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Review Article

Western Diet and Cognitive Impairment: Links to Potential Mechanisms: A Review

Betul Aslan*

Department of Anatomy, Faculty of Medicine, Maltepe University, Istanbul, Turkey

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**Corresponding author:*
Betul Aslan, PhD Candidate;
Department of Anatomy, Faculty of Medicine, Maltepe University, Istanbul, Turkey.
Tel: +5306869035
Email: betlasln35@gmail.com
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ABSTRACT

Animal studies in recent years have shown that a Western diet style (WD-style) which is high in saturated fat and refined carbohydrates causes obesity, metabolic syndrome and cardiovascular diseases. In addition, results demonstrated that it can damage the structures that make up the nervous system. Accordingly, there is an evidence that systemic changes associated with the Western diet lead to blood-brain barrier (BBB) disruption, microglia activation, and the development of neuroinflammation. These changes are then followed by synaptic transmission dysfunction, neurodegeneration, and finally memory and cognitive deterioration. This review summarizes research on the mechanisms that show Western diet consumption is associated with cognitive impairment, with emphasis on learning and memory functions that depend on the integrity of the hippocampus.

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Introduction

While the consumption of oil and sugar was less due to limited production in previous times, great changes occurred in the production of oil and sugars with the agricultural and industrial revolution. The introduction of livestock during the agricultural revolution allowed the consumption of meat and high-fat dairy products with much higher saturated fat content (1). The developments in technology that came with the industrial revolution also increased the production and consumption of refined grains, sugars and vegetable oils (2). One of the lifestyle changes that has occurred in Westernized societies in recent years is the increased consumption of Western-style diets (WD-style). These diet are poor in fibers, vitamins and minerals, including processed foods, “fast food”, convenience foods, snacks and sugary soft drinks. Increasingly, these food products and their consumption have spread further from high-income countries to low-income countries. However, there has been a simultaneous increase in diseases associated with Western diets (3, 4). Changes in dietary fat and sugar content were accompanied by adverse health consequences (5).

The western-style diet is one of the experimental diets that mimics the highly palatable and high-energy diets, first pioneered by Rothwell and Stock in the 1970s, also called the cafeteria or supermarket diet. Cafeteria diets consist of palatable human foodstuffs offered to rodents in addition to normal feed. This cafeteria diet is one of many approaches used to study the development of obesity in laboratory rodents. Since these diets are mainly based on unsaturated high fat and cholesterol intake, if consumed, they can cause disruption in the normal functioning pathways in the body (6). WD-style represents a calorie-dense food that is highly heterogeneous in quantity and quality of

fat (saturated vs unsaturated), carbohydrates (high glycemic vs. low glycemic) and protein content (7). This dietary pattern is also poor in grain, fiber, and content of mono and polyunsaturated fatty acids (MUFA, PUFA) including anti-inflammatory omega-3, -6, and -9 acids (8).

WD-style components and their percentages have been used on the effects of WD-style feeding on brain health in animal models, such as diets containing 35-60% fat with high concentrations of saturated fatty acids (SFA) and additional amounts of simple sugars and cholesterol (7). Also, WD-styles are high-energy diets and have a high glycemic index, which means they can cause a rapid spike in blood sugar (9). Therefore, WD-style consumption can result in high caloric intake for short periods, rapid increases in plasma glucose and insulin, and subsequent absorption of nutrients into adipose tissue. These characteristics of WD-style consumption can cause rapid weight gain compared to balanced diets (10). Considering that diet plays a very important role in the regulation of energy metabolism, WD-STYLE is an important factor as a pathophysiological risk factor (7).

Recently, studies in rodents and humans have revealed that Western dietary patterns are associated with elevated serum markers of inflammation (11, 12). Accordingly, long-term WD-style diet may impair normal physiology and affect health by increasing weight gain, pathological changes in lipids and energy metabolism, and activation of the immune system. Therefore, the impaired immune-metabolic system can lead to a number of chronic metabolic diseases, especially obesity, type 2 diabetes (T2DM), cardiovascular diseases, and neurodegenerative and autoimmune diseases (13). There is an evidence to suggest that systemic changes are associated with WD-style lead to the development of neuroinflammation in parallel with the disruption of the blood-brain barrier (BBB). These changes are then followed by dysfunction of synaptic transmission, neurodegeneration, and finally memory and cognitive deterioration (8).

