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Review article

Damaging effects of a high-fat diet to the brain and cognition: A review of proposed mechanisms

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The prevalence of obesity is growing and now includes at least one-third of the adult population in the United States. As obesity and dementia rates reach epidemic proportions, an even greater interest in the effects of nutrition on the brain have become evident. This review discusses various mechanisms by which a high fat diet and/or obesity can alter the brain and cognition. It is well known that a poor diet and obesity can lead to certain disorders such as type II diabetes, metabolic syndrome, and heart disease. However, long-term effects of obesity on the brain need to be further examined. The contribution of insulin resistance and oxidative stress is briefly reviewed from studies in the current literature. The role of inflammation and vascular alterations are described in more detail due to our laboratory's experience in evaluating these specific factors. It is very likely that each of these factors plays a role in diet-induced and/or obesity-induced cognitive decline.

Keywords: Cognition, Brain Health, Obesity, Inflammation, Cerebrovascularization

Obesity: a public health issue

The prevalence of obesity is growing and now includes at least one-third of the adult population in the United States. Another third of the population is characterized as overweight.^{1,2} Body mass index (BMI) is used to define overweight and obesity as between 25–30 kg/m² and over 30 kg/m², respectively.² BMI is calculated by dividing weight in kilograms by height in meters squared (kilogram per square meter).³ With the current growth of this public health problem, it is projected that overweight and obesity rates will reach epidemic proportions in the United States during the next decade (as much as 75% of the population in 2015).² Comparing these statistics to data collected in 1960 on the prevalence of obesity in the United States, the current population now includes almost triple the number of obese people (13.4% in 1960 compared to 35.7% in 2010).^{1,4} Worldwide, it is estimated that one billion people are overweight or obese.⁵

Obesity is a risk factor for many conditions including, but not limited to, diabetes, hypertension, dyslipidemia, stroke, heart disease, certain cancers, and arthritis.^{1,6} Although overall mortality rates continue to decline in our country due to medical and technological advancements, mortality linked to obesity-related disorders is increasing. It is clear that obesity is damaging to the health and wellness of our population, but biological mechanisms for its damaging effects are less explored. Future research must focus on the aspects of our current diet and lifestyle that lead to obesity, and the full extent of obesity-related effects on all organs of the body, including the brain.

'The western diet'

One of the greatest factors contributing to the prevalence of obesity is choice of diet. A term to describe the unhealthy diet eaten by many Americans as well as other westernized populations is 'the western diet'. Simply put, it is a diet that contains large amounts of red meat, refined sugars, high fat foods, and refined grains. This is in contrast to a healthier diet that is high in fruits, vegetables, lean protein, and fiber.⁷

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Fat consumption has been found to be a key player in the obesity epidemic.^{7–9} The western diet often contains large amounts of saturated (SFA) and trans fatty acids (TFA) compared to a healthier diet containing more *n*-3 polyunsaturated fatty acids (PUFAs).^{10,11} The major sources of SFAs in the United States include fatty meats, baked goods, cheese, milk, margarine, and butter.^{8,12,13} Long-term consumption of the 'western diet' can lead to obesity and consequently damaging effects on general health. However, an area that has not yet been well evaluated is the damaging effects of the 'western diet' on the brain. This topic is the focus of the current review.

High-fat diets and cognition

Dementia by definition is a progressive deterioration in two or more modalities of cognitive performance. Diagnosis of dementia requires repeated analysis of the subject's ability to perform complex tasks, activities of daily living, as well as changes in personality and mood. Within this review, we primarily refer to 'cognitive decline' or 'cognitive impairment' in order to examine a large spectrum of symptoms that may be affected by high-fat diets and/or obesity.

In the last decade, more scientific interest in nutrition-related effects on brain function has emerged. Rates of obesity, diabetes, and dementia continue to climb and both retrospective and prospective studies suggest that obesity and increased consumption of high-fat diets increases risk for development of dementia.^{14–20} As early as 1990, Greenwood and Winocur²¹ published one of the first studies revealing effects of a high SFA diet on learning and memory in rats. In this study, 1-month-old Long Evans rats were fed either a high SFA (lard-based diet, 40% calories

from fat), a high PUFA diet (soybean oil-based, 40% calories from fat), or a standard rat chow diet (Purina, 4.5% w/w) for three months. Rats were evaluated on three different tasks: Olton's radial arm maze, a variable interval delayed alternation task, and the Hebb-Williams maze series. Rats on the lard-based diet performed the worst on all three of these tasks, revealing damaging effects of this type of diet on the brain.²¹ However, the biological mechanisms involved to cause these effects were not evaluated at this time.

