and can significantly decrease amyloid plaques 43-50% (Lim et al. 2001, Ye and Zhang 2012). Curcumin treatment in lowering the β -amyloid plaque burden had the greatest impact in the hippocampus and the cortex (Lim et al. 2001). Low-dose curcumin also increased cell viability and reduced neuronal death (Ye and Zhang 2012).

Curcumin is able to cross the BBB based on its ability to attenuate β -amyloid and reduce its toxicity in low doses making a potential candidate for drug development (Ye and Zhang 2012). Curcumin has been found to be effective in clearing β -amyloid and preventing its aggregation because it has a larger affinity, or ability to bind, to β -amyloid compared to other β -

amyloid inhibitors and prevent it from clumping together (Shinzato et al. 2020). Curcumin derivatives are capable of acting as potent β -amyloid inhibitors, especially with the β -amyloid₄₂ peptide, not just by binding to β -amyloid itself but some curcumin derivatives also bind to APP (Shinzato et al. 2020). The curcumin derivative known as “curcumin XIV”, for example has a large binding affinity to APP which is the protein responsible for producing β -amyloid peptides in the first place through proteolysis (Priller et al. 2006, Shinzato et al. 2020). By binding to APP, curcumin derivative XIV can inhibit the production of β -amyloid peptides all together by preventing the protein from cleaving β -secretase to form β -amyloid peptides (Shinzato et al. 2020). Curcumin derivatives also promote β -amyloid clearance by enhancing the uptake of β -amyloid by macrophages (Zhang et al. 2006). People with AD have defects in phagocytosis in the clearance of β -amyloid, and treatment of the macrophages with curcumin derivatives increase the uptake of β -amyloid by binding to the macrophages thus leading to its clearance (Zhang et al. 2006).

Summary

Both DHA and curcumin cross the BBB and are capable of clearing β -amyloid from the brain. Both substances also act to lower the plaque formation in the hippocampal and cortical regions of the brain. Reducing β -amyloid by using DHA and curcumin allows other issues induced by β -amyloid to be modulated as will be demonstrated in the following sections.

Promoting development of brain DHA in AD

DHA O3PUFAs

DHA is capable of modulating many of the physiological hallmarks of AD induced by β -amyloid. DHA improves cholesterol metabolism in AD by improving HDL cholesterol levels in

the brain (Ole and Lone 2000, Di Paolo and Kim 2011). The ability of DHA to increase HDL cholesterol levels is important for slowing the progression of AD because HDL helps to remove LDL cholesterol from the blood, HDL helps clear β -amyloid from the brain, and HDL is crucial for synapse generation (Ole and Lone 2000, Zuliani et al. 2010, Di Paolo and Kim 2011). DHA also increases ChAT levels and thus acetylcholine levels in the brain that were reduced by β -amyloid (Minami et al. 1997). DHA has been found to improve synapses, promote synaptogenesis, and alleviate β -amyloid-induced synaptic toxicity (Lukiw et al. 2005). Using dietary DHA to improve synaptic function is crucial because synapses are normally enriched with DHA, and brain DHA is essential to post-synaptic signaling in neural communication as well as neuroprotection (Calon et al. 2004). DHA reduces oxidative stress and inflammation in the brain as well. DHA, because it is able to cross the BBB, has been found to strengthen the structural integrity of the BBB (Yan et al. 2019). DHA has also been found to promote hippocampal neurogenesis and cell proliferation thus helping to improve the AD prognosis (Lukiw et al. 2005, Kawakita et al. 2006). Memory and learning ability have also been shown to be rescued by DHA supplementation (Minami et al. 1997).

Curcumin

Even though curcumin is capable of alleviating β -amyloid-induced hallmarks of the AD pathology on its own, curcumin also promotes the development of brain DHA, and DHA modulates all of these aforementioned factors as well (Wu et al. 2015). Curcumin stimulates DHA synthesis through its precursor acid, α -linolenic acid, and also raises the levels of the enzymes FADS2 and elongase 2 which are involved in DHA synthesis in the hippocampus (Wu et al. 2015). This means that curcumin increases DHA content by increasing enzyme pool

available to facilitate the conversion of DHA from ALA which is DHA's precursor (Wu et al. 2015). Curcumin being able to increase brain DHA is important because a large population of people today thrive on a plant-based or vegan diet and are unable to obtain adequate levels of DHA through dietary means to support cognitive development. This issue is alleviated with dietary curcumin because curcumin is plant-based and is capable of enhancing DHA synthesis thus raising the amount of DHA in the brain which can aid in treating cognitive disorders like AD (Wu et al. 2015).

Summary

Both dietary DHA and curcumin are capable of increasing DHA levels in the brain. Dietary DHA has been found to increase brain DHA levels which not only modulates β -amyloid clearance and toxicity, but also participates in alleviating other parts of the AD pathophysiology and prevents apoptosis (Lim et al. 2005, Lukiw et al. 2005). Promoting brain DHA by using dietary DHA and curcumin is neuroprotective in that it helps to clear β -amyloid, improve cholesterol levels, improve acetylcholine levels in the AD brain, improve synapses and alleviate synaptic toxicity, alleviate inflammation and oxidative stress, preserve the BBB, promote neurogenesis, preserve memory and learning, and prevent apoptosis. DHA effectively acts to modulate all of the aforementioned factors induced by β -amyloid which is why brain DHA promotion via dietary DHA and curcumin is important.