Figure 1 depicts what might be termed a ‘‘Vicious Circle’’ model of obesity. This model starts with the conventional assumption that an ‘‘unhealthy diet’’ is one that includes too many highly palatable foods that are rich in saturated fat and refined sugar. This diet is considered unhealthy to the extent that consuming it interferes with or degrades a critical hippocampal function. This function involves the ability to inhibit the activation of the memories of food or of the rewarding consequences of eating. If this inhibitory function is disturbed, these memories and the environmental cues that retrieve them will have increased power to evoke appetitive responses that are instrumental to obtaining and - consuming food. Based on the assumption that the inhibition of these memories and the responses they trigger is normally strongest under conditions of positive energy balance, weakening of this type of control would result in energy intake in excess of energy needs (14). In the light of this information, the aim of this review is to investigate the effects of WD-style nutrition on cognitive functions through potential mechanisms.

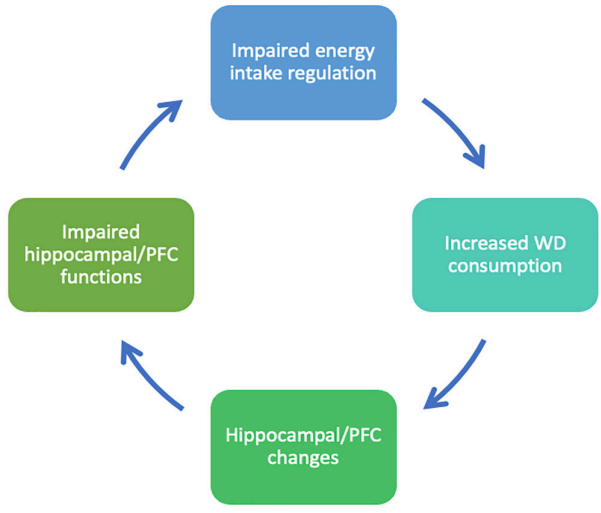

Figure 1: A ‘‘Vicious circle’’ model of obesity whereby Western diet consumption induces neurological changes to the hippocampus and prefrontal cortex (PFC), affecting cognitive functions that are involved in energy intake regulation and subsequently causing increased consumption of this same diet (14, 15).

Potential Mechanisms

Several potential mechanisms have been proposed, as consumption of a high-fat diet has been found to result in decreased performance on tests of cognitive functions.

1. Insulin and Leptin Regulation

Effects of high-fat diets on energy metabolism and cognitive functions are high expression of the insulin receptor in the hippocampus and cortex, while synaptic insulin signaling is critical for learning and memory. Besides, peripheral insulin insensitivity may have dramatic effects on the central nervous system (CNS) (16, 17). Consistent with the potential role of insulin in learning and memory, it was found that cognitive impairment associated with a high-fat (HF) diet was also associated with impaired peripheral and central insulin signaling (18). It was shown that leptin resistance is associated with cognitive deficits and also delivery of leptin to the hippocampus modulation, while increasing long-term potentiation (LTP) (19).

