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LOMA LINDA UNIVERSITY
School of Behavioral Health
in conjunction with the
Department of Psychology

Dietary Fatty Acids and the Brain: Mechanisms Behind
Neurodegeneration and Neuroprotection

by

Bianca Kdeiss

A Project submitted in partial satisfaction of
the requirements for the degree
Doctor of Psychology

September 2022

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Each person whose signature appears below certifies that this doctoral project in her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Psychology.

_____, Chairperson
Grace J. Lee, Professor of Psychology

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ABBREVIATIONS

ACh	Acetylcholine
ALA	α -Linolenic-Acid
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CREB	Cyclic AMP-Response Element-Binding Protein
COX	Cyclooxygenase
EPA	Eicosapentaenoic Acid
DHA	Docosahexaenoic Acid
HbA1c	Hemoglobin A1c
HPA	Hypothalamic-Pituitary-Adrenal
IL-1 β	Interleukin-1 β
IL-6	Interleukin-6
LTP	Long-Term Potentiation
LDL	Low-Density Lipoprotein Cholesterol
MCI	Mild Cognitive Impairment
MI	Myocardial Infarction
MUFA	Monounsaturated Fatty Acids
PUFA	Polyunsaturated Fatty Acids
PGE ₂	Prostaglandin E ₂
ROS	Reactive Oxygen Species
SFA	Saturated Fatty Acids
TFA	Trans Fatty Acids

TNF- α

Tumor Necrosis Factor- α

T2DM

Type 2 Diabetes Mellitus

ABSTRACT OF THE DOCTORAL PROJECT

Dietary Fatty Acids and the Brain: Mechanisms Behind Neurodegeneration and Neuroprotection

by

Bianca Kdeiss

Doctor of Psychology, Graduate Program in Psychology
Loma Linda University, September 2022
Dr. Grace J. Lee, Chairperson

The impact of dietary fat intake on cognitive function has generated growing interest as the incidence of neurodegenerative disorders continues to increase. No known cures for neurodegenerative disorders exist at this time and available pharmacological treatments are limited in their efficacy. As such, prevention and early detection have been emphasized, particularly in the context of modifiable lifestyle factors, such as diet. Despite a recognized association between dietary fat intake and cognition, limited research exists delineating the impact of different types of fat on cognitive function. In this review, research examining the association between cognition and specific dietary fatty acids—such as trans fatty acids (TFA), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA)—was investigated. Further, the mechanisms by which these fatty acids impact cognition were explored. Findings from the literature identified cardiovascular function, inflammation, oxidative stress, brain-derived neurotrophic factor, and insulin resistance as the most explored biological mechanisms to date. As such, each biological mechanism is briefly defined and considered in the context of a neuropsychological profile, followed by a review of the influence of fatty acids on these mechanisms.

CHAPTER ONE

INTRODUCTION

Cognitive decline is an inevitable aspect of the aging process (Colsher & Wallace, 1991), and, while some degree of decline may be considered a “normal” part of aging, more significant difficulties may reflect underlying neuropathology once the decline is severe enough to interfere with daily functioning. The specific areas of cognition, as well as the course of decline, vary considerably across individuals (Deary et al., 2009; Salthouse, 2004), depending on a variety of factors such as genetics, age-related brain changes, obesity, cardiovascular disease, and lifestyle factors such as diet and exercise.

To date, there are no known cures for neurocognitive disorders, and the potential benefits of select pharmacological treatments are limited (Buckley & Salpeter, 2015; Fink et al., 2018; Raina et al., 2008). As such, prevention and early detection are becoming principal areas of emphasis in research. One avenue of investigation that is increasingly prominent is diet. Diet is easily modifiable and has been significantly associated with brain and cerebrovascular health. As such, dietary factors present a feasible, cost-effective approach to the improvement of cognitive functioning.

Despite the existing research exploring cognitive functioning and dietary factors, there is still much that is unknown. Preliminary findings have been inconsistent with regard to specific foods, micronutrients, and dietary patterns associated with cognitive functioning. One area of recent interest has been the influence of dietary fatty acids. Some dietary fatty acids are thought to have a positive, and others negative, impact on the brain. This review will examine the connection between dietary fatty acids and cognitive

functioning and explore the mechanisms by which these dietary fatty acids influence cognitive functioning.

Age-Related Cognitive Decline

Age-related cognitive decline (ARCD) refers to mild levels of cognitive decline that are non-pathological and typical of normal aging (Petersen et al., 2001). The onset of ARCD has been widely debated. Many findings suggest that some aspects of ARCD can begin as early as in one's 20s or 30s (Salthouse, 2009). It is often the case that there are no observable symptoms of this subtle age-associated type of decline, but it is still generally believed that all aging humans will eventually progress to some level of cognitive decline (Colsher & Wallace, 1991). ARCD may simply be the result of an aging brain, but it may also indicate a more serious but treatable medical condition that requires attention (Small, 2002). ARCD usually impacts cognitive domains associated with processing speed, working memory, and executive functioning. Previous findings have demonstrated that a decrease in processing speed may be typical of aging (Salthouse, 2010; Harada, Love, & Triebel, 2013). Deficits in acquiring and retrieving new information may also be expected, however, attention generally remains unaffected (Craik & McDowd, 1987; Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992; Rabinowitz & Craik, 1986; Small, Stern, Tang, & Mayeux, 1999). Additionally, it is well-documented that the efficiency of executive functioning declines with normal aging (Buckner, 2004; Harada, Love, & Triebel, 2013).

While some decline in cognition is considered a normal part of the aging process, in some cases, it may represent an early symptom of an underlying pathological process

that could eventually progress to more severe cognitive dysfunction. Mild cognitive impairment (MCI) is a term used to denote a level of decline that exists between normal aging and dementia. Individuals with MCI may experience mild impairments in domains of attention, processing speed, language, visuospatial functioning, executive functioning, and memory; however, these impairments are not severe enough to impact daily functioning (Petersen, 2004). Widely accepted clinical and research criteria generally identify performance that is 1.5 standard deviations below the mean in one or more domains to be consistent with an MCI diagnosis (Petersen et al., 1999). Individuals with MCI have a higher likelihood of progressing to dementia, although it is not necessarily guaranteed that their diagnosis will progress in this manner (Palmer, Fratiglioni, & Winblad, 2003; Petersen, 2004). Additionally, this likelihood depends on a variety of other factors, including the initial severity of cognitive impairment, the pattern of domains impacted, reductions in brain volume—especially hippocampal volume, genetic contribution, and lifestyle factors (Morris et al., 2001; Whitwell, 2007; Jack et al., 1999; Petersen et al., 1995; Etgen, Sander, Bickel, & Förstl, 2011).