Regulating HDL and LDL cholesterol

DHA O3PUFAs

Maintaining cholesterol metabolism helps to modulate the production and subsequent accumulation of β -amyloid since cholesterol controls the processing of amyloid precursor protein

and the synaptotoxic signaling of β -amyloid formation (Hashimoto et al. 2005). DHA O3PUFAs improve cholesterol metabolism in AD by improving HDL cholesterol levels in the brain (Ole and Lone 2000, Di Paolo and Kim 2011). The ability of DHA to increase HDL cholesterol levels is important for slowing the progression of AD because HDL helps to remove LDL cholesterol from the blood, and HDL clears β -amyloid (Zuliani et al. 2010, Di Paolo and Kim 2011). HDL also helps to clear β -amyloid from the brain, and HDL is crucial for synapse generation (Ole and Lone 2000, Zuliani et al. 2010, Di Paolo and Kim 2011). LDL cholesterol leads to β -amyloid accumulation by inducing the processing of APP and the cleavage of β -amyloid (Yao and Papadopoulos 2002, Di Paolo and Kim 2011). Although DHA does not decrease LDL cholesterol directly, it increases HDL, and HDL acts to lower LDL levels (Ole and Lone 2000, Zuliani et al. 2010, Di Paolo and Kim 2011).

Curcumin

Curcumin also improves cholesterol metabolism in AD by improving HDL cholesterol levels in the brain which helps to clear LDL cholesterol (Arafa et al. 2005, Santoso et al. 2008). Curcumin is most effective in modulating cholesterol metabolism in low doses because curcumin has poor water solubility, and curcumin can get to the brain faster in low doses (Santoso et al. 2008). In addition to raising HDL cholesterol levels, administration of curcumin in low-doses reduced total LDL cholesterol levels in the brain directly (Santoso et al. 2008).

Summary

Both DHA and curcumin improve HDL cholesterol levels in the brain which helps to remove LDL cholesterol from the blood, and clear β -amyloid. DHA does not lower LDL cholesterol directly, but promotes an increase in HDL cholesterol so that LDL cholesterol can be

lowered. Curcumin, on the other hand lowers LDL cholesterol directly in addition to also promoting increased levels of HDL cholesterol.

Improving Acetylcholine levels

DHA O3PUFAs

Cholinergic dysfunction is a hallmark of AD pathology induced by β -amyloid accumulation in that β -amyloid aggregation reduces ChAT levels and thus acetylcholine levels in the hippocampus (Minami et al. 1997, Hashimoto et al. 2005). DHA O3PUFAs have been found to increase acetylcholine levels (Minami et al. 1997, Machová et al. 2006). DHA treatment stimulates ChAT activity in the brain thus increasing acetylcholine levels (Machová et al. 2006). DHA has also been found to prevent the degeneration of the cholinergic system in rats infused with β -amyloid by preventing ChAT levels from decreasing (Machová et al. 2006, Belkouch et al. 2016). Despite the fact that DHA improves ChAT levels and acetylcholine levels in the brain, DHA does not affect AChE activity at all (Aïd et al. 2003, Shahdat et al. 2004).

Curcumin

Curcumin has also been found to increase acetylcholine levels in the brain by increasing ChAT levels in the hippocampus (Ishrat et al. 2009). ChAT dysfunction, which causes the amount of acetylcholine produced in the hippocampus to be reduced, was reversed and elevated by curcumin treatment (Liu et al. 2016). Curcumin has also been found to be neuroprotective to cholinergic neurons in mice models (Liu et al. 2016). Curcumin derivatives have also been found to inhibit the activity of AChE in the hippocampus and frontal cortex, the enzyme that cleaves acetylcholine (Ahmed et al. 2009, Akinyemi et al. 2017). Curcumin inhibits AChE activity by crossing the BBB and inhibiting the enzyme in order to provide more time for acetylcholine to

stimulate postsynaptic receptors (Ahmed et al. 2009, Akinyemi et al. 2017). Curcumin derivatives acting as an AChE inhibitor make it a potential candidate for an AD drug.

Summary

Both DHA and curcumin increase ChAT activity as well as acetylcholine levels which helps to strengthen and improve synaptic function as well as counteract β -amyloid-induced cholinergic dysfunction. Dietary DHA has no effect on decreasing AChE activity. Unlike DHA, curcumin acts to decrease AChE activity.

Improving synapses between neurons in AD/alleviating synaptic toxicity

One of the issues characteristic of the AD pathogenesis is gradual synaptic dysfunction that occurs as a result of β -amyloid accumulation (Kokawa et al. 2015). β -amyloid is a modulator of synaptic plasticity because β -amyloid disrupts communication between neurons (Kokawa et al. 2015). A synapse is the junction between two neurons through which neurotransmitters diffuse across to communicate with other neurons thereby making the synapse the physical location of neural communication.