Leptin binds to leptin receptors (ObRs) located in CNS and peripheral tissues. As leptin receptors are expressed in the hippocampus, in this context, it has been shown that leptin has direct effects on the electrophysiological and anatomical plasticity of the hippocampus. Morphologically, leptin increases synaptic density in hippocampal primary cultures and also increases cell proliferation/neurogenesis in the dentate gyrus. On the other hand, the results found that decreased synaptic plasticity in experimental leptin resistance models may cause learning and memory deficits and depression-like behaviors (20). In recent years, the data obtained attracted attention to the neuroprotective effects of leptin in Alzheimer's disease (AD), Parkinson's, epilepsy, ischemia and glaucoma. For example, leptin prevents hippocampal synaptic degradation and neuronal cell death induced by beta amyloid (Aβ). It also shows beneficial effects on the memory of transgenic mice in the object recognition test and the T maze foot shock avoidance test (21). Increasing evidence indicates that the emotional, cognitive, and stress-reducing effects of leptin act through its receptors located in different brain regions (22, 23). Recent evidence suggests that leptin signaling, like insulin, may have a critical role in hippocampus-dependent learning through regulation of synaptic plasticity and neurotransmitter receptors (24, 25).

2. Oxidative Stress and Inflammation

It is known that fatty acids increase the oxidative stress load and increase inflammation, which have negative effects on cognitive functions (26). In fact, chronic inflammation in adipose tissue (AT) is thought to greatly contribute to the effects of HF diet and obesity on insulin sensitivity, which can affect learning and memory (27, 28). Based on the results of several studies reviewed, many of them found that HF diet increases oxidative stress in the hippocampus and cortex, as well as increases inflammatory cytokines in the hippocampus and cortex (29, 30).

Several events trigger and propagate chronic inflammation associated with obesity caused by WD-style. Overexposure of immune cells in the AT to free fatty acids (FFA) leads to initiate cellular toll like receptor 2/4 (TLR2/4) activation, which leads to activation of proinflammatory signaling pathways. This results in secretion of proinflammatory agents such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin 1β (IL-1β), nitric oxide synthase (iNOS), C-reactive protein (CRP), intercellular adhesion molecules (ICAM), and monocyte chemotactic protein 1 (MCP-1) from adipocytes and AT-resident immune cells. They lead to lipotoxicity, insulin resistance, and induction of T2DM (31-39).

The chronic inflammatory state in AT is characterized by changes in various immune cells that are typical for both innate and adaptive immune responses. The total number of T and B cells is increased, with activated T cells. These cells secrete many chemokines that attract macrophages to AT, where inflammation is enhanced by intense secretion of interferon-γ (IFN-γ) (37, 40). At the same time, some compensatory anti-inflammatory responses occur in the AT. These responses are mediated mainly by anti-inflammatory macrophages, which B cells produce interleukin -4, -10, and -13 (IL-4, -10, -13). However, this process is insufficient to stop the spreading inflammation (34, 36, 41). In addition, animal studies have shown that a high-fat/high-cholesterol diet not only causes cognitive impairment; but also increases neuroinflammation (42, 43). Neuroinflammation is a hallmark of neurodegenerative diseases associated with WD-style, including high fat consumption and fiber deficiency (15, 44).

Proinflammatory cytokines are often induced by WD-style, such as IL-1β and IL-6, that can disrupt neural circuits involved in cognition and memory (45). Also, evidence showed that WD-style consumption leads to inflammatory changes that lead to brain insulin resistance (46). Besides, neuronal pathologies caused by WD-style are exacerbated by mitochondrial dysfunction, including decreased citrate synthase activities and complexes I and III, and increased mitochondrial reactive oxygen species (ROS) production (47, 48). The brain is vulnerable to mitochondrial defects as it depends on mitochondrial function for neurogenesis, neurotransmitter synthesis, calcium homeostasis, and neuronal survival, plasticity and excitability (49).

The gut microbiota has been reported to modulate adult hippocampal neurogenesis and neurological function by controlling the maturation and function of microglia in germ-free and antibiotic-treated specific pathogen-free (SPF) mice. This may be the major event where a change in the gut microbiota (intestinal dysbiosis) initiates neuroinflammation and subsequent neuronal damage. That is, dietary fructose disrupts hippocampal energy homeostasis, causing neuroinflammation and neuronal damage (50). As a result, consumption of the WD-style exacerbates metabolic disorders and oxidative stress throughout the body, causing microglial activation in the cortex as well as motor dysfunctions (51).