Dementia

Unlike ARCD, dementia is not considered part of the normal aging process. It is a pathological condition that signifies a significant change from premorbid functioning that interferes with an individual's ability to function in their daily life. As individuals begin to exhibit symptoms of decline in multiple cognitive domains, independent living becomes a significant challenge. It is estimated that approximately 50 million people around the world are living with dementia, with nearly 10 million new cases diagnosed each year (World

Health Organization [WHO], 2017). Dementia can be caused by a number of different underlying neuropathological diseases, some of which are irreversible while others tend to be progressive, with cognitive difficulties worsening over time. The two most prevalent underlying causes of dementia are Alzheimer's disease and vascular dementia.

Alzheimer's Disease

Alzheimer's disease, the most common type of dementia, is a progressive, neurodegenerative condition in which there is a decline in multiple cognitive domains that eventually impact one's ability to live and function independently. Alzheimer's disease accounts for approximately 60%-70% of dementia cases and is the sixth leading cause of death in the United States (WHO, 2017; Alzheimer's Association, 2019). Memory impairment is often the primary indicator of an Alzheimer's disease diagnosis, with further impairment in other domains such as language and visuospatial functions to follow. With Alzheimer's disease, there is typically an insidious onset of the disease, and the course of decline is characteristically gradual and progressive. The exact cause is still unknown; however, research suggests two major neuropathological hallmarks of Alzheimer's disease, namely extracellular amyloid plaques and intracellular neurofibrillary tangles.

According to the amyloid hypothesis, an atypical accumulation of plaques in the medial temporal lobe, particularly in the hippocampal formation and entorhinal cortex, is identified to be a significant feature of the Alzheimer's disease process (Wirhth, Multhaup, & Bayer, 2004). These brain regions are essential to learning and memory, which in part explains why memory impairment is typical with the progression of Alzheimer's disease pathology. These extracellular plaques are predominantly composed of amyloid- β ($A\beta$)

peptides. The formation of these peptides is primarily a result of the cleavage of larger amyloid precursor proteins (APP) by two proteases, β -secretase and γ -secretase, into insoluble chains of 39-43 amino acids (Vassar et al., 1999; Oakley et al., 2006). Following cleavage by these enzymes, these A β peptides begin to cluster in significant areas of the brain, sticking to each other and developing into amyloid plaques. The presence of these plaques begins to disrupt neuronal function and communication, ultimately resulting in neuronal cell death. Plaque buildup often goes unnoticed for some time, as there is initially no clinical presentation of decline during these early accumulation periods. Early detection is central in managing the progression of the disease, but since the disease is often asymptomatic in initial stages, early detection proves to be especially challenging.

The tau hypothesis proposes that the hyperphosphorylation of tau protein results in the atypical accumulation of neurofibrillary tangles within cells, which additionally plays a role in the development of Alzheimer's disease (Grundke-Iqbal et al., 1986). Tau is highly soluble and typically functions to stabilize microtubules by interacting with tubulin (Medeiros, Baglietto-Vargas, & LaFerla, 2011; Weingarten, Lockwood, Hwo, & Kirschner, 1975). In Alzheimer's disease, tau phosphorylation occurs at greater rates, ultimately resulting in fibrillization and accumulation (Alonso, Grundke-Iqbal, & Iqbal, 1996). These uncharacteristic amounts of tau aggregating within neurons generate neurofibrillary tangles which disrupt neuronal function and communication.

Cerebrovascular Disease

Vascular dementia is the second most common type of dementia (WHO, 2017). It has been estimated that vascular dementia constitutes approximately 5%-10% of dementia

cases diagnosed, although this is seen as a conservative estimate as vascular dementia is often underdiagnosed (AA, 2019). Vascular dementia is said to result from impaired blood circulation to various regions of the brain, ultimately leading to impairment in a range of cognitive domains. Several complications may lead to a disruption of blood flow, but stroke and blood vessel damage most commonly explain this disruption. The types of cognitive deficits exhibited with vascular dementia can vary widely, as such deficits largely correspond to the areas of the brain in which there exists sufficient damage of the blood vessels. As such, there is no single impairment or constellation of impairments that signifies a vascular dementia diagnosis (Jellinger, 2007), and determining a single, well-defined classification of vascular dementia has proven to be challenging, as a wide range of etiologies is often involved in contributing to the underlying cerebrovascular disease (CVD). Any vascular change that impacts the brain's blood vessels or blood supply can be classified as CVD. CVD most often presents in the form of ischemic strokes or cerebral ischemic injury (Kalaria, 2018). Two of the main forms of CVD, small-vessel disease and large-vessel disease, help further explain the etiology of vascular dementia.

Large-vessel disease (LVD) is primarily characterized by multiple, large cortical infarcts or strategic infarcts (Kalaria, 2018; Johns, 2014). Large cortical infarcts are a series of strokes that damage large areas of the brain, resulting in significant consequences, such as brain atrophy. Consequences of these strokes are dependent on the area of the brain in which the stroke occurred. By contrast, strategic infarcts are territorial strokes that occur in areas of the brain that control fundamental tasks, such as the basal ganglia, thalamus, or hippocampus (Kalaria, Akinyemi, & Ihara, 2016). Despite LVD as a significant contributing factor, small vessel disease is now recognized as the most prominent indicator

of vascular dementia (Wardlaw, Smith, & Dichgans, 2013).

Cerebral small-vessel disease (SVD) is the most common pathological feature associated with vascular dementia (Johns, 2014; Kalaria, 2018). SVD is a term that refers to irregularities associated with the small blood vessels in the brain. SVD can encompass a wide range of irregularities such as lacunar infarcts or white matter hyperintensities (Staekenborg et al., 2010). These irregularities are often a consequence of arteriosclerosis, the hardening of the artery walls. Such rigidity is problematic, as it becomes difficult for blood vessels to dilate and constrict in order to accommodate fluctuations in blood pressure (Johns, 2014). This limited elasticity of the blood vessels commonly leads to small strokes referred to as lacunar infarcts. One type of arteriosclerosis, also known as atherosclerosis, additionally explains SVD pathology. Atherosclerosis, an accumulation of plaque in the walls of arteries, can result in damaged blood vessels as well. When small blood vessels are damaged, the typical outcome is ischemia, restricted blood flow to the brain, or hemorrhage, substantial blood flow to the brain, ultimately resulting in the death of brain cells. Other consequences of SVD include edema and damage to the blood-brain barrier (Wardlaw, 2010).