Following this study, eight more manuscripts were published by Greenwood and Winocur describing a link between a high fat diet and cognitive function.^{22–29} Later studies by this group explored the role of glucose and insulin resistance in the observed decline in cognitive function. In 2005, they published a review including results from both human epidemiological studies and rodent experiments that found insulin resistance to be at least one mechanism by which chronic consumption of a high fat diet is linked to cognitive decline and dementia.²³ At this time, only a few other researchers were exploring the relationship between high-fat diets and cognition as well as the mechanisms involved. A manuscript from our research group demonstrated detrimental effects of a high-fat/high-cholesterol diet on performance in a radial arm maze in middle-aged rats, associated with reduced hippocampal dendritic integrity and activation of microglial cells in the hippocampus.³⁰ All rodent studies exploring a correlation between a high-fat diet and cognitive impairment presented herein are summarized in Table 1.

In human epidemiological studies, it has been shown that intake of a high-fat diet that includes

Table 1 Rodent studies: effect of diet on cognition

Diet composition	Cognitive results	Postulated biological mechanism	References
Lard-based diet (40% calories from fat)	Worse performance on working memory and retention	Not discussed	21
Lard & corn oil (39% energy)	Worse performance on Morris water maze	Oxidative stress, reduced BDNF levels	31
High fat diet (45% calories from fat)	Worse performance on operant-based delayed matching to position task	Insulin resistance	32
High fat, high glucose diet supplemented with high fructose corn syrup	Worse performance on a spatial learning task	Insulin resistance, Reduced BDNF levels	33
High saturated fat and cholesterol	Worse performance on the Water Radial Arm Maze	Inflammation, reduced dendritic integrity in the hippocampus	34
'Western diet' (41% calories from fat) or Lard (60% calories from fat)	Impaired retention on behavioral test for 60% fat but not 'Western diet'	Oxidative stress	35
High fat diet (45% calories from fat) + Metformin	Improved performance on operant-based task	Insulin sensitivity	36
High-fat high-carbohydrate + Vitamin E	Improved performance on Water Radial Arm Maze	Oxidative stress	37
High fat diet (45% calories from fat)	Impaired performance on Fear Conditioning Task	Oxidative stress	38
High fat diet + Sugar	Impaired performance on serial feature negative task	Vascular/adiposity	39

mostly omega-6 and SFAs is associated with worse performance on a cognitive task.^{14,40–43} Furthermore, studies have shown that a diet containing mostly SFAs and TFAs is associated with increased risk for Alzheimer's disease (AD).^{15,40,44} On the other hand, a lower fat diet consisting of omega-3 fatty acids had a protective effect against cognitive decline in healthy older subjects.⁴⁵ It has also been determined that high consumption of total fats, SFAs, and cholesterol is associated with increased cholesterolemia, risk of cardiovascular disease, and impaired intellectual function, suggesting that the circulating levels of cholesterol are closely associated with cognitive performance in humans.⁴⁶ Ortega *et al.*⁴¹ and Greenwood and Winocur²³ have also found that high-fat diets and those that lack proper vitamins and minerals consumed late in life can worsen the course of age-related cognitive decline. All human studies exploring a correlation between a high-fat diet and cognitive impairment presented herein are summarized in Table 2. During the last decade, more studies have focused on biological mechanisms for these observed cognitive effects of high-fat diets. The major proposed biological mechanisms include insulin resistance, developmental disturbances, altered membrane functioning, oxidative stress, inflammation, and altered vascularization.^{32,33,35,45,47,48} A summary of the proposed mechanisms for high-fat diet-induced cognitive decline is presented in Fig. 1, and will be discussed in detail in the next section of this review.