3. BBB Dysfunction

WD-style-induced metabolic syndrome and

systemic inflammation combine at the BBB, resulting in its disruption and neuroinflammation. The BBB is a structural complex of endothelial cells that interact with pericytes, glial cells, and neurons that span the microvascular networks within the CNS (52). The BBB acts as a crucial regulator for the transport of nutrients and other compounds essential for healthy brain functions from the blood to the brain, while also blocking the entry of circulating cells and potentially harmful macromolecules such as proinflammatory factors and toxins. In contrast, the BBB transport system reversely removes neurotoxic molecules and metabolic wastes from the brain (53).

BBB endothelial cells are connected by tight junctions consisting of proteins such as zonula occludens (ZO-1, -2), occludin and claudins (CLDN-3, -5, -12) that regulate the permeability of various substances and protect the BBB. Peptides, proteins, receptors for hormones, and a transport-receptor protein system for certain classes of nutrients from the circulation, such as glucose and vitamins, are important components of brain endothelial cells that contribute to BBB permeability (52, 54). In recent studies, one of the important results observed in elucidating the molecular mechanisms are responsible for BBB function is BBB disruption in neurological diseases (55).

Studies on the role of dietary factors in BBB integrity have also been a focus for many years. Among others, WD-style-induced increased permeability of the BBB has been demonstrated in several animal models. In rodents, WD-style disrupted active transport of various neuroendocrine molecules, including leptin and ghrelin, via the BBB (56). In addition, exposure to typical WD-style components such as glucose, cholesterol, and lipids led to disruption of retinal pericytes, which are essential for maintaining a properly functioning BBB. Studies in rats and mice confirmed not only the direct role of WD-style in increasing BBB permeability, but also memory impairment (57). For example, sodium fluorescein (NaF1) is a molecule that normally excluded from brain entry with an intact BBB. It reduces BBB permeability and mRNA expressions of the tight junction proteins ZO-2, CLDN-5, and CLDN-12. In mice fed WD-style with NaF1 for 90 days, hippocampus-related memory disorders have been observed (57). In the results of another study, BBB hyperpermeability associated with neuroinflammation and tight junction molecule changes in the hippocampus were also observed in mice fed HFD for 7 weeks (58). These data fully demonstrated that in wild-type animals, WD-style can cause BBB damage, changes in the hippocampus, and memory impairment, with both the susceptibility to obesity and the degree of impairment depending on the duration of exposure to WD-style (8).

WD-style-induced obesity, metabolic syndrome (MetS), and gut microbiota dysbiosis, followed by low-grade systemic inflammation can cause BBB impairment. It was shown that high adiposity and MetS increased levels of circulating inflammatory factors (39). Metabolic and systemic inflammation have been shown to lead to upregulation of specific endothelial surface adhesion molecules, including platelets and endothelial cells. This resulted in cell adhesion molecule 1, E-selectin and ICAM1, increased leukocyte migration and adhesion and BBB permeability (52). It is known that due to increased BBB permeability, cytokines and chemokines, as well as circulating immune cells, infiltrate the CNS from the periphery and contribute to the development of neuroinflammation (59).

In particular, mice fed long-term WD-style showed increased BBB infiltration in immune cells, including activated monocytes/macrophages and neutrophils (60). These cells secrete numerous factors that can impair BBB function, including ROS, proteolytic enzymes, cytokines, lymphotoxins or vascular endothelial growth factor. These factors can alter BBB function by acting on the endothelial cytoskeleton, junctional proteins, and endothelial glycocalyx. Additionally, leukocytes can disrupt calcium signaling and endothelial transcriptional activity leading to induction of proinflammatory gene expression, which ultimately disrupts barrier of junctional complexes and induces endothelial cell retraction (61). In line with these results, the results of a study showed that a WD-style or hyperlipidemia in mice can alter brain glucose uptake and metabolite levels, activate resident inflammatory cells (microglia), increase brain factor VIII vascular expression and BBB transfer coefficient. All these factors cause moderate cognitive impairment (61).