Risk factors for vascular dementia include many of the same risk factors for cardiovascular disease, stroke, or other associated diseases that contribute to vascular changes (Gorelick, 2004). The major vascular risk factors identified include hypertension, diabetes mellitus, and hyperlipidemia (Baumgart et al., 2015; Breteler, 2000). Hypertension, specifically during midlife, is a risk factor for stroke and coronary heart disease, ultimately leading to an increased risk of developing vascular dementia (Breteler, 2000; Van De Vorst et al., 2016). Hypertension also contributes to a greater incidence of

senile plaques and neurofibrillary tangles in the brain, as seen in Alzheimer's disease (Sparks et al., 1995). Diabetes mellitus, another risk factor of vascular dementia, is associated with micro- and macro-vascular changes. The presence of diabetes mellitus has been connected with a greater likelihood of developing coronary, cerebrovascular, and peripheral arterial disease and additionally contributes to vascular irregularities through characteristic features of the disease, such as insulin resistance and the increased presence of fatty acids (Creager et al., 2003). Finally, hyperlipidemia is a risk factor for cerebrovascular disease as well as a dementia (Van De Vorst et al., 2016). Particularly, hyperlipidemia is associated with increased levels of low-density lipoprotein and triglycerides, increasing atherosclerosis and ischemic stroke risk (Freiberg, Tybjærg-Hansen, Jensen, & Nordestgaard, 2008).

Treatment Options

There are a limited number of pharmacological treatments available for the management of dementia. Pharmacological treatments for Alzheimer's dementia typically include NMDA receptor antagonists, such as memantine, or cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine. These treatments can result in modest benefits for the individuals taking them, however, these benefits are limited. No particular pharmacological treatments approved by the U.S. Food and Drug Administration (FDA) are available for the management of vascular dementia; however, findings from clinical trial research indicate that particular pharmacological treatments approved for Alzheimer's dementia may yield modest benefits for individuals with vascular dementia (AA, 2019). Disease modifying pharmacological treatments are not yet established. Additionally, other

forms of treatment, such as psychological and behavioral treatments, have limited efficacy at this time.

Dietary Fatty Acids

The consumption of dietary fat in significant amounts is often associated with adverse effects on the body, such as obesity, metabolic syndrome, and chronic illness (Abete, Astrup, Martínez, Thorsdottir, & Zulet, 2010). Despite these identified negative effects, however, certain dietary fats are both beneficial and necessary to the functioning of the body. Fatty acids are fundamental sources of energy for cells and are found in various foods and oils. Additionally, different fats are necessary for good health, normal metabolism, and vitamin absorption and transportation (Di Pasquale, 2009).

Dietary fatty acids are generally categorized into four major groups: trans fatty acids (TFA), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). The type of fatty acid is determined by its chemical structure. PUFAs, in particular, can be classified into either omega-3 (n-3) or omega-6 (n-6) fatty acids. The n-3 PUFAs can be further broken down into α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA); the n-6 PUFAs include linoleic acid (LA) and arachidonic acid (Caracciolo, Xu, Collins, & Fratiglioni, 2014). Notably, ALA and LA are considered essential fatty acids, because unlike other fatty acids, they are not able to be synthesized within the body but are necessary for the body (McNamara, Asch, Lindquist, & Krikorian, 2018; Kummerow, 2009; Simopoulos, 1991).

Dietary Fatty Acids and Cognition

Diet is becoming a prominent focus of research in intervention and treatment planning, as dietary adjustments are often more accessible and cost-efficient than other suggested methods of cognitive health maintenance or cognitive decline prevention, such as medication use or cognitive training. Diets high in TFAs and SFAs have been identified as risk factors for cognitive functioning (Solfrizzi et al., 2008; Eskelinen et al., 2008; Greenwood & Winocur, 1996). SFA, in particular, has been shown to impair learning and memory performance in rats (Greenwood & Winocur, 1990; Winocur & Greenwood, 1993). High SFA intake at midlife is also associated with an increased risk of mild cognitive impairment (MCI) as well as reductions in global cognitive function and prospective memory (Eskelinen et al., 2008). In contrast, greater dietary proportions of MUFA and PUFA to SFA have been observed to decrease rates of cognitive decline and even be neuroprotective (Morris & Tangney, 2014; Roberts et al., 2010; Solfrizzi et al., 2008). Greater PUFA intake at midlife is associated with enhanced semantic memory, and greater PUFA to SFA ratio is associated with improved psychomotor processing speed and executive functioning (Eskelinen et al., 2008). Preliminary evidence suggests that PUFA intake decreases β -amyloid ($A\beta$) levels, a peptide implicated in the development of Alzheimer's disease (Solfrizzi et al., 2008).

Select reviews have begun to address the mechanisms underlying the associations between high fat diets and cognitive impairment (Freeman, Haley-Zitlin, Rosenberger, & Granholm, 2014; Kanoski & Davidson, 2011). Current research provides limited information regarding the neurodegenerative or neuroprotective properties of each major dietary fatty acid and the mechanisms responsible. This review further examines and

delineates these mechanisms in the context of each dietary fatty acid to further our understanding of the potential benefits of modifying diet to prevent or delay cognitive decline.

CHAPTER TWO

MECHANISMS

Despite what is generally understood about diet-induced cognitive changes, the mechanisms by which dietary fatty acids affect cognitive functioning have not been well-established. At this time, the most explored biological mechanisms include cardiovascular function, inflammation, oxidative stress, brain-derived neurotrophic factor, and insulin resistance. We review each of these mechanisms, placing particular emphasis on the different types of dietary fatty acids and their potential roles in neurodegeneration or neuroprotection. Although each mechanism is discussed in its respective section, it is important to recognize these mechanisms likely do not work in isolation; rather, many co-occur or even influence the function of other mechanisms. As such, understanding the complex nature of these mechanisms is a necessary initial step in approaching nutrition as a primary preventative strategy regarding cognitive functioning.

Cardiovascular Function

Cardiovascular functioning concerns the heart and overall vasculature of the body. Relevant issues include, but are not limited to, atherosclerosis, stroke, high blood pressure, myocardial infarction, and coronary artery disease. Notably, cardiovascular dysfunction has often been linked to frontal-executive impairment, including decreased performance in cognitive flexibility, selective attention, logical abstract thinking, and immediate verbal retrieval (Santangelo et al., 2010; Garrett et al., 2004). In a study exploring amnesic MCI and MCI with a vascular etiology, the most prominent difference identified in the cognitive profile was the impairment of frontal functions observed in individuals with a vascular

contribution (Galluzzi, Sheu, Zanetti, & Frisoni, 2005). Further, nondemented individuals with vascular abnormalities (e.g., lacunar infarcts in the deep white matter) exhibit significant frontal lobe dysfunction compared to nondemented individuals without vascular lesions, as measured on a task of verbal fluency (Santangelo et al., 2010). Finally, frontal dysfunction in individuals with vascular risk factors also impacts global cognitive functioning as well as domains of attention, processing speed, and learning and memory (Jones, Laukka, Small, Fratiglioni, & Bäckman, 2004; Waldstein & Wendell, 2010).