DHA O3PUFAs

DHA has been found to strengthen synapses, promote synaptogenesis, and alleviate β -amyloid-induced synaptic toxicity (Lukiw et al. 2005). One of the ways in which DHA promotes synapse growth and formation is through NPD1, whose precursor is DHA, being biosynthesized by the sAPP α peptide from APP via the α -secretase pathway (Lukiw et al. 2005). This is because sAPP α elicits the growth and formation of synapses (Lukiw et al. 2005). Loss of synapses and

synaptotoxicity largely stems from β -amyloid accumulation which is why DHA helping to clear β -amyloid subsequently improves synaptic dysfunction as well (Lukiw et al. 2005, Kokawa et al. 2015). Using dietary DHA to improve synaptic function is crucial because synapses are normally enriched with DHA, and brain DHA is essential to post-synaptic signaling in neural communication as well as neuroprotection (Calon et al. 2004). Repletion of DHA in an AD brain with low levels of DHA helps to prevent synaptic loss (Calon et al. 2004). DHA also promoted the expression of synaptic proteins synapsin I and CaMKII to improve synapses (Wu et al. 2008).

DHA also improved synapses through modulating cholesterol levels. HDL cholesterol not only aids in β -amyloid clearance, but is also crucial for synapse generation, maturation, and synaptic plasticity in that it increases the number of synaptic vesicles which have high cholesterol levels (Mauch et al. 2001, Zuliani et al. 2010, McGrowder et al. 2011). Synapses are improved by DHA in that it acts to increase of acetylcholine levels which are also crucial modulators of synapses, because cholinergic disruption is increased in patients with AD (Minami et al. 1997). DHA's ability to preserve synaptic integrity is important to functions involving learning and memory in AD (Minami et al. 1997, Calon et al. 2004, Lukiw et al. 2005). DHA also improves long-term potentiation in the brain which is a persistent strengthening of synapses based on patterns of activity (Fujita et al. 2001, Hashimoto et al. 2005, Cook et al. 2006). DHA is crucial for the initiation of long-term potentiation, and DHA therefore, enhances synapse strength (Fujita et al. 2001, Hashimoto et al. 2005).

Curcumin

Curcumin has also been found to strengthen synapses, promote synaptogenesis, and alleviate β -amyloid-induced synaptic toxicity (Hoppe et al. 2013a). Curcumin counteracts synaptic dysfunction in the hippocampus through β -amyloid clearance since β -amyloid is synaptotoxic and causes neuronal circuits and synapses to dismantle over time (Hoppe et al. 2013a). Curcumin also prevented synaptic dysfunction by regulating the synaptic proteins synapsin I and CaMKII thus showing the neuroprotective and synaptoprotective role of curcumin (Ye and Zhang 2012, Hoppe et al. 2013a, Hoppe et al. 2013b). Both CaMKII and synapsin I are the key proteins involved in presynaptic neurotransmitter release, and both of these synaptic proteins are crucial to maintaining synaptic plasticity which is the ability of synapses to strengthen over time (Ye and Zhang 2012, Hoppe et al. 2013a, Hoppe et al. 2013b). Curcumin promoted synaptogenesis by preventing the β -amyloid-induced inactivation of CaMKII and synapsin I which improved synapses in the hippocampus (Ye and Zhang 2012, Hoppe et al. 2013a, Hoppe et al. 2013b). Curcumin also increased number of synapses in the brain, and promoted the ultrastructure or structural integrity of the synapses (Chen et al. 2018).

Curcumin improves synapses through modulating cholesterol levels as well. HDL cholesterol not only aids in β -amyloid clearance, but is also crucial for synapse generation, maturation, and synaptic plasticity in that it increases the number of synaptic vesicles which have high cholesterol levels (Arafa et al. 2005, Santoso et al. 2008). Synapses are improved by curcumin in that it acts to increase of acetylcholine levels which are also crucial modulators of synapses, because cholinergic disruption is increased in patients with AD (Arafa et al. 2005, Santoso et al. 2008). Unlike DHA, curcumin also modulates the over activity of AChE which allows acetylcholine to remain in the synapse long enough to be effective in communicating to a

post-synaptic neuron AD (Arafa et al. 2005, Santoso et al. 2008). Curcumin derivatives also rescue long-term potentiation and thus modulate synapses by enhancing synapse strength (Ahmed et al. 2011).

Summary

DHA and curcumin have both been found to strengthen synapses, promote synaptogenesis, promote long-term potentiation, and alleviate β -amyloid-induced synaptic toxicity. Both are capable of doing so by clearing β -amyloid, increasing the expression of synaptic proteins, CaMKII and synapsin I, and by modulating cholesterol levels. DHA, in particular, is adept at strengthening synapses through NPD1, a molecule for which DHA is the precursor. Curcumin, in particular, is adept at strengthening synapses by inhibiting AChE activity.

Anti-inflammation/antioxidant properties

DHA O3PUFAs

Oxidative stress is one of the pathological hallmarks of AD induced by β -amyloid aggregation. DHA has been found to exhibit neuroprotective effects with its anti-inflammatory, anti-oxidative, anti-apoptotic properties (Lukiw et al. 2005, Van et al. 2019). NPD1, the substance that had DHA as its precursor, regulates anti-inflammatory, and anti-apoptotic gene-expression that promotes the survival of neurons (Lukiw et al. 2005). DHA has also been found to reduce damage occurring as a result of β -amyloid-induced oxidative stress (Hashimoto et al. 2005, Lim et al. 2005, Lukiw et al. 2005). The oxidation of lipids is known as lipid peroxidation, and it is the degradation of lipids that results from the destructive process of oxidation (Pham-

Huy et al. 2008). DHA was found to suppress the increases of lipid peroxide and reactive oxygen species in the cerebral cortex and the hippocampus of in rats infused with β -amyloid demonstrating that DHA increases anti-oxidative defenses (Hashimoto et al. 2005).