4. Brain-derived Neurotrophic Factor (BDNF)

One of the most important intracellular factors for neural plasticity is neurotrophins. The most well-known of these is BDNF. BDNF is a small protein of 13.5 kDa responsible for the development of neurons. Although mostly synthesized in neurons, it is also overexpressed in the cerebral cortex and hippocampus (62). BDNF can be characterized as hippocampal and hypothalamic depending on its location. Hypothalamic BDNF inhibits food intake, and increases energy expenditure. That means, it provides a negative energy balance. BDNF plays a role in energy metabolism and affects blood glucose and lipid levels. It is another evidence that serum BDNF levels decrease in T2DM and MetS. If it is

found in sufficient amount in the serum, it lowers blood glucose and increases insulin sensitivity. Hippocampal BDNF is particularly effective in learning and memory. It plays a role in the plasticity of neurons and the formation of new neurons. It plays a role in the growth and development of neurons, as well as in the function of the synaptic pathway and in the regulation of branching of axons and dendrites. It also has positive effects on the development of noradrenergic and serotonergic neurons. BDNF mRNA expression changes in physiological and pathological conditions and BDNF mRNA expression is increased in cases such as learning and memory stimulation (63).

However, its deficiency has been shown to decrease in depression and neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and Amyotrophic lateral sclerosis (64). The role of BDNF has been scientifically proven, especially in psychiatric disorders. So, since these are also involved in hippocampal plasticity and synaptic activity, the neurotrophic hypothesis of depression has become very popular in the last decade. It is claimed that the decrease in BDNF level causes depression, while the increase in brain BDNF levels creates an antidepressant effect (63, 64). Another example is that high-fat and high-sugar diets reduce BDNF expression, which has been associated with memory deficits. For example, feeding rats with a high-fat and high-sucrose diet for 2 months, 6 months and 2 years was found to decrease hippocampal BDNF mRNA and protein levels (65).

There is a compelling evidence that the regulation of BDNF and adult hippocampal neurogenesis can be altered through diet. Animal models have shown that WD-style high in fat and sucrose can impair neurogenesis and lower BDNF levels in the hippocampus, negatively impacting cognitive performance (66). Finally, multiple studies have found that HF diet intake is associated with decreased BDNF expression in both the hippocampus and cortex; this suggests the adverse effects of HF diet consumption on learning and memory that may be partially mediated by alteration of BDNF-related synaptic plasticity (18).

5. Mitochondrial Dysfunction

Impairments in cognitive functions are consistent with both central and peripheral mitochondrial dysfunction and decreased biogenesis. Impaired oxidative phosphorylation and impaired mitochondrial ATP production can lead to neuronal plasticity dysfunction and decreased neurogenesis (67). Significant preclinical evidences suggest that malnutrition may contribute to mitochondrial dysfunction. A high-fat diet is also associated with increased free radical production, inflammation, and abnormal mitochondrial biogenesis associated with insulin resistance. A hypercaloric high-carb diet leads to similar pathways as does a high-salt diet; these are essential components of a low-quality WD-style (66).

6. Gut Microbiota

A rapidly growing literature has shown that the gut microbiota is involved in regulating physiological processes, including cognitive function, neuropsychiatric disorders, and behavior through the microbiota-gut-brain axis (68). The gut microbiome is one of the first body systems to interact with food consumed. Because of this, it may lead to involvement in the pathophysiology of depression via many other mechanisms like inflammation, neurogenesis, etc. (69). The gut microbiota thus offers a potentially critical mediation pathway in the link between diet and brain health. Data from animal models have supported this. Dietary-based changes in the gut microbiota may contribute to behavioral changes that mimic symptoms of common mental disorders such as anxiety and depression. For example, a high-fat, WD-style resulted in rodent patterns of decreased exploratory behavior, increased anxiety-like behavior, and reduced memory, along with an increased Firmicutes/Bacteroidetes ratio (70, 71). Other preclinical studies have shown that high-calorie diets increase Clostridiales, Ruminococcaceae, and Bacteroidales abundance, leading to impairment in social and object recognition as well as cognitive flexibility (72, 73). Prebiotic supplementation (fructo and galacto oligosaccharide) reverses chronic stress-induced changes in the gut microbiota by preventing the reduction of beneficial microbes such as Bifidobacterium or Lactobacillus. It normalizes chronic stress-induced proinflammatory cytokines and depressive-like behaviors in mice, modulating brain function and behavior (66). Other animal studies have come to the same conclusion, observing that transferring microbiota from animals exposed to a high-fat diet that can lead to behavioral changes such as exploratory and cognitive behavior in the absence of the diet (74).