Studies demonstrate the effects of dietary fats on cardiovascular function. Mice placed on a high TFA diet exhibit significantly larger atherosclerotic lesions than mice on either a MUFA or control diet (Monguchi et al., 2017). Further, following nonfatal myocardial infarction, rats on a TFA diet demonstrated aortic atherosclerotic lesions, early-stage plaque development, and reduced collateral growth (vascular remodeling to bypass arterial occlusions; Siddiqui et al., 2009). Additionally, SFA may influence vascular functioning through hypertension. SFA, along with sodium and added sugars, should be reduced in dietary intake, as they promote obesity and hypertension (Livingstone & McNaughton, 2017). Several epidemiological studies also demonstrate the association between dietary fat intake and cardiovascular function. In one analysis of the Nurses' Health Study, a direct relationship between TFA and coronary heart disease risk was noted, particularly among women under age 65 or with a body mass index of ≥ 25 kg/m². Coronary heart disease risk was defined as incidence of nonfatal myocardial infarction (MI) or coronary heart disease related death (Oh, Hu, Manson, Stampfer, & Willett, 2005). Findings from the Health Professionals Follow-Up Study, a study conducted to compliment the Nurses' Health Study, support the idea that SFA and cholesterol intake are similarly

associated with coronary heart disease in middle age and older men (Ascherio et al., 1996). Additionally, findings from the Seven Countries Study further suggest that dietary intake of SFA, TFA, and cholesterol contribute to high mortality rates from coronary heart disease (Kromhout et al., 1995). Taken together, these findings generally suggest a detriment of TFA and SFA intake on cardiovascular functioning.

In contrast to TFA and SFA, moderate PUFA intake is associated with decreased cardiovascular risk. Post-MI survival in rats is improved by a PUFA diet compared to a TFA diet, and PUFA intake prevented the development of atherosclerotic lesions and vascular dysfunction (Siddiqui et al., 2009). Similarly, low-density lipoprotein cholesterol (LDL) receptor knockout mice were placed on either an n-6 PUFA rich diet or a MUFA rich diet. These two groups of mice were then crossed over to a high fat diet. The initial n-6 PUFA rich diet group demonstrated reduced aortic lesions and plasma lipids even after the high fat conversion (Penumetcha, Song, Merchant, & Parthasarathy, 2012). Analyses from the Nurses' Health Study also suggest a decreased risk of coronary heart disease with greater PUFA intake, likely through an omega-3 fatty acids mechanism such as the acids found in fish (Oh, Hu, Manson, Stampfer, & Willett, 2005; Hu et al., 2002). The benefits of fish consumption were corroborated in an analysis using data from the Cardiovascular Health Study. Specifically, n-3 PUFAs, chiefly DHA and EPA, have been shown to reduce the risk of fatal ischemic heart disease in a geriatric population (Lemaitre et al., 2003). As greater n-6 PUFA to n-3 PUFA ratio is characteristic of the Western diet, cardiovascular disease risk was also examined in rats fed diets with similar total fat amounts but varying n-6 PUFA to n-3 PUFA ratios (i.e., 1:1, 5:1, 10:1, 20:1). Less n-6 PUFA to n-3 PUFA intake is associated with lower serum levels of cholesterol, LDL, interleukin-6 (IL-6),

tumor necrosis factor- α (TNF- α), and oxidative stress, which in turn decreased cardiovascular disease risk (Yang et al., 2016). Diets high in ALA have also been shown to decrease serum lipid and lipoprotein levels, in turn decreasing cardiovascular risk in those with moderate hypercholesterolemia and a body mass index between 25-35 kg/m² (Zhao et al., 2004). Additionally, the Health Professionals Follow-Up Study revealed an inverse relationship between LA and MI risk (Ascherio et al., 1996). Overall, PUFA intake, n-3 PUFA in particular, appears to promote the best cardiovascular outcomes compared to other dietary fatty acids.

Inflammation

Inflammation is the immune system's response to infection, illness, or injury. The inflammatory response activates to counter the effects of pathogens or injury. Although initially beneficial, if the body's inflammatory response becomes sustained or chronic there are negative consequences. Microglia, cells present in the central nervous system, serve as resident macrophages, generally existing at down-regulated levels when no threat exists to the body (Minghetti, 2005). When pathogens enter the body or other damage occurs, however, microglia are among the first to respond to the threat in defense of the immune system, secreting a variety of inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β ; DeLegge & Smoke, 2008). When overactivated, microglia produce these pro-inflammatory factors in excess, ultimately resulting in harm to the body through a cycle of persisting inflammation (Block, Zecca, & Hong, 2007). Another source of harm to the body resulting from chronic inflammation is the increased biosynthesis of prostaglandins in inflamed tissue (Ricciotti & FitzGerald,

2011). Prostaglandins are produced by the enzyme cyclooxygenase (COX) at the site of inflammation and tissue damage to aid in recovery. COX exists in two forms: COX-1 and COX-2. Prostaglandin E2 (PGE₂), a product of COX-2, along with abundant COX-2 expression, has been implicated in the production of acute and chronic inflammatory conditions as well as neurodegenerative pathology (Bartels & Leenders, 2010).

Cognitive impairment resulting from inflammation is a consequence of either a chronic or acute, higher-level inflammatory response (Simone & Tan, 2011). Inflammation may be widespread throughout the body and affects cognitive functioning both indirectly through other mechanisms and directly through the influence of inflammatory markers on brain structures. Indirect influences of inflammation on cognitive functioning operate through cerebrovascular disease, amyloid plaques and neurofibrillary tangles, reactive oxygen species, and/or hypothalamic-pituitary-adrenal axis dysfunction (Sartori, Vance, Slater, & Crowe, 2012). Direct influences of inflammatory cytokines on cognitive functioning have been observed. Specifically, IL-6 and C-reactive protein (CRP) have demonstrated associations with global cognitive functioning, as evidenced by performance on the Mini-Mental State Examination (MMSE; Wright, 2006; Yaffe, 2003). Further, deficits in memory, processing speed, and motor functioning are associated with elevated concentrations of the proinflammatory chemokine, interleukin-8 (IL-8; Baune et al., 2008). Finally, a significant number of enzymes involved in the inflammatory response are present in limbic structures, such as the hippocampus and basal ganglia, that are associated with learning and memory (Raz & Rodrigue, 2006; Sartori, Vance, Slater, & Crowe, 2012).