Curcumin

Curcumin has been found to exhibit neuroprotective effects with its anti-inflammatory, anti-oxidative, anti-apoptotic properties (Lim et al. 2001, Ishrat et al. 2009, Xu et al. 2009, Wu et al. 2015). Curcumin was found to resist lipid peroxidation which is important because many structures in the brain, including the cell membranes of cells, are composed of lipids and preventing their β -amyloid-induced peroxidation is crucial to neurons being able to maintain their structure (Ishrat et al. 2009). Curcumin supplementation also increased the activity of anti-oxidative enzymes in both the hippocampus and the cerebral cortex (Ishrat et al. 2009). In this way, curcumin enhanced the anti-oxidant defenses in the brain (Lim et al. 2001, Ishrat et al. 2009, Xu et al. 2009). Curcumin also acts to inhibit neuroinflammation by promoting the activity of the peroxisome proliferator-activated receptor ($PPAR\gamma$) (Liu et al. 2016). $PPAR\gamma$ is a target of curcumin that acts to alleviate neuroinflammation, and activating this receptor modulates the inflammatory response to oxidation (Liu et al. 2016). Nano-curcumin, a curcumin derivative, has also been found to relieve inflammation and oxidative stress by reducing the activation of microglia 1 (M1) which a mediator of pro-inflammatory responses (Wang et al. 2019).

Summary

Both dietary DHA and curcumin reduce inflammation and oxidative stress induced by β -amyloid. Both dietary substances also prevent lipid peroxidation to protect the structures of cell

membranes. DHA does so through NPD1, a molecule with DHA as a precursor. Curcumin does so through promoting PPAR γ activity and by reducing M1 activation.

Preserving the BBB and enhancing LRP-1 levels in AD

DHA O3PUFAs

Vascular damage plays a role in the pathogenesis of AD since the loss of structural integrity of the BBB in AD allows blood plasma containing β -amyloid to enter the brain (Hooijmans et al. 2007, Zipser et. al 2007). The BBB becomes compromised when inflammation from oxidative stress weakens the BBB by increasing its permeability to β -amyloid (Magaki et al. 2018). DHA supplementation modulates the integrity of the BBB (Hooijmans et al. 2007). DHA, because it is able to cross the BBB, has been found to strengthen the structural integrity of the BBB (Yan et al. 2019). DHA promotes BBB clearance of β -amyloid, and the removal of β -amyloid from the brain promotes the strengthening of the BBB (Hong et al. 2015, Pan et al. 2018, Yan et al. 2019). This is because β -amyloid adheres to astrocytes (glial cells that support the neuron and regulates synapses) when it enters the brain thus weakening the glial cells that support the neurons in the BBB (Hooijmans et al. 2007, Zipser et. al 2007). Clearing β -amyloid from the brain and alleviating the amyloid plaque burden, consequently, preserves the BBB (Lim et al. 2005, Yan et al. 2019). The BBB is dependent on LRP-1 to clear β -amyloid from the brain, and DHA has been found to enhance the production of LRP-1 receptors in mice models meaning that more β -amyloid can be removed from the BBB (Yan et al. 2019).

Dietary DHA also protects against BBB being compromised by enhancing the expression of fatty acid-binding protein 5 (FABP5) (Pan et al. 2018). DHA's ability to travel across the BBB is modulated by FABP5, and low brain DHA is associated with low BBB expression of FABP5 (Pan et al. 2018). Supplementation with dietary DHA enhances the upregulation of

FABP5 which facilitates the transport of DHA across the BBB (Pan et al. 2018). Enhancing the transport of DHA across the BBB strengthens the integrity of the BBB because DHA helps to clear that β -amyloid (Yan et al. 2019).

DHA modulates the integrity of the BBB by increasing HDL cholesterol levels which act to decrease β -amyloid production and strengthen the BBB (Arafa et al. 2005, Hooijmans et al. 2007, Santoso et al. 2008). The excessive intake of LDL cholesterol impairs the vasculature of the BBB causing vulnerable areas of the brain to experience hypoperfusion, or reduced blood flow, which leads to β -amyloid accumulation, and CAA (Hooijmans et al. 2007). DHA also increased regional cerebral blood flow to the brain thus improving blood circulation in the brain (Hooijmans et al. 2007). DHA's ability to cross the BBB makes it a potential candidate for drug development (Yan et al. 2019).

Curcumin

Curcumin promotes BBB clearance of β -amyloid as well (Jiang et al. 2007). Curcumin is able to cross the BBB based on its ability to attenuate β -amyloid and reduce its toxicity in low doses (Ye and Zhang 2012). The removal of β -amyloid from the brain also promotes the strengthening of the BBB (Ye and Zhang 2012). Curcumin derivatives at low concentrations can preserve the BBB by alleviating β -amyloid toxicity as well as the amyloid plaques burden (Lim et al. 2019). The neuroprotective effect of curcumin lies within its high affinity for β -amyloid which is why curcumin binding to β -amyloid not only decreases the plaque burden but also helps to preserve the BBB (Lim et al. 2019, Shinzato et al. 2020). Insofar as enhancing the structural integrity of the BBB goes, curcumin has not been found to directly enhance LRP-1 levels in the BBB.