7. Microglia Activation

The mechanisms by which WD-style activates microglia are still under investigation. Microglial activation to a proinflammatory state has been shown to involve KCa3.1 and Kv1.3 potassium channels (75). Accordingly, under WD-style conditions, levels of KCa3.1 and Kv1.3 increased in parallel with

the increase in mRNA levels of proinflammatory genes such as IL-1β, IL6, TNF-α or ICAM1 in mouse brains and isolated microglia (75, 76). A number of studies highlight the critical role of SFA in microglial activation and neuroinflammation. Brain SFA homeostasis is dependent on circulating SFA levels. Under WD-style conditions, increased blood SFAs cross the BBB causing increased SFA accumulation in the brain (77, 78). WD-style-derived SFA in the brain impairs microglial function through activation of the microglial CD14-TLR4-MD2 complex, which induces NF-κB signaling that triggers neuroinflammation and secretion of proinflammatory cytokines (79). Activation of brain microglial cells by WD-style-derived SFA via the TLR4 receptor inhibits autophagy in these cells. Microglial autophagy, which occurs as an accumulation of autophagic vacuoles, influences microglial activation and inflammatory responses. The finding that the degradation of extracellular Aβ fibrils by microglia is dependent on their autophagy revealed a mechanistic link between autophagy and amyloidopathy in AD development (80).

Autophagy disorder in microglia has received much attention recently as a novel driver and therapeutic target of neurodegeneration and aging (81). A key mediator in microglial activation and autophagy dysfunction is IL-1β (82). In cultures of purified microglia, IL-1β treatment induces the production of multiple cytokines and inhibites mammalian rapamycin target (mTOR)-dependent autophagy signaling, while blocking IL-1β reduces proinflammatory cytokine production and increases microglial phagocytosis of Aβ (83). Autophagy regulates not only the immune response of microglia, but also microglial metabolism and phagocytosis. These data suggests that autophagy plays an important role in the disruption of WD-style-induced microglial phagocytosis and the inflammatory profile in AD development and progression. Altogether, the data reviewed indicate that WD-style, and in particular diet-derived SFA, causes reprogramming of microglia from a beneficial phagocytic state to an active state, and also it causes the release of large amounts of proinflammatory mediators that are associated with impaired autophagy and Aβ phagocytosis.

8. Maternal Diet

High-fat diet consumption during pregnancy has been shown to cause maternal obesity and to increase oxidative stress. This is thought to play a role like other stress factors that cause stress-related metabolic or behavioral deterioration (84). Recently, it has been shown that WD-style feeding of animals during early development not only promotes obesity and metabolic disorders in later life, but also affects adult behavior, especially when animals are fed during lactation periods (6). A growing body of evidence suggests that maternal diet during pregnancy and the postpartum period may have a profound and long-lasting effect on the offspring's brain, behavior and metabolism. For example, maternal HF diet consumption has been found to result in increased body weight and offspring adiposity in the early perinatal period. Additionally, maternal consumption of HF diet has been shown to increase food intake and body weight and preference for HF diet among adult offspring. The results of a study using a mouse model found that maternal exposure to a 60% HF diet increases the risk of developing diet-induced obesity in offspring; while also altering leptin sensitivity and digestive behavior. Regarding the potential mechanisms underlying these changes, changes in placental transport of nutrients and hormones may also be involved, in which maternal HF diet consumption increases hippocampal inflammation, increases plasma leptin, and decreases hippocampal BDNF. All evidences to date indicate that exposure to the HF diet early in life affects cognition and may have lasting effects on metabolism (18) (Figure 2).