In general, a high intake of fat increases neural inflammatory responses through elevated PGE₂ and COX-2 levels (Zhang, Dong, Ren, Driscoll, & Culver, 2004). Mice on

a high fat lard diet demonstrated more impaired cognitive functioning and brain inflammation (i.e., increased TNF- α , IL-6, MCP-1, reactive astrocytosis, and microgliosis) compared to mice on a western diet, despite the western diet containing higher levels of SFA (Pistell et al., 2010). This evidence supports that greater composition (60%) of overall dietary fat is more detrimental than moderate consumption (41%) of any specific unhealthy fat (Pistell et al., 2010).

Specifically, increased SFA and TFA intake are implicated in promoting inflammation. For example, mice fed high levels of SFA for four weeks exhibited elevated levels of several inflammatory response markers in the hypothalamus, such as IL-6, IL-1 β , TNF- α , and COX-2, compared to mice on a standard diet (Tu, Kim, Yang, Kim, & Kim, 2019). In rats fed diets differing in fatty acid amount and composition for 90 days, TFA increased brain damage risk through increased levels of TNF- α in the cortex and hippocampus, suggesting the importance of fat quality (i.e., saturated versus unsaturated) and not just quantity (Longhi et al., 2017). Others have found that in mice, TFA diets predict greater inflammation in both plasma and tissues, as evidenced by increased levels of inflammatory cytokines such as TNF- α and IL-1 β (Monguchi et al., 2017). Overall, these studies suggest that SFA and TFA intake generally endorse an inflammatory response that can ultimately lead to harmful outcomes in the brain.

Even brief dietary alterations have the potential to influence cytokine production. Young women on a diet high in MUFA and low in SFA for two weeks demonstrated lower plasma concentrations of IL-6 and IL-1 β compared to those on a diet high in SFA (Dumas et al., 2016). An investigation of the association between dietary fatty acids and inflammatory markers in the ATTICA study found inverse relations between total plasma

MUFA, PUFA, n-3, and n-6 levels with inflammatory markers such as IL-6, TNF- α , CRP, and fibrinogen (Kalogeropoulos et al., 2010). Unsaturated fatty acid also has beneficial effects on inflammation through elevated LA, both in the hypothalamus and entire brain of mice by targeting microglial cells (Tu et al., 2019). Of the different classes of PUFA, n-3 PUFAs have been identified to have anti-inflammatory properties. In a study of healthy adults, an inverse relationship between PUFA, specifically EPA and DHA, and TNF receptor levels was reported (Pischon et al., 2003). Additionally, high dietary ALA intake, compared to LA intake and the average American diet (high in SFA and MUFA), reduces the production of IL-6, IL-1 β , and TNF- α via peripheral blood mononuclear cells as well as reduced serum TNF- α concentrations (Zhao et al., 2007). Moreover, the proportion of n-3 PUFA to n-6 PUFA intake may also influence the effect of PUFA. When n-3 intake is lower than n-6 intake, n-6 appears to promote elevated levels of inflammation; however, when n-3 intake is higher than n-6 intake, the lowest levels of inflammation are observed (Pischon et al., 2003). Therefore, it is recommended that dietary intake of n-3 PUFA be greater than n-6 PUFA to yield lower levels of inflammation.

Oxidative Stress

Reactive oxygen species (ROS), oxygen-derived molecules including free radicals and other nonradicals are implicated as a primary source of cellular damage when accumulated (Bedard & Krause, 2007). To manage or prevent the damage produced by accumulated ROS, the body responds by increasing endogenous and exogenous antioxidants (Pham-Huy, He, & Pham-Huy, 2008). Cells existing in environments of imbalance between ROS and antioxidants, whether due to increased ROS levels or

decreased cellular antioxidant capacity, are said to be under oxidative stress (Sies, 2000; Ray, Huang, & Tsuji, 2012). Chronic exposure to oxidative stress is associated with cell injury and death, and as such, explains in part the pathology of neurodegenerative disease (Gemma, Vila, Bachstetter, & Bickford, 2007; Mariani, Polidori, Cherubini, & Mecocci, 2005).

Particular deficits in cognitive functioning have been noted with increased levels of cell injury via oxidative stress in a variety of brain structures, including the hippocampus, hypothalamus, amygdala, and prefrontal cortex (Wang et al., 2005; Siqueira, Fochesatto, da Silva Torres, Dalmaz, & Netto, 2005; Salim, 2017). Research has focused primarily on the direct and indirect impact of oxidative stress on the hippocampus. The hippocampus is sensitive to the secretion of stress hormones that are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Notably, the HPA axis, particularly the hypothalamus and adrenal cortex, is susceptible to increased levels of ROS (Costantini, Marasco, & Møller, 2011; Reagan, 2007; Magri et al., 2006). The hippocampus is also directly vulnerable to the impact of increased ROS levels (Massaad & Klann, 2011). These indirect and direct influences impact neuropsychological performance in the domains of global cognitive functioning, short-term memory, long-term memory, spatial memory, problem solving, and processing speed (Massaad & Klann, 2011). Specifically, with regard to learning and memory, increased ROS levels demonstrate a neurotoxic effect on the hippocampus, negatively impacting synaptic plasticity through the accumulation of oxidative damage on long-term potentiation (LTP; Massaad & Klann, 2011).

In general, high fat diets, regardless of fat type, are a source of elevated oxidative stress, ultimately leading to declines in cognitive functioning. Greater cerebral ROS levels

as well as subsequent cognitive impairment have been documented in mice fed a high fat diet (Freeman et al., 2013). Rats fed high fat lard diets for five months demonstrate increased cerebral ROS generation (Zhang, Dong, Ren, Driscoll, & Culver, 2004). Similarly, rats exposed to a high fat lard diet for 16 weeks demonstrated hippocampal oxidative damage (Morrison et al., 2019). Diet-induced obesity also increased free radicals in rats fed both high calorie, high fat diets and high calorie, normal fat diets (Beltowski, Wojcicka, Gorny, & Marciniak, 2000). These studies identify an association between high fat consumption and indicators of oxidative stress; however, it is necessary to explore each particular dietary fatty acid in order to have a more precise understanding of the risks and benefits of fat consumption with regard to oxidative stress.

TFAs have been implicated in the elevation of oxidative stress levels and reduction of cellular antioxidant capacity. In a study exploring the deleterious effects of TFAs on neurological function in rats, TFA intake increased cortical ROS levels, consequently resulting in exacerbated oxidative stress and brain damage (Longhi et al., 2017). Additionally, mice with increased TFA intake demonstrate greater levels of oxidative stress (Monguchi et al., 2017). The effects of SFA intake, however, are less well-established. In a study of high-fat diet consumption on myelin integrity in the central nervous system, elevated oxidative stress was observed in mice on a high SFA fat diet compared to mice on low SFA diet (Langley et al., 2020). Conversely, other findings indicate possible beneficial impacts of SFA intake with regard to oxidative stress. In a study of middle-aged adults, an inverse association between SFA intake and oxidative stress was identified, suggesting that SFA intake may actually decrease levels of oxidative stress (Nakamura et al., 2019). It is likely that these seemingly contradictory findings are related to features of each study

design as well as quantity of SFA intake. Further research is necessary to better understand the relationship between SFA and oxidative stress, however, at this time, studies of this kind are limited.