Curcumin also regulates the permeability of the BBB through curcumin derivatives known as “nano-curcumin” that protect the BBB by reducing M1 microglial activation (Jiang et al. 2007, Wang et al. 2019). M1 is a protein that mediates pro-inflammatory responses in the brain (Wang et al. 2019). Nano-curcumin protects the BBB by reducing oxidative stress and the resulting inflammation since inflammation weakens the structural integrity of the BBB by making it more permeable to toxic substances (Wang et al. 2019). Curcumin is also capable of protecting the ultrastructure of the BBB and reducing edema, or swelling caused by inflammation (Yu et al. 2012). Curcumin further modulates the strength of the BBB by increasing HDL cholesterol levels which act to decrease β -amyloid production (Arafa et al. 2005, Hooijmans et al. 2007, Santoso et al. 2008). Decreasing β -amyloid production means that there is less β -amyloid that can adhere to astrocytes and weaken the BBB. Since curcumin is able to cross the BBB, it is a potential candidate for drug development (Ye and Zhang 2012, Wang et al. 2019, Shinzato et al. 2020).

Summary

DHA and curcumin can both cross the BBB and are capable of strengthening the BBB that was compromised from β -amyloid making them good candidates for drug development. Both dietary substances also help modulate the BBB by increasing HDL cholesterol levels which acts to decrease β -amyloid. Decreasing β -amyloid production means that there is less β -amyloid that can adhere to astrocytes and weaken the BBB. DHA enhances the production of LRP-1 receptors thus enhancing β -amyloid clearance and making it so that more DHA can cross the BBB. Conversely, curcumin has not been found to directly enhance LRP-1 levels in the brain. Aside from clearing β -amyloid, DHA protects against disruption by enhancing FABP5

expression. Curcumin protects the BBB by reducing M1 activation and by reducing edema caused by inflammation. Although curcumin can cross the BBB just like dietary DHA, it is only effective in low doses on account of curcumin's low water solubility whereas dietary DHA can be effective in high doses as well as low.

Neurogenesis

In AD, the neurological process of neurogenesis, particularly in the hippocampus and cortex, is reduced (Scopa et al. 2020). Neurogenesis is yet another physiological process inhibited by the attenuation of β -amyloid peptides in AD (Haughey et al. 2002). Neurogenesis is the process by which neurons, the cells in the brain, are produced from neural stem cells (Gilbert et al. 2014). Contrary to popular belief, the process of the brain forming new neurons through neurogenesis is something that occurs throughout the adult life. Neurons, unlike somatic cells, do not divide through mitosis to form new neurons which is why they are formed from neural stem cells (Gilbert et al. 2014). Adult neurogenesis also occurs at a slower rate with low efficiency, compared to when neurogenesis occurs at the beginning of human life in embryos (Gilbert et al. 2014, Van et al. 2019).

In the average human adult, about 700 new neurons are added to the hippocampus each day (Spalding et al. 2013). The newly formed neurons, however, correspond to a high turnover rate, and the rate of neurogenesis declines with age as well (Spalding et al. 2013, Van et al. 2019). Neurogenesis in adults primarily occurs in the olfactory bulb and in the dentate gyrus of the hippocampus which is the region heavily involved in learning and memory (Alvarez-Buylla and Lim 2004, Kawakita et al. 2006). Neuronal differentiation is the process by which cells become specialized for a particular function and mature (Gilbert et al. 2014). Neural stems cells are capable of differentiating into either neurons or glial cells (the non-neuronal cells that support

and protect neurons) which is called fate-decision (Gilbert et al. 2014). Fate-decision is what the cells are determined to become before they differentiate (Gilbert et al. 2014). Promoting neurogenesis is important because β -amyloid and the other β -amyloid-induced factors that progress AD cause neurodegeneration and cell death which shrinks the AD brain. Neurogenesis helps to replace the neurons that have died off, and increasing the number of neurons also correlates with better cognitive performance (He et al. 2009, Dong et al. 2012).

DHA O3PUFAs

DHA has been found to promote hippocampal neurogenesis and cell proliferation thus helping to improve the AD prognosis (Lukiw et al. 2005, Kawakita et al. 2006). NPD1, which has DHA as a precursor, has its biosynthesis stimulated by α -secretase of APP which reduces β -amyloid in the hippocampus (Lukiw et al. 2005). Soluble APP- α peptide (sAPP α) promotes neurogenesis and long-term survival of hippocampal and cortical neurons (Lukiw et al. 2005, Kawakita et al. 2006). Neurogenesis is a type of neurogenesis and is the process of forming neurites which develop into the axons and dendrites of a neuron (Lukiw et al. 2005, Kawakita et al. 2006). NPD1, which is formed from DHA, causes sAPP α to further increase neurogenesis, and the development of dendrites and axons is what allows neurons to communicate (Lukiw et al. 2005, Kawakita et al. 2006).

DHA also increases neurogenesis by promoting the differentiation of neural stem cells into neurons (Kawakita et al. 2006). DHA plays an important role in the function of neurons and their development because neural stem cells have been shown to require lipids like DHA for the initiation of neurogenesis and for the neuronal proliferation making DHA important to the neurobiology of neural stem cells (Van et al. 2019). Lipidogenesis with DHA, therefore largely determines neural cell differentiation (Van et al. 2019). DHA promotes neural cell differentiation

into neurons by promoting cell cycle exit by suppressing apoptosis (Kawakita et al. 2006). DHA prevents the death of differentiating neural stem cells, and increases the survivability of newborn neurons (Kawakita et al. 2006). DHA also impacts the fate-decision of neural stem cells into neurons (Van et al. 2019). The maturation of neurons that have differentiated from neural stem cells is also promoted by DHA (Kawakita et al. 2006). Adequate intake of dietary DHA is important because it reduces the β -amyloid burden which stops neurogenesis from being inhibited by the toxic peptides (Haughey et al. 2002, Van et al. 2019).