Insulin resistance

In a study by McNeilly *et al.*,³² rats were fed a high-fat diet (45% calories from fat) for 12 weeks which made the rats overweight and induced insulin resistance, as measured by elevated fasting plasma glucose and insulin levels. The rats consistently performed poorer

than control animals on an operant-based delayed matching to position task.³² This study revealed a role for insulin resistance on behavioral flexibility. Furthermore, in a recent study by McNeilly *et al.*,³⁶ the authors found that rats fed the high-fat diet (45% calories from fat) did not reveal any changes in insulin signaling-related proteins in the hypothalamus, hippocampus, striatum, or cortex. Rats that were treated with metformin had reduced weight gain and improved insulin sensitivity compared to those on the high-fat diet alone. However, metformin had no effect on behavioral performance suggesting the effects of insulin resistance on the brain and cognition include alternate or additional mechanisms. In another study utilizing diet-induced insulin resistance by Stranahan *et al.*,³³ they fed rats a high fat, high glucose diet that was supplemented with high fructose corn syrup. The alterations to energy and lipid metabolism included elevated fasting glucose, cholesterol, and triglyceride levels which were similar to those described for clinical diabetes. After 8 months on this diet, the rats performed worse than controls on a spatial learning ability task, had reduced hippocampal dendritic spine density, reduced long-term potentiation (LTP) at Schaeffer collateral CA1 synapses, and reduced hippocampal brain-derived neurotrophic factor (BDNF) levels.³³ With the increasing incidence of type II diabetes in the US population, the secondary effects of this disease including cognitive decline must be explored. In fact, recent work by Craft *et al.* describes an important link between insulin resistance and AD, with intranasal administration of insulin as a novel intervention candidate to improve cerebral glucose metabolism and cognitive ability.^{20,49–51} This work is new and growing; it may reveal important connections between diabetes and AD, leading to novel treatment options for this severe neurological disorder.

Table 2 Human studies: effect of diet on cognition

Diet composition	Cognitive results	Postulated biological mechanism	References
High linoleic acid intake	Worse performance on Mini Mental State Exam	Oxidative stress	14
Poor diet resulting in impaired glucose tolerance	Worse performance on Mini Mental State Exam	Disturbed glucose metabolism	47
Low intake of monounsaturated and saturated fat	Best performance on the Mini-Mental State Examination and Pfeiffer's Mental Status Questionnaire	Oxidative Stress, lack of micronutrients such as vitamin C, folate, zinc	41
Higher intakes of saturated fat and trans-unsaturated fat	Decline in performance on: East Boston Tests of Immediate and Delayed Recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test	Cholesterol levels – atherogenic	42
High intake of <i>n</i> -3 polyunsaturated fatty acids and docosahexaenoic acid (22:6 <i>n</i> -3)	Reduced risk of Alzheimer's disease	not discussed	44
Increased caloric intake and increased cholesterol intake	Poorer performance on simple reaction time, symbol-digit substitution, and serial digit learning	not discussed	43