On the other hand, PUFA and MUFA have antioxidant properties that may benefit cognitive functioning through effects on cerebrovascular disease risk and amyloid pathology (Roberts et al., 2010). Diets high in MUFA have been shown to decrease the expression of oxidative phosphorylation genes, which are implicated in the generation of ROS (van Dijk et al., 2012). PUFA, particularly, EPA and DHA, have also been shown to reduce or partially prevent damage from oxidative stress in the hippocampus, and in brain tissue more generally, of rats with cerebral ischemia by providing protection from apoptotic cell death and decreasing cerebral lipid peroxides (Ueda, Inaba, Nito, Kamiya, & Katayama, 2013; Bas et al., 2007; Choi-Kwon et al., 2004). However, unsaturated fat is highly sensitive to oxidization, as a result of unstable electrons near their double bonds (Quiles, Barja, Battino, Mataix, & Solfrizzi, 2006). Typically, the oxidation of PUFAs negatively impacts food quality and shelf life, but the effects on one's health are thought to be dependent on the concentration of the oxidized PUFA metabolites; specifically, oxidative stress and inflammation may be induced at high concentrations of metabolites whereas antioxidant effects may be induced at low concentrations of metabolites (Tao, 2015). As such, moderation in unsaturated fatty acid intake is encouraged to decrease cellular oxidative stress.

Brain-Derived Neurotrophic Factor

Neurotrophins are a family of related proteins that are essential for the survival of neurons. Major functions of neurotrophins include the promotion of neuronal development, survival, and plasticity (Huang & Reichardt, 2001; Ivanisevic & Uri Saragovi, 2013). A particular type of neurotrophin, brain-derived neurotrophic factor (BDNF), has been identified as a necessary protein in the survival of neurons and growth of neurons and synapses; as such, BDNF has been associated with proper brain development and synaptic plasticity (Fumagalli, Racagni, & Riva, 2006). An important function of BDNF is the modulation of proteins such as cyclic AMP-response element-binding protein (CREB) and synapsin I (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Wu, Ying, & Gomez-Pinilla, 2004b). These proteins have a well-established role in the regulation of neurotransmitter release and promotion of LTP (the strengthening of synaptic connections between neurons resulting from patterns of activity), and as such, are necessary for learning and memory as well as brain plasticity (Greengard, Valtorta, Czernik, & Benfenati, 1993; Silva, Kogan, Frankland, & Kida, 1998). Another recognized function of BDNF in the hippocampus is to instigate the release of acetylcholine (ACh) in neurons, a neurotransmitter involved in cognitive function which is deficient in individuals with dementia (Knipper et al., 1994).

Although the implications of BDNF and its effectors are vast, for the purposes of this review, we focus primarily on the influence of BDNF on learning, memory, and brain plasticity, as it relates to the aging brain. BDNF is recognized for its expression in the hippocampus, a brain structure predominantly associated with learning and memory (Komulainen et al., 2008). BDNF levels decrease with age and are associated with

decreased hippocampal volume (Erickson et al., 2010). BDNF expression also impacts the parietal lobe (Weinstein et al., 2014). These structural changes are associated with reduced performance in areas of global cognitive function and memory (e.g., spatial memory), while other domains (e.g., executive functioning) remain relatively intact (Komulainen et al., 2008). Interestingly, decreased circulating BDNF levels are also associated with cardiovascular dysfunction, inflammation, and insulin, all of which are individual mechanisms directly impacting one's neuropsychological profile (Mondelli et al., 2011; Krabbe et al., 2007; Nakagawa et al., 2000; Chaldakov et al., 2004; Manni et al., 2005).

In general, it has been suggested that high fat diets negatively impact levels of BDNF in the brain (Pistell et al., 2010). In a study examining the impact of SFA on BDNF levels in the hippocampus, mice placed on a high fat diet (45% fat by energy) for seven weeks demonstrated decreased levels of BDNF in the hippocampus and decreased levels of newly generated cells in the dentate gyrus of the hippocampus compared to mice on a normal diet (10% fat by energy; Park et al., 2010). Furthermore, high SFA intake has been observed to impair cognitive function through reduced levels of BDNF, synapsin I, and CREB, with oxidative stress possibly mediating these effects (Wu, Ying, & Gomez-Pinilla, 2004a). In a study exploring hippocampal levels of BDNF in rats, impaired learning and memory in rats fed a diet high in SFA and MUFA were associated with decreased levels of BDNF and CREB in the hippocampus, ultimately suggesting reduced brain plasticity (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). Diets composed of high levels of SFA and simple sugars also compromise synaptic plasticity through reductions in hippocampal BDNF expression and dendritic spine density (Stranahan et al., 2008). Taken together, these findings demonstrate that diets high in fat, particularly SFA, are implicated

in negative outcomes to the expression of BDNF, particularly in the hippocampus.

Despite the harm that may arise from the consumption of certain fats or the overconsumption of fat in general, hypotheses regarding the neuroprotective role of PUFA, particularly with regard to BDNF, are being tested. In one study, the inclusion of n-3 PUFAs into the diet of rats that had sustained a traumatic brain injury was shown to normalize levels of BDNF, synapsin I, and CREB in the hippocampus (Wu, Ying, & Gomez-Pinilla, 2004b). Further, rats deprived of n-3 PUFA for 15 weeks demonstrated decreased levels of DHA in the frontal cortex, ultimately resulting in reduced expressions of BDNF and CREB in the frontal cortex (Rao et al., 2007). Insufficient n-3 PUFA during critical periods of brain maturation have also illustrated the importance of PUFA consumption in brain plasticity. In one study, deficient n-3 PUFA levels during the early development of rats reduced BDNF levels in the hypothalamus and hippocampus, which negatively impacted prospective brain functioning in adulthood (Bhatia et al., 2011). The predominant focus of past research in this area appears to be PUFA, and more specifically, n-3 PUFA. N-3 PUFA may have a role in neuroprotection, and as such, increasing n-3 PUFA intake is highly encouraged. To date, research regarding BDNF as a mechanism influencing cognitive functioning is still limited. Particularly, the relationship between TFA or MUFA and BDNF is not well-established. One explanation for this is the complex nature of the mechanisms mediating dietary fat intake and cognition; research supports the idea that changes in BDNF expression may be an outcome of other mechanisms, such as oxidative stress, inflammation, insulin resistance, etc. As such, additional research is necessary to further examine these relationships and identify the impacts of TFA and MUFA intake on BDNF levels.