Curcumin

Curcumin has also been found to promote hippocampal neurogenesis in order to improve the AD prognosis (Xu et al. 2009, Tiwari et al. 2013). An increased concentration of curcumin increases the number of dendritic branches in hippocampal neurons (Xu et al. 2009). Curcumin specifically promoted neurogenesis by targeting endogenous neural stem cells to modulate neural differentiation and neurogenesis (Tiwari et al. 2013). Curcumin induces the proliferation of neural stem cells in the hippocampal and cortical regions by altering mRNA transcription in genes, and promotes neuronal differentiation in mice models (Dong et al. 2012, Tiwari et al. 2013).

The expression of genes related to neuronal growth were promoted by curcumin treatment showing that curcumin reverses impaired hippocampal neurogenesis through altering gene expression (Dong et al. 2012). The expression of the NeuroD1 gene, a gene that promotes neurogenesis and the survival of neural stem cells, was enhanced in the cortex of curcumin-treated rats (Dong et al. 2012). The NeuroD6 gene, which regulates neuronal differentiation and energy metabolism, promoted neuronal survival and the expression of this gene was also

enhanced by curcumin treatment (Dong et al. 2012). The expression of the Wnt2 gene, which is involved in dendritic arborization (branching) and growth in adult neurogenesis, was upregulated in the hippocampus as a result of curcumin treatment (Dong et al. 2012). The Tiam1 gene, a gene vital to neurite outgrowth that modulates neuronal morphology (shape), was enhanced in the cortex from curcumin treatment (Dong et al. 2012). Curcumin also increases the expression of genes involved in neuronal differentiation such as neurogenin, neuro D1, neuregulin, neuroligin, and Stat3 (Tiwari et al. 2013).

The ability of curcumin to improve neurogenesis and cell proliferation primarily lies in curcumin's ability to up-regulate or enhance the expression of genes in the brain associated with neuronal development (Dong et al. 2012, Tiwari et al. 2013). Another important feature about the gene profiles of rats with prolonged curcumin treatment is that the genes that were previously indicated to participate in the neurodegenerative processes of AD represented a large percentage of the total number of genes altered by curcumin (Dong et al. 2012). Prolonged curcumin treatment has the potential to act as a mechanistic mediator for governing the adult neurogenesis and cell proliferation in the cortex and hippocampus by enhancing gene expression and modulating neuronal networks that coordinate neurogenesis (Dong et al. 2012, Tiwari et al. 2013).

Summary

DHA and curcumin both promote hippocampal neurogenesis and cell proliferation thus helping to improve the AD prognosis. Both DHA and curcumin also promote neuriteogenesis, neural stem cell differentiation, and neuronal fate decision. DHA promotes neurogenesis and cell proliferation through NPD1 interacting with sAPP α , promoting the maturation of neurons, and by promoting the differentiation of neural stem cells. Curcumin promotes neurogenesis and cell

proliferation by increasing the number of dendritic branches, targeting endogenous neural stem cells to modulate neural differentiation, and by promoting the expression of genes that promote neurogenesis.

Improving memory and learning

DHA O3PUFAs

Deficits in short-term memory and learning ability are a characteristic part of AD largely caused by synaptic dysfunction and amyloid plaques. Dietary DHA has been found to benefit cognition and learning, and has been found to alleviate some deficits in memory (Minami et al. 1997, Gamoh et al. 1999, Moriguci and salem 2003, Lim et al. 2005). It was found using a mice model that feeding multiple generations of mice diets lacking DHA O3PUFAs limits their learning ability and spatial task performance, but learning was restored when their diets were switched to ones that were supplemented with DHA (Moriguci and salem 2003). It was also found that animals given a DHA-rich diet since birth or weaning were able to achieve almost the same level of brain DHA and spatial task performance as the same animals that were maintained on a DHA-rich diet for three generations (Moriguci and salem 2003). This demonstrates that some loss of brain function associated with low DHA levels can be reversed through a DHA-rich diet (Moriguci and salem 2003).

DHA administration for 12 weeks was also found help modulate reference and working memory errors as well as spatial cognition in rats infused with β -amyloid as results from the Morris water maze navigation task demonstrated (Gamoh et al. 1999, Hashimoto et al. 2005). Reference memory involves using information that remains constant over time whereas working memory involves holding on to information that is only pertinent within a short period of time.

Following the administration of a DHA-rich diet, the number of working memory errors in young rats decreased (Gamoh et al. 1999). DHA administration improved long-term memory in both young and old rats (Gamoh et al. 1999, Hashimoto et al. 2005). DHA administration also increased both the cortical and the hippocampal levels of DHA which suggested the improvement of impaired spatial cognition learning ability (Hashimoto et al. 2005). Long-term potentiation, the strengthening of synapses based on patterns of activity, was also improved by DHA supplementation (Minami et al. 1997, Hashimoto et al. 2005). DHA is crucial for long-term potentiation because it DHA not only reverses impairment in long-term potentiation, but DHA triggers the expression of long-term potentiation (Minami et al. 1997, Hashimoto et al. 2005).