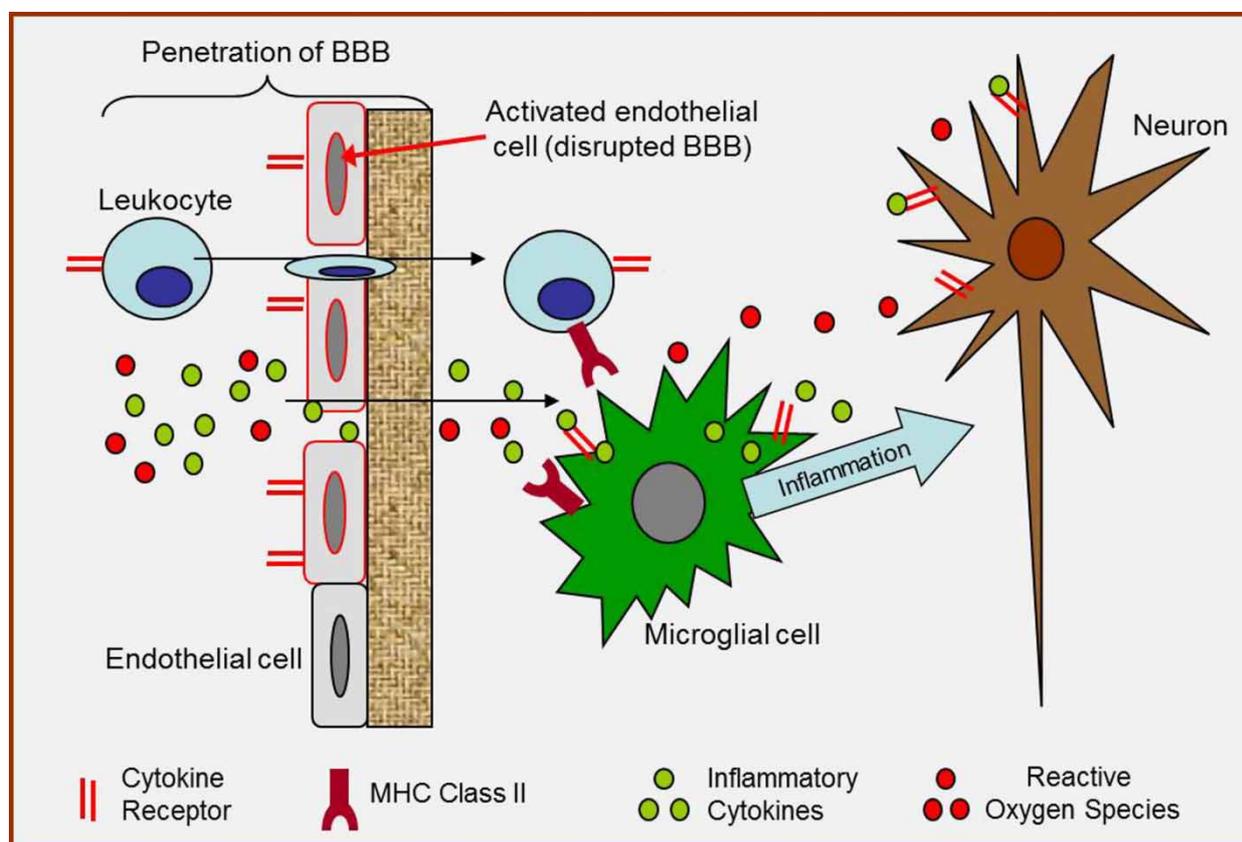


Figure 1 Possible mechanisms of diet-induced cognitive decline. Mechanisms described in this review likely act in concert to cause cognitive decline. These mechanisms include, but are not limited to, altered vascularization and BBB integrity, inflammation, and oxidative stress. In this diagram, we show activation of endothelial cells which increases BBB penetration allowing more inflammatory molecules and ROS to enter the brain. Then, microglial cells perpetuate the inflammatory cascade causing damage to neuronal health.

Oxidative stress

It has previously been determined that chronic elevation of oxidative stress by diet or by genetic alterations can lead to cognitive decline.^{52,53} In a study by our laboratory using a transgenic mouse model for Down syndrome, with a triplicated segment of murine chromosome 16, we discovered cognitive impairment in these mice associated with increased oxidative stress in brain⁵⁴ further contributing to the literature that states oxidative stress plays a role in cognitive decline. In our study, vitamin E supplementation in the diet prevented age-related cognitive impairment, suggesting that antioxidant supplementation may prevent brain-related oxidative stress effects and enhance cognitive performance.⁵⁴ Additional research has focused on the ability of antioxidant supplementation to reverse high levels of oxidative stress as well as declines in neuronal function and cognitive performance. For example, the Gomez-Pinilla laboratory investigated the interaction between increased oxidative stress from a high SFA diet (lard-based), BDNF levels, and cognition performance in a spatial task.³¹ It was found that high-fat diet-induced oxidative stress led to decreased levels of BDNF and impaired performance on the

maze. Furthermore, treatment with vitamin E reversed these effects³¹ adding support to the hypothesis that oxidative stress causes diet-induced damage to the brain and cognition. This has also recently been shown following administration of a high-fat high-carbohydrate diet (HFCD). Rats that received the HFCD for 6 weeks had reduced levels of superoxide dismutase and catalase activity and increased thiobarbituric acid reactive substances and glutathione oxidase levels in the hippocampus. These animals were also impaired on the radial arm water maze revealing deficits in spatial learning and memory. However, rats given vitamin E concurrently with the HFCD had improved maze performance as well as reduced oxidative stress measures.³⁷ In a study by Beltowski *et al.* in 2000,⁵⁵ it was also found that a high-fat diet increases the tissue levels of free radicals. In a recent study by Morrison *et al.*,³⁵ C57Bl/6 mice were fed either a 'western diet' containing 41% calories from fat, or a higher fat lard diet containing 60% calories from fat for 16 weeks. The very high-fat lard diet, but not the 'western diet' led to oxidative damage (as measured by protein carbonyls) in the hippocampus and impaired retention on a behavioral test (the 14-unit T-maze),³⁵ therefore suggesting a type of

'dose-response' effect of the diets on oxidative stress measures in hippocampus. Lastly, we have recently shown elevated levels of total ROS in the brain due to diet-induced obese (DIO). Mice fed a high-fat diet (45% kcals from fat) had significantly higher levels of total ROS, superoxide, and peroxynitrite compared to mice fed a control diet (10% kcals from fat). The level of oxidative stress was highly related to the level of adiposity. The DIO animals also displayed impairments on a cognitive task.³⁸ These studies present a role for oxidative stress in diet-induced cognitive impairment, and clearly suggest that oxidative stress is involved in cognitive impairment caused by high-fat diets.