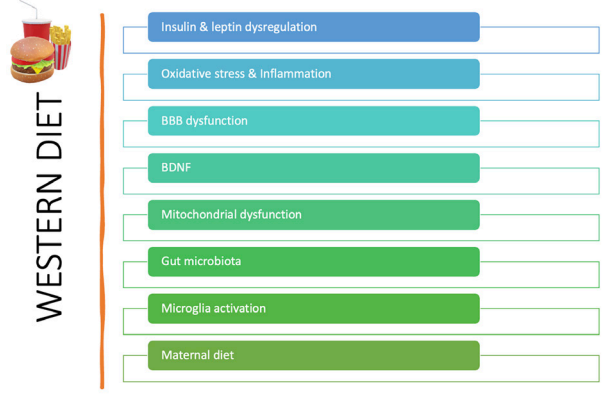

Figure 2: Overview of the role of Western style diet on impairment of cognitive functions implicated potential mechanisms.

The Relationship between Western Diet and Cognition

Cognitive functions are affected by HF diets. Memory, attention, working memory, seem to be predominantly performed by two brain regions; hippocampus and PFC (15). Basically, the hippocampus has important roles in memory, mood, position and orientation. Therefore, the hippocampus has been the most studied tissue for experimental and clinical studies on rodents. The hippocampus has a well-known role in supporting memory function, while damage to this structure

is associated with major impairments in episodic memory in humans. Animal data suggests that hippocampal lesions impair memory performance in the Morris Water Maze (MWM), Radial Arm Maze, and object recognition tests. The PFC is known to be involved in most cognitive functions, including attention, verbal fluency, and working memory (15). It is important to note that it is difficult to separate the hippocampal-dependent memory function from cognitive functions such as attention and working memory supported by the PFC (85). However, these brain regions have been the focus of much of the animal literature on the effects of HF diets on cognitive function.

Obesity and diabetes are often associated with WD-style intake, also play a role in the development of dementia. In contrast, a healthy diet enriched with vegetables, grains, fish and low-fat dairy products protects against the development of dementia (76). WD-style may affect mutual cognition and social interactions. Human and animal studies suggest that increased dietary consumption of fat/cholesterol plays an important role in behavioral abnormalities associated with social behavior, aggression, and brain plasticity. The mechanisms underlying the reduced social interactions and brain plasticity are associated with WD-style may overlap. It is suggested that the reason for the increase in aggression-like behaviors is due to the decrease in cognitive functions in general. According to current literature reports, animals which are exposed to high fat and high cholesterol diets have decreased learning abilities and impaired cognitive functions (86).

Although WD-style contains various combinations and concentrations of different macro- and micronutrient sources, researches have primarily focused on cognitive impairment resulting from the consumption of the two main components of this diet, namely saturated fats and simple sugars (87). Evidence from studies using rodent models is also consistent with the hypothesis that SFA intake can lead to cognitive impairment. Greenwood and Winocur have shown that a high SFA diet with a source of complex carbohydrates can impair learning and memory performance in mice (88). One study evaluated the effects of three months of exposure to a diet high in SFA, PUFAs, or MUFAs on the ability of rats to learn an appetitive operant conditioning task and found that mice on the SFA diet were poor at learning the task, whereas PUFA or MUFA intake had little effect on performance compared to the low-fat control diet. Thus, diets high in SFA appearred to have a greater disruptive effect on cognitive function in rodents than diets high in unsaturated fats or low in total fat (89).

It also appears that the effects of consuming simple compared to complex carbohydrates on cognitive function may vary depending on factors such as the type of learning used or memory assessment. For example, simple carbohydrate versus complex carbohydrate intake is associated with impairments in various measures of delayed verbal memory in adult subjects with well-controlled T2DM, whereas only marginal impairments are found in the one-digit working memory task (90). Contrary to these findings, however, a study using healthy children as subjects showed impaired verbal memory immediately, rather than delayed, following simple carbohydrate intake relative to complex carbohydrates (91).