Cholinergic dysfunction in AD causes more β -amyloid peptides to be produced, and is partially responsible for impaired learning ability (Minami et al. 1997). DHA rescues learning ability and improves passive avoidance performance by ameliorating the reduction in acetylcholine levels in the brain (Minami et al. 1997). Spatial learning performance also increased with enhanced DHA-induced neurogenesis (He et al. 2009). This is because growth in terms of neuronal proliferation, or the number of neurons, correlates with improved spatial memory (He et al. 2009). DHA's ability to decrease oxidative stress also improved short-term memory in terms of immediate recall (Mazereeuw et al. 2017).

Curcumin

Curcumin has also been found to benefit cognition and learning, and has been found to alleviate some deficits in memory (Hoppe et al. 2013b). Curcumin treatment was found to improve both short-term and long-term recognition memory in rat models indicating that

curcumin enhanced the animals' ability to distinguish between familiar and new one objects (Hoppe et al. 2013b). Cognitive performance in rat models in the passive avoidance task and spatial task performance when the Morris water maze navigation task was used was improved with curcumin treatment (Ishrat et al. 2009, Xu et al. 2009). The passive avoidance task measures the ability for an organism to avoid an area or path where an adverse stimulus was delivered, and the spatial task measures the ability to perceive spatial relationships in respect to body orientation amidst environmental distractions. Specifically, curcumin reversed impaired spatial memory in the the Morris water maze navigation task as evidenced by decreased escape latencies (Xu et al. 2009, Liu et al. 2016).

Learning and memory impairments in the β -amyloid infused rat model of the AD phenotype can also be rescued by curcumin's ability to induce neurogenesis and cell proliferation (Dong et al. 2012, Tiwari et al. 2013). An increase in the number of neurons from curcumin-induced hippocampal proliferation correlates with improved spatial memory which shows the memory-enhancing ability of curcumin in the promotion of neurogenesis (Dong et al. 2012). For this reason, spatial memory was improved significantly after 12 weeks of curcumin treatment (Dong et al. 2012). Curcumin's ability to alleviate oxidative stress also improves spatial memory deficits (Ishrat et al. 2009, Dong et al. 2012). Curcumin derivatives also rescue long-term potentiation and thus modulate synapses by enhancing synapse strength through long-term potentiation (Ahmed et al. 2011).

Curcumin supplementation also restored ChAT activity and promoted cholinergic neuronal function in the hippocampus, and this restoration ameliorated the deficits in learning and memory (Ahmed et al. 2009, Ishrat et al. 2009, Liu et al. 2016). This is important because cholinergic neurons play a crucial role in memory function, and cholinergic dysfunction

underlies most of the short-term memory loss observed in the AD disease pathology (Ahmed et al. 2009, Liu et al. 2016).

Summary

Both dietary DHA and curcumin have been found to improve memory and learning. DHA-induced neurogenesis and curcumin-induced neurogenesis both correlated with improved spatial memory. Both substances improved short as well as long-term memory, working memory, reference memory, and long-term potentiation. Both DHA and curcumin also improved spatial memory deficits by promoting cholinergic function since cholinergic neurons play a crucial role in memory and underlie most of the short-term memory loss in AD.

Human trials of these Dietary Substances

Many trials and experiments testing the effectiveness of dietary substances in improving the AD prognosis use mice or rat models to demonstrate findings *in vivo*. Mice and rat models provide invaluable insight about the effect of dietary substances on brain areas, since mice share over 90% of DNA and genes with humans and have the same areas of the brain (Chinwalla et al. 2002). They are also useful laboratory models because experiments are able to be done on them that may not be feasible or ethical in humans. Despite the fact that there are many benefits to using animal models, and despite the fact that discoveries about the impact of dietary substances on the brain are comparable to the likely effect on human brains, it is still important to examine studies that show the impact of these substances on humans nevertheless.

DHA O3PUFAs

In the Levi et al. 2014 study, 33 patients were examined with 18 receiving the DHA supplement and 15 receiving placebo in a double-blind, placebo-controlled randomized study (Levi et al. 2014). At 6 months, the DHA supplement group showed significant increases in DHA levels in the cerebrospinal fluid whereas no changes were observed in the placebo group (Levi et al. 2014). Levels of DHA in the cerebrospinal fluid were correlated with prolonged DHA oral supplementation suggesting the transfer of DHA across the BBB (Levi et al. 2014). The transfer of DHA across the BBB, therefore, improved after oral dietary supplementation with DHA as evidenced by the profile of the cerebrospinal fluid (Levi et al. 2014). These findings are consistent with experiments done in mice models showing that DHA treatment reduces β -amyloid and improves AD-related deficits (Levi et al. 2014). Increased DHA content is associated with improved cognition and a decreased risk of cognitive loss in normal aging largely because of its ability to reduce β -amyloid in the brain and improve synaptic function (Levi et al. 2014).