Inflammation

IL-1, IL-6, and TNF- α are examples of pro-inflammatory cytokines orchestrating the inflammatory response to many stimuli, both systemically and in the brain. Most importantly, these cytokines have also been shown to cross the blood brain barrier (BBB). Pro-inflammatory cytokines can also be produced by cells within the brain parenchyma, specifically by microglial cells, astrocytes, and endothelial cells of the BBB.⁵⁶⁻⁵⁸ IL-1 and IL-6 receptors are located all over the brain, but they are especially enriched in the hippocampus,⁵⁸ a critical component of the learning and memory circuitry. Pro-inflammatory cytokines have been shown to have direct detrimental effects on hippocampal circuitry and cognition. For instance, a systemic or intraventricular IL-1 β injection gives rise to spatial memory impairments in rats,^{59,60} and significant effects of injected IL-1 β on the win-shift paradigm of the radial arm maze have been reported.⁶¹ Bickford *et al.* have previously shown that an indirect IL-1 blockade, using a caspase -1 inhibitor, has significant improvement effects on memory in aged rats, suggesting that IL-1 is involved in impaired performance on memory tasks with aging.⁶² IL-1 has also been shown to be an important player in inflammation-induced memory impairments in rodents, following a chronic inflammation paradigm.⁶³ Chronic inflammation due to an intra-hippocampal injection of heat-killed bacillus Calmette-Guérin gave rise to impaired performance in a hippocampal dependent task (the Y-maze), but was alleviated by the IL-1 receptor antagonist IL-1Ra.⁶³ Pro-inflammatory cytokines have been found to impair hippocampal development, and alterations in their levels can also affect the hippocampus into adulthood.⁶⁴ Specifically, IL-1 has been shown to inhibit N-Methyl-D-aspartate (NMDA)-mediated and non-NMDA mediated synaptic potentiation, LTP, and glutamate release in the hippocampus,⁶⁵ providing a physiological explanation for inflammation-induced memory impairment in rodent

models. Furthermore, IL-1 has been shown to affect learning and memory, BDNF expression, neurogenesis, and microglial activation,⁶⁶ as indicated in the schematic drawing in Fig. 1. As outlined here, inflammation can cause damage to the brain, especially in the hippocampus. However, inflammation caused by consumption of a high fat diet has not yet been well studied.

A few recent studies from our laboratory and others have begun to investigate the role of a high fat diet on neuroinflammation and cognitive decline. Thirumangalakudi *et al.*⁶⁷ fed a high fat/high cholesterol diet for 8 weeks to normal C57BL/6 mice and low density lipoprotein receptor (LDLR)-deficient mice (LDLR $^{-/-}$). Mice fed the high fat/high cholesterol diet showed impaired working memory performance compared to controls and the LDLR $^{-/-}$ mice also had impaired working memory ability regardless of the diet they were fed. The LDLR $^{-/-}$ mice were used in this study because they naturally develop moderate hypercholesterolemia, a potential inducer of neuroinflammation and vascular damage. The high fat diet-fed and LDLR $^{-/-}$ mice revealed increased activated microglia and astrocytes in the hippocampus and increased mRNA expression of various pro-inflammatory cytokines/mediators such as TNF- α , IL-1 β , IL-6, nitric oxide synthase 2, and cyclooxygenase 2 in the hippocampus.⁶⁷ Pistell *et al.*⁶⁸ fed a high fat diet to C57BL/6 mice as well and found increased body weights, impaired cognition as measured by the Stone T-maze, increased brain inflammation, and decreased BDNF levels. Cytokine protein levels were measured in the cortex and revealed an increase in TNF- α , IL-6, and the chemokine monocyte chemoattractant protein-1. Interestingly, these effects were only found in the high fat diet that consisted of 60% calories from fat (pork fat) but not the high fat diet that consisted of 41% calories from fat (butterfat and corn oil) with 29% sucrose.⁶⁸ In multiple studies from our laboratory, we have shown morphological changes within the rat hippocampus following consumption of a high fat diet, mostly consisting of a combination of hydrogenated coconut oil (10% of diet) and 2% cholesterol.^{30,34,69,70} Consistent throughout our studies has been an increased number of activated microglia in rats fed the high fat diet compared to control-fed rats, which likely points to a role of neuroinflammation in diet-induced neurodegeneration and cognitive disturbances.^{30,34,69,70} The activated microglia were labeled with an MHC Class II marker, OX-6, and were abundant particularly in the white matter overlying the hippocampal formation. In one of our studies, treatment of middle-aged rats with different sources of fat or increased cholesterol at equal concentrations to the combined high-fat diet were tested in order to better understand which