These studies suggest that simple carbohydrates may impair post-meal memory performance for both immediate and delayed information, and that the effects of simple carbohydrates on memory performance may depend on the age and/or diabetic status of the subjects (87). A cross-sectional study of a middle-aged population showed that saturated fat intake is associated with an increased risk of cognitive functions, including memory, speed, and flexibility (92). Another group found that higher saturated fat intake was associated with greater declines in cognitive scores (consisting of immediate and delayed memory, processing speed, and attention) over 6 years after adjusting for age, gender, race, education, and antioxidant intake (93). Another recent study evaluated cognitive function before and after consuming the HF diet. Twenty men aged 25-45 years were fed a standard diet (17% fat) for 3 days followed by HF diet (74%) for 7 days. Cognitive assessment was performed before and after HF diet consumption and showed that attention was significantly reduced following dietary intervention (94).

A randomized controlled trial of two healthy men aged 19-28 years on HF (70% fat) or standard diet (24% fat) showed significantly lower attention and processing speed compared to standard diet after 5 days of HF diet consumption (95). According to the results of a study conducted in 14-year-old students in Australia, it was concluded that long-term feeding with a WD-style resulted in poor cognitive performance after 3 years. These results were found to be associated with impairments in visuospatial learning, long-term memory, and reaction times (65). It has been reported that these deteriorations in cognitive performance are caused by excessive consumption of SFAs in the diet. In contrast, higher intake of PUFA and PUFA to SFA ratio is associated with better memory function and reduced risk of memory impairment (96). The results of another study showed that feeding with

a WD-style in experimental animal models would lead to impaired cognitive functions by impairing hippocampal-dependent learning and memory processes involved in spatial memory and executive memory functions (97).

A number of studies have used the eight-arm radial maze to assess the effects of diets high in SFA and simple sugars on hippocampal-dependent spatial learning and memory function based on appetitive reinforcers (87). The radial maze task can be structured like this: the trials a certain number of the arms of the maze are always baited with a food pellet and other arms are never baited. The ability of the rats to enter only the baited arms and to refrain from entering the unbaited arms is considered to be an index of reference memory. On the other hand, entering an arm on a given trial that is never baited would be recorded as a reference memory error (98).

The radial arm maze can also be used to assess working memory, which involves remembering which arms have already been visited on a given trial and which have not. Working memory errors occur when rats return to an arm (previously baited or nonbaited) that they have already visited on the current trial. Both reference memory and working memory with spatial cues are impaired as a consequence of selective damage to the hippocampus (99). Similarly, deficits in both spatial reference and spatial working memory have been reported in rats that have been maintained on a WD-style (100). In addition, several studies have shown that consuming low micronutrient components of a WD-style can also disrupt learning and memory performance in the MWM task. Rodents were fed *ad libitum*, the diets with high levels of both SFA and sucrose or the diets with more complex carbohydrates and high levels of fat several months. Then these animals were impaired in learning the location in the MWM task relative to control animals (87).

Conclusion

In the last 10 years, the number of studies on the effects of nutrition on brain function has been increased. These studies showed that obesity and increased consumption of high-fat diets increased the risk of developing dementia. Consumption of high-fat or high-glycemic index diets is thought to cause brain damage through oxidative stress, inflammation, insulin resistance and deterioration in vascularization, which is known to negatively affect cognition. According to these results, behavioral disorders due to consumption of high-fat diet, high-calorie diet, high-fat and high-sugar diets best explain the deterioration in memory associated with depression-like behaviors. In this review, the relationships between the WD-style and the potential mechanisms that cause cognitive impairment are discussed. Therefore, it is very important for us to understand how an unhealthy diet impairs cognition and how affects diseases or disorders can cause in humans at more advanced levels.

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Conflict of Interest

None declared.

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