Insulin Resistance

Another proposed mechanism that has been associated with dietary fat intake and cognitive functioning is insulin resistance (Greenwood & Winocur, 2005). Insulin resistance refers to a condition in which cells of the body have developed an abnormal response to insulin, also known as low insulin sensitivity, which results in the accumulation of glucose in the blood, and in turn causes the body to secrete more insulin to compensate (Reaven, 1988). This results in hyperinsulinemia, a term referring to high insulin levels in the blood. A common method used to assess insulin resistance is through the measurement of blood glucose, or hemoglobin A1c (HbA1c) levels. Managing insulin resistance is essential, as insulin resistance is often a precursor of type 2 diabetes mellitus (T2DM) and other serious conditions included in metabolic syndrome (Risérus, 2006; Cnop, 2008). Diabetes mellitus, in particular, is associated with micro- and macro-vascular changes. The presence of diabetes mellitus has been connected with a greater likelihood of developing coronary, cerebrovascular, and peripheral arterial disease and additionally contributes to vascular irregularities through characteristic features of the disease, such as insulin resistance and the increased presence of fatty acids (Creager et al., 2003).

Insulin resistance has been shown to adversely impact cognitive functioning. Specifically, insulin receptors are densely concentrated in the hippocampus, influencing learning, memory, and plasticity (Cordner et al., 2019; Magri et al., 2006). In a study of learning and memory in rats, obese rats exhibited impaired hippocampal insulin receptor signaling, as evidenced by decreased levels of insulin-regulated glucose transporter (GLUT4) in hippocampal plasma membrane and increased levels of plasma insulin, leptin, and corticosterone (Winocur et al., 2005). Diet-induced insulin resistance

also impairs cognitive performance on certain tasks of spatial learning and working memory in rats fed high fat diets for 12 weeks (McNeilly, Williamson, Sutherland, Balfour, & Stewart, 2011). In humans, insulin has also been largely associated with impairments in verbal and visual memory (Craft & Watson, 2004). Notably, HPA axis function is a possible explanation for the impact of insulin resistance on the hippocampus. Impaired insulin receptor signaling negatively modulates HPA function, which in turn harms the hippocampus through its sensitivity to hormone release (Reagan, 2007; Magri et al., 2006).

With regard to fat intake, several studies have proposed a direct association between dietary fatty acid intake and insulin resistance. In a study examining the potential impact of long-term fat intake across a six-year period, monkeys on a TFA diet demonstrated significant weight gain, impaired insulin sensitivity, and compromised insulin receptor signaling (Kavanagh et al., 2007). TFAs have further been linked T2DM through an identified direct relationship between TFA intake and T2DM risk (Salmeron et al., 2001). Further, increased SFA and TFA intake in women with T2DM has been associated with greater risk of cognitive decline (Devore et al., 2009). In another study with women exploring the impacts of hydrogenated vegetable oils (high in TFA and SFA content) on insulin resistance, those who consumed hydrogenated vegetable oils had a greater risk of developing insulin resistance (Esmailzadeh & Azadbakht, 2008).

In comparison, non-hydrogenated vegetable oil consumption (high in PUFA content) was inversely associated with insulin resistance, suggesting nutritional benefits of increased PUFA intake (Esmailzadeh & Azadbakht, 2008). Improvements in insulin sensitivity have also been noted in healthy adults randomly assigned to a diet high in MUFA, compared to those assigned a diet high in SFA, but only in instances where total

fat intake was not high (Vessby et al., 2001). Further, increasing PUFA intake relative to SFA or TFA intake may reduce risk of cognitive decline in women with T2DM and may reduce risk of T2DM in women without existing T2DM (Salmeron et al., 2001; Devore et al., 2009).

Notably, however, many studies have identified no significant difference in insulin sensitivity in relation to dietary fat intake. In a study conducted on healthy, lean subjects, no significant effect of SFA or TFA on insulin sensitivity or resistance was observed (Lovejoy et al., 2002). Another study examining healthy, young women and consumption of TFA and MUFA found no effect of TFA intake on insulin sensitivity in comparison to MUFA intake (Louheranta, Turpeinen, Vidgren, Schwab, & Uusitupa, 1999). In a study investigating insulin sensitivity following three weeks of dietary intervention in obese individuals with insulin resistance and accompanying T2DM, no significant change in HbA1c levels or insulin sensitivity was observed for either the MUFA diet or PUFA diet (Brynes et al., 2000). In a review exploring the effects of TFA on insulin resistance in healthy individuals and individuals with T2DM, insufficient support for the impact of TFAs on insulin resistance was reported in healthy individuals; however, limited evidence suggests that greater TFA intake to MUFA intake may further impair insulin sensitivity in individuals with insulin resistance or T2DM (Risérus, 2006). This inconsistent evidence was further reported in another review examining the relationship between dietary fat intake and risk for T2DM (Bradley, 2018).

Of all the mechanisms discussed in this review, the research regarding insulin resistance proved to be the most controversial. Despite general acknowledgment that insulin resistance proposes harmful effects on the body, and on cognitive functioning more

specifically, limited research supports the idea that insulin resistance is directly associated with dietary fatty acid intake; rather, other modifiable factors, such as body weight and physical activity, have indirectly linked fat consumption to insulin resistance.

CHAPTER THREE

CONCLUSIONS

Age-related cognitive changes can be influenced by a myriad of factors, including diet, physical health, physical exercise, mood, social stimulation, and cognitive stimulation, as well as more pathological processes such as Alzheimer's disease and cerebrovascular disease. There are presently no established cures for neurocognitive disorders, and the potential benefits of pharmacological treatments are limited; as such, the focus of research is shifting to prevention and early detection. Dietary modifications, in particular, are becoming an increasingly prominent area of focus, as changes to one's diet are often more feasible and cost-effective than alternative approaches. A significant amount of existing research has explored the role of dietary fat intake on cognitive functioning, determining which fats promote neuroprotection and which fats promote neurodegeneration. Broadly speaking, research supports limiting total fat intake, as increased levels of total fat harm the body in many respects. It is recommended that dietary fats constitute less than 30% of total energy intake, with SFA intake comprising less than 10% and TFA less than 1% (WHO, 2019; USDHHS & USDA, 2015). Research tends to promote unsaturated fat intake over saturated fat intake, as unsaturated fats benefit the body and may be essential in several ways. Foods high in unsaturated fats include fish, avocado, nuts, and sunflower, canola, and olive oils whereas foods high in saturated fats include fatty meat, butter, palm and coconut oil, cream, cheese, ghee and lard; notably, TFAs are found in processed food, fast food, frozen food, etc. and should be eliminated from one's diet as much as possible (WHO, 2019). Nevertheless, despite this general understanding of dietary fat intake, a limited amount of information exists to explain the mechanisms

underlying its relationship with age-related cognitive decline. The most prominent biological mechanisms to date include cardiovascular function, inflammation, oxidative stress, brain-derived neurotrophic factor, and insulin resistance. This review aimed to provide an overview of the existing research regarding fat intake and cognitive functioning and further investigate and delineate these proposed mechanisms.