component of the 'Western Diet' contributes to hippocampal morphological changes including the increased abundance of activated microglia. We determined that all components of this complex diet, including SFAs, TFAs, and cholesterol led to morphological alterations in hippocampal morphology and inflammatory activation, marked by increased activation of microglial cells, with SFAs having the greatest effect.³⁴

However, microglia have a complex role in the brain. Although a set number of quiescent microglial cells are always present, and needed for normal function, activation of these inflammatory cells is typically correlated with the occurrence of an inflammatory event.⁵⁶ For example, a single injection of the endotoxin lipopolysaccharide (LPS) results in a significant increase in activated microglia in the brain.^{71,72} It is well known that these cells function as macrophages in the brain, with the job of surveying the area and controlling any disturbance/foreign invader via phagocytosis.⁷¹ Microglia can release either pro- or anti-inflammatory cytokines and chemokines when stimulated.⁵⁶ If they are exposed to a chronic stimulus, activated microglia remain 'on' and can also release toxic free radicals, as well as anti-inflammatory cytokines, including IL-10 and TGF- β .^{56,73,74} This suggests that microglial cells can be both 'bad' and 'good' for brain function depending on a set of triggers that are determined both by internal and external events. Microglia can switch between the classical phenotype (inflammatory), also called M1, and the alternative, neuroprotective, phenotype, also called M2.⁷⁴ Therefore, when activated microglia are visualized using immunohistochemical staining, it is difficult to discern which phenotype is expressed: M1 or M2. In support of the damaging role of microglia, the studies by Thirumangalakudi *et al.*⁶⁷ and Pistell *et al.*⁶⁸ reported increased levels of pro-inflammatory cytokines following high-fat diet treatment, suggesting a compensatory ramping up of the immune defense mechanisms. The source of inflammatory molecules is also an important factor that needs to be better understood. In a recent study, Buckman *et al.* demonstrated recruitment of peripheral immune cells into the CNS due to DIO. Using green-fluorescent protein (GFP) labeled peripheral immune cells, flow cytometry was utilized in order to quantify the number of immune cells present in the brain. Mice fed a high fat diet had a 30% increase in GFP+ cells compared to control mice. Additionally, the immune cells were further characterized and it was determined that they displayed characteristics of microglia/macrophages and were found in the parenchyma suggesting recruitment of immune cells into the CNS.⁷⁵ However, it is still difficult to conclude the role of activated microglia in diet-induced neurodegeneration. This is a 'chicken

or egg' -type question because we have not shown whether the activated microglia are the cause of neuronal damage or simply helping to remove cellular debris following neuronal loss. In future studies, the relationship between different microglial phenotypes should be examined more closely, in order to design better treatment paradigms during inflammatory insults to the brain. Nevertheless, inflammation as a key player in diet-induced and/or obesity-induced cognitive decline continues to be at the top of the list for mechanisms involved in this process.