Another study done by Morris et al. 2003 followed a random sample of a geographically defined community from 1993 to 2000 with participants being followed up for 3.9 years on average for the development of AD (Morris et al. 2003). The study was comprised of 815 people total aged 65-94 years old who were unaffected by AD and completed a dietary questionnaire 2.3 years prior to clinical evaluation for AD through neurological examination via 4 cognitive tests in a 90-minute interview (Morris et al. 2003). A total of 131 participants developed AD, and it was found that participants who consumed fish as a source of DHA had a 60% less risk of AD compared with those that never or seldom ate fish (Morris et al. 2003). This demonstrates that

dietary intake of DHA was associated with a lower risk of AD which aligns with similar studies done on mice models (Morris et al. 2003). These findings are significant because it provides the epidemiologic evidence supporting the link dietary DHA and cognitive performance in human subjects (Morris et al. 2003).

Curcumin

In the Zhang et al. 2006 study, the macrophages of 6 patients were treated *in vitro* with curcumin derivatives so that β -amyloid uptake using fluorescence and confocal microscopy could be examined and compared to 3 controls also with AD (Zhang et al. 2006). Following the treatment of the macrophages with curcumin, 3 out of 6 AD patients showed a significant decrease in β -amyloid, whereas there was no change in the controls (Zhang et al. 2006). The confocal microscopy of the AD macrophages displayed surface binding of curcumin to β -amyloid in untreated macrophages in response to the treatment (Zhang et al. 2006). Curcumin strongly stimulated uptake of β -amyloid by macrophages in the participants that the experiment had an effect on (Zhang et al. 2006). These results are consistent with other literature on mice models that show curcumin modulating β -amyloid levels (Zhang et al. 2006). This demonstrates curcumin's ability to help stimulate the immune system to clear more β -amyloid, and makes sense given curcumin's ability to cross the BBB (Zhang et al. 2006).

Another study done by Ng et al. 2006 examined the association between curcumin consumption through curry and cognitive function by following the dietary habits of a random sample of 1,092 adults aged 60-93 from 2003-2004 based on how often they consumed curry which is primarily made from curcumin (Ng et al. 2006). The study compared mini-mental state examination (MMSE) scores of the participants based on three categories of curry consumption: never or rarely, occasionally, and often or very often (Ng et al. 2006). It was found that

participants who consumed curry occasionally or often/very often has significantly better MMSE scores in comparison to subjects that consumed curry never or rarely (Ng et al. 2006). Increased consumption of curry is associated with better cognitive performance in participants, and curry consumption also lowered the risk for dementia and AD in the elderly (Ng et al. 2006). Despite these findings, higher levels of curry consumption were not associated with better cognitive performance due to the lack of statistical significance in differences between the “occasional” and “often” curry consumption groups (Ng et al. 2006). This is consistent with experiments done in mice models showing that low rather than high-dose curcumin treatment reduces β -amyloid and improves AD-related deficits (Ng et al. 2006). These findings are significant because it provides the first epidemiologic evidence supporting the link between curry consumption and cognitive performance in human subjects (Ng et al. 2006).

Summary

DHA and curcumin were both found to be effective in older adults. DHA and curcumin both reduced the risk of developing AD. Dietary DHA increased the amount of DHA in cerebrospinal fluid, and was associated with a reduced risk of AD. Curcumin was found to be effective in the treatment of AD macrophages in β -amyloid clearance, and was associated with a reduced risk of AD. The findings for the effects of DHA and curcumin in humans align with experiments that tested these same hypothesis on mice models. These human experiments exploring the neurological impact of both DHA and curcumin are significant because it provides epidemiologic evidence supporting the link between diet and cognitive performance in human subjects.

Conclusion

Both DHA O3PUFAs and curcumin have both been scientifically proven to be effective in clearing β -amyloid and modulating other β -amyloid induced factors in the AD pathogenesis. DHA O3PUFAs and Curcumin clear β -amyloid and have been found to promote DHA development in the brain, improve cholesterol levels, improve acetylcholine levels in the AD brain, improve synapses, alleviate inflammation and oxidative stress, preserve the BBB, promote neurogenesis, improve memory and learning, and prevent cell death.

A poor or a healthy diet not only impacts the body, but also plays a major role in brain health (Hanson et al. 2013). Typical American diets far exceed the recommended daily intake of calories, and many foods contain a superfluous amount of LDL cholesterol, sugar, sodium, fat, and processed chemicals that increase the risk for cognitive decline. With the treatment options for AD being both limited and expensive, exploring the link between diet and AD is such a crucial endeavor to undertake in order to slow the progression of the disease. The fundamental goal of this research was to examine both DHA O3PUFAs and curcumin in order to investigate their ability to clear β -amyloid and alleviate aspects of the AD pathology induced by β -amyloid.

Eating a diet with more of these substances can help in clearing β -amyloid as well as mediating the aspects of AD pathology induced by β -amyloid. While many AD treatments target one aspect of the disease, AD, as demonstrated by the sections above, is a multi-faceted disease, the cause of which is not completely understood with many factors being involved. Exploring dietary substances as viable treatment options is worth looking into because only five FDA-approved drugs are currently used to treat AD, so exploring more treatment options is necessary (Alzheimer's Association). A dietary increase in DHA O3PUFAs and curcumin has the potential to exhibit widespread effects in treating AD without the harmful side-effects of pharmaceutical drugs which often serve as a "one-size-fits-all" solution to a complex problem. Learning about

what natural dietary substances increase slow the progression of AD has serious implications for improving the conditions of the millions of people living with AD in terms of increasing life expectancy, creating a healthier way of life, and coming closer to eventually finding a cure for AD.

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