In exploring these mechanisms, we discovered interconnected relationships, suggesting that the impact of one mechanism can influence the role of other mechanisms. For example, cardiovascular dysfunction has been associated with increased levels of inflammation in the body; conversely, inflammation has been implicated in the increased prevalence of cardiovascular diseases (Puntmann, Taylor, & Mayr, 2011; Sartori, Vance, Slater, & Crowe, 2012). Further, proinflammatory markers have been related to negative consequences resulting from the accumulation of amyloid plaques and neurofibrillary tangles as well as increases in levels of oxidative stress and the chronic stress response (Sartori, Vance, Slater, & Crowe, 2012). BDNF expression has additionally be linked to neuroinflammation, insulin resistance, and hypertension (Komulainen et al., 2008; Passaro et al., 2015). Furthermore, insulin has been demonstrated to impact the secretion of inflammatory markers as well as promote the production or clearance of A β peptides (Lyra e Silva et al., 2019; Craft & Watson, 2004). Finally, ROS has been identified to increase levels of A β peptides, which is a hallmark feature of Alzheimer's disease pathology (Massaad & Klann, 2011). Although a comprehensive review of the synergistic relationships between mechanisms is beyond the scope of the current paper, it is important to note that no single mechanism is isolated, as the body is sensitive to changes in all mechanisms.

The impact of dietary fats on these mechanisms, and more particularly on cognitive functioning, has been further connected to neurodegenerative outcomes, such as Alzheimer's disease and vascular dementia. Associations between cardiovascular risk factors (e.g., hypertension, dyslipidemia, diabetes, sleep apnea, etc.) and neurodegenerative diseases have been linked through changes in cerebral circulation. Some studies suggest that chronic brain hypoperfusion resulting from cardiovascular risk factors can result in lacunar infarcts, white matter lesions, and even excessive A β accumulation in the brain, promoting the development of neurodegenerative diseases (de La Torre, 2012; ElAli, Thériault, Préfontaine, & Rivest, 2013). Similarly, high blood pressure has been connected to outcomes such as brain atrophy, white matter disease, microinfarcts, microhemorrhages, and amyloid accumulation, which are all sources of brain injury correlated with neurodegenerative outcomes (Iadecola, 2014). A bidirectional relationship between inflammation and neuronal injury has also been described, resulting in a cycle of damage that promotes neurodegenerative outcomes (Block & Hong, 2005). Evidence for the harmful effects of chronic inflammation can be noted through active microglia and astrogliosis surrounding plaques that further give rise to pro-inflammatory factors, as reported in post-mortem Alzheimer's-diseased brains (Glass, Saijo, Winner, Marchetto, & Gage, 2010). Impacts of an inflammatory response have been observed to exacerbate A β accumulation and tau hyperphosphorylation and to contribute to vascular events (Kinney et al., 2018; Sullivan, Sarembock, & Linden, 2000). Oxidative stress has also been implicated in the pathogenesis of Alzheimer's disease and vascular dementia. Specifically, the accumulation of extracellular A β plaques promotes elevations in ROS that lead to neuronal cell death and contribute to the formation of intracellular neurofibrillary tangles;

additionally, elevations in ROS have been linked to cerebral ischemia and other vascular risk factors associated with vascular dementia (Bennett, Grant, & Aldred, 2009). Studies have also suggested an association between serum BDNF and dementia. Specifically, lower serum BDNF has been linked to an increased risk of stroke/transient ischemic attack (TIA), Alzheimer's disease, vascular cognitive impairment, and other types of dementia whereas higher serum BDNF is thought to be more neuroprotective (Pikula et al., 2013; Weinstein et al., 2014; Ventriglia et al., 2013). Insulin resistance has been identified as another risk factor of vascular dementia and is associated with micro- and macro-vascular changes. The presence of diabetes mellitus, a common outcome of uncontrolled insulin resistance, has particularly been connected to a greater likelihood of developing coronary, cerebrovascular, and peripheral arterial disease, and as such, a greater likelihood of vascular dementia (Creager et al., 2003).

It is also important to recognize the role of overweight and obese status in cognitive decline, although the mechanisms explaining this relationship are poorly understood at this time (Xu et al., 2011). It has been suggested that overweight and obese status, especially in midlife, increases risk for dementia later in life and is associated with brain atrophy, other structural changes in the brain, and reduced integrity of white matter (Singh-Manoux et al., 2018; Verstynen et al., 2012). High-fat diets are a primary cause of overweight and obese status, and chronically elevated levels of circulating free fatty acids tend to influence vascular risk, inflammation, oxidative stress levels, and insulin resistance, which in turn promotes neurodegenerative outcomes (Pugazhenthii, Qin, & Reddy, 2017). Additionally, overweight and obese status is thought to alter endocrine function through hormones and adipokines due to increased body mass index (BMI; Kiliaan, Arnoldussen, & Gustafson,

2014). However, these mechanisms only explain the impact of fat on neurodegenerative outcomes in part. It is likely that there are other factors operating in this relationship which are not yet fully understood or identified at this time.

Limitations and Future Directions

Despite findings discussed in this review supporting the role of cardiovascular function, inflammation, oxidative stress, brain-derived neurotrophic factor, and insulin resistance in cognitive functioning, there are a number of limitations to consider. Many animal studies were available for review, but a limited number of studies directly associated with the human brain are available at this time. Longitudinal studies are limited as well. Further, isolating fat intake was challenging, as foods rarely contain only one type of fat; many of the studies considered proportions of dietary fat intake, possibly overlooking the extent of the influence of each individual dietary fat. Fat quantity was also important to consider, as fat quality was not the only factor observed to have an influence. As such, breadth of research, inexact dietary measurements and compositions, and other potential confounding variables may further explain some of the reported findings in the reviewed studies. Finally, limited research was available to review that explored dietary fat, mechanisms, and cognitive function together in the same study. Incorporating this knowledge into the design of future studies is necessary in order to better understand the role each mechanism has in arbitrating the relationship between dietary fat intake and cognitive functioning.

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