Dysfunctional vascularization

Few studies have explored the correlation between a high fat diet or obesity and cerebral vascular changes. Studies have mostly examined the peripheral vasculature in these conditions or secondary effects of obesity/high fat diets such as metabolic syndrome and its effects on vasculature. The current studies that have explored the relationship between a high fat diet and altered cerebrovascularization include studies from our laboratory as well as a few others. For example, Constantinescu *et al.*⁷⁶ fed a hyper-lipidemic diet to hamsters and reported not only fatty streaks in the carotid artery after 3 months on the diet and atherosclerotic plaques after 6 months, but altered micro-vascular pathology in the cerebral cortex as well. The changes to brain micro-vessels were reported to include: irregularly shaped vessels with large perivascular spaces, enlarged endothelial cells and some lumen filled with lipoprotein particles.⁷⁶ In a study with LDLR-/- mice and C57BL/6J control mice fed either a high cholesterol diet or control diet, the LDLR-/- mice (regardless of diet) and control mice fed a high cholesterol diet revealed an increased microvessel diameter, vascular degeneration, and thicker basement membranes; features which were described to be similar to those found in an AD brain.⁷⁷ In terms of diet-induced effects on the BBB, Kanoski *et al.* found decreased mRNA for claudin-5 and claudin-12, two tight junction proteins found at the BBB, in rats fed a high-energy diet compared to those fed a control diet. Furthermore, leakage of the BBB following the high-energy diet was determined with sodium fluorescein passage from the blood to the brain; interestingly, this was only found in the hippocampus.⁷⁸ A follow-up study with rats fed the high-energy diet also found deficits in completing behavioral tasks. Rats were split into two groups: high-energy diet resistant (HE-DR) and high-energy diet-induced obese (HE-DIO). The HE-DIO revealed leakage of sodium fluorescein into the hippocampus and impairments on a hippocampal-dependent serial feature negative task. The HE-DR group did not exhibit BBB permeability or issues with the behavioral task and neither group was impaired on a hippocampal-

independent simple discrimination problem.³⁹ In a recent study from our laboratory, we also explored the effects of a high-fat diet on the BBB, with a focus on the hippocampus.⁶⁹ First, no significant differences in glucose transporter 1 immunoreactivity (Glut-1; a transporter involved in moving glucose across the BBB and is therefore abundant on blood vessels in the brain) were found in the cornu ammonis 1 (CA1), cornu ammonis 3 (CA3), or dentate gyrus of the hippocampal formation. BBB integrity was measured using the antibody SMI-71 (an antibody specific to rat endothelial barrier protein, EBA), which has been shown in previous studies to accurately label an intact BBB.^{79,80} A significant decrease in SMI-71-ir was observed in the CA1 region of the hippocampus as well as parietal cortex of HFHC-fed rats. There were no significant differences observed in the CA3 region of the hippocampus, suggesting a high regional sensitivity to this type of diet. Results from the SMI-71 immunofluorescence experiment point to a possible disruption of the BBB for HFHC-treated animals. When BBB proteins such as the tight junction protein, occludin, and scaffold protein, ZO-1^{81,82} were evaluated, decreased expression of occludin was found on blood vessels throughout the hippocampus. Interestingly, an up-regulation of occludin was found in neurons of the dentate gyrus and mossy fibers of the CA3 region (an area spared by BBB disruption according to our SMI-71 results), suggesting a possible compensation in neuronal occludin expression following the decrease observed in vascular occludin expression. These findings add to the hypothesis that a high-fat diet can alter vascular components of the brain, leading to BBB disruption and dysfunction of brain endothelial cells, but more studies are necessary to determine the direct mechanisms. A summary of plausible events following diet-induced changes in the brain vasculature is shown in Fig. 1. Taken together, these recent studies point to an alteration in cerebro-vascularization following a high-fat diet. Future studies should include exploration of the role of high-fat diets on cerebral blood flow and BBB integrity, and the subsequent effects on cognition as well as the interaction between inflammatory and vascular factors upon hippocampal function.

Contribution of the aging process

While high fat diet-induced neuroinflammation and cognitive decline have not been extensively explored, the role of neuroinflammation in aging and cognitive decline has been well studied. In fact, neuroinflammation has been proposed to be in the center of pathological alterations occurring in almost all age-related neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), AD, and Parkinson's disease,

as well as normal aging.^{83–85} During the aging process, there is a shift in the brain toward a pro-inflammatory state which leads to a chronic increase in activation of microglial cells. Studies have reported increased levels of TNF- α , IL-1, and IL-6 in brain tissue and serum of aged humans, as well as animal models.^{45,86,87} Levels of cyclooxygenase, lipoxygenase, prostanooids, and eicosanoids, all components of inflammatory pathways, have also been shown to be elevated in the brain with aging.^{45,88,89} Furthermore, it has been shown that there is a progressive deterioration of the immune response with increased aging, including time to build a response, level of activation, and speed in which the response is ended.^{90–92} This altered immune response occurs in the periphery as well as in the brain.⁹³ It has also been shown that this process is coupled to a decrease in anti-inflammatory molecules which together create an environment for an exaggerated immune response.⁹⁴ Age-induced neuroinflammation has been correlated with neurodegeneration and cognitive decline.^{95–97} Cytokines such as TNF- α and IL-6 have demonstrated a role in age-related neuroinflammation and neuronal dysfunction. However, IL-1 beta has been described as especially important for inflammatory changes occurring with aging.^{98–100} For example, Trompet *et al.*¹⁰¹ revealed better cognitive performance in an elderly population that had a genetic variation in the IL-1 beta converting enzyme (ICE) causing lower levels of IL-1 beta compared to those without the genetic variation.

Aging itself can also lead to disrupted cerebral blood flow and decreased angiogenesis.¹⁰² In fact, many human studies have revealed increased BBB permeability for elderly, healthy subjects compared with young, healthy subjects.^{103,104} Changes also occur during aging at the level of endothelial cells such as a decreased number of endothelial cell mitochondria, impaired endothelium dependent vasodilation, and a loss of elongation in endothelial cells.^{45,105–107} The mechanisms proposed to be involved in age-related BBB breakdown include increased oxidative stress,¹⁰⁸ inflammation and hypertension.^{109–111} Further clinical evidence for vascular changes during aging includes visualization of white matter hyper-intensities (WMHs) which occur in 30% of healthy adults over 60 years old.¹¹² WMHs are observed on T2-weighted magnetic resonance imaging scans as areas with increased signal. The reason for WMHs is controversial; however, they are believed to be involved in ischemia, hypoperfusion, BBB leakage, inflammation, and/or neurodegeneration.^{113–115} Neuropathological evaluations post-mortem have revealed various findings to explain WMHs and include arteriosclerosis, demyelination, and gliosis.^{116,117} While age is the strongest predictor of WMHs, hypertension, atherosclerosis, and decreased cortical blood vessel density

have been found to be correlated as well.^{118–121} *In vitro* experiments have begun to explain at least one mechanism by which opening of the BBB occurs with aging. It is known that aging is associated with increased inflammation^{122,123} and that microglia and astrocytes can release pro-inflammatory cytokines such as IL-1, IL-6, and TNF α .^{124–126} These pro-inflammatory cytokines activate cerebral endothelial cells to produce eicosanoids which then open the BBB.¹²⁷ It has also been determined that the type I IL-1 receptor is expressed directly on cerebral endothelial cells further explaining the mechanism by which increased inflammation can open the BBB¹²⁷ (Fig. 1). Increased permeability of the BBB leads to migration of monocytes across the barrier, as well as infusion of other pro-inflammatory cytokines, such as TNF α , and further perpetuates an already increased neuroinflammatory environment caused by aging. This phenomenon has been observed in cerebral inflammatory diseases such as multiple sclerosis and bacterial meningitis.^{128,129} However, this has not been thoroughly evaluated in a model producing chronic inflammation from a poor diet or obesity. The only evidence to date that alludes to this connection include the following: (i) high-fat diet consumption and obesity increases risk of cerebral stroke¹³⁰ possibly by altering cerebral perfusion^{45,131} and (ii) in a study by Osmond *et al.*,¹³² adult obese Zucker rats that exhibited moderate hypertension and severe insulin resistance also revealed increased cerebral vascular myogenic tone and inward cerebral vascular remodeling.¹³² The contributions of these age-related changes to inflammation and vascularization to obesity have important implications for the susceptibility and progression of cognitive decline.

Summary

As described above, a number of factors have been proposed to cause high-fat diet-induced damage to the brain, especially with aging, including oxidative stress, insulin resistance, inflammation, and changes to vascularization/BBB integrity. The contribution of insulin resistance, essential fatty acid consumption, and oxidative stress may be coordinated with inflammatory and vascular alterations to cause overall changes in brain function with consumption of high-fat and high-glycemic index-type diets. However, not enough studies have been conducted to fully understand the role of each of these cascades for high-fat-induced cognitive impairment. Based on the epidemic proportions of diabetes and obesity in the United States today, it is important to reveal these factors. A diagram illustrating our current thoughts regarding mechanisms involved, as outlined in this review is shown in Fig. 1. Our studies strongly suggest that aged individuals are more susceptible to damaging

effects of high-fat diets than young subjects, making diet intervention and exercise programs even more valuable from the standpoint of preventing further cognitive decline in elderly patients.

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