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Obesity-related cognitive impairment: The role of endothelial dysfunction

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Abstract

Obesity is a global pandemic associated with macro- and microvascular endothelial dysfunction. Microvascular endothelial dysfunction has recently emerged as a significant risk factor for the development of cognitive impairment. In this review, we present evidence from clinical and preclinical studies supporting a role for obesity in cognitive impairment. Next, we discuss how obesity-related hyperinsulinemia/insulin resistance, systemic inflammation, and gut dysbiosis lead to cognitive impairment through induction of endothelial dysfunction and disruption of the blood brain barrier. Finally, we outline the potential clinical utility of dietary interventions, exercise, and bariatric surgery in circumventing the impacts of obesity on cognitive function.

Keywords

hyperinsulinemia; insulin resistance; inflammation; gut dysbiosis; diet; memory

Introduction

Obesity, a pandemic impacting over 1 billion people in the world and 90 million Americans, is a risk factor for cardiovascular disease, cognitive impairment, and dementia (Toth et al., 2017). Age and cardiovascular risk factors adversely affect vascular health, which is critical to normal brain function including cognitive function (DeCarli et al., 2001; Hanon et al., 2005; Hoth et al., 2007; Panza et al., 2006; Solfrizzi et al., 2004). Disruptions in the vascular

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Competing interests

The authors declare no competing interests.

system, which involves the macro- and microvasculature and the endothelium, occurs prior to the onset of cognitive impairment (Corriveau et al., 2016). In fact, this is now widely recognized as a broad-spectrum disorder referred to as vascular contributions to cognitive impairment and dementia (VCID) (Gorelick et al., 2011).

Endothelial cells have distinct functions in vascular biology. Endothelial cells are responsible for maintaining vascular tone, regulating blood flow, modulating the inflammatory response, and the trafficking of molecules between the periphery and the brain. Endothelial dysfunction disrupts blood flow, reduces vascular tone, and impairs the blood brain barrier (BBB) (Wardlaw et al., 2013). This is mediated in part by disruption in specialized receptors on endothelial cells that transduce mechanical and chemical stimuli to facilitate the release of signaling molecules such as nitric oxide (NO), endothelin, and prostanoids.

Both clinical and preclinical studies demonstrate that obesity reduces the bioactivity of NO (Bender et al., 2007; Bourgoin et al., 2008; Damjanovic and Barton, 2008; Rask-Madsen and King, 2007). Severely obese children display evidence of endothelial dysfunction (Tounian et al., 2001). Furthermore, severely obese (body mass index, [BMI] ≥34 kg/m^2) insulin resistant individuals demonstrate impairments in blood flow and vascular tone (Steinberg et al., 1996). This is likely due the downstream signaling consequences associated with hyperinsulinemia/insulin resistance. Insulin resistance is characterized by reductions in phosphoinositide 3-kinase (PI3K) signaling and increased mitogen-activated protein kinase signaling, which leads to decreased NO production, a characteristic of endothelial dysfunction (Williams et al., 2002). These processes work synergistically to promote continuous blood flow to the brain, a process known as neurovascular coupling. Obesity induced disruption of NO has been linked to impaired neurovascular coupling in preclinical models (Tarantini et al., 2018; Tucsek et al., 2014b). Furthermore, this impairment in neurovascular coupling has been associated with cognitive impairment and neurodegeneration (Riddle et al., 2003; Troen et al., 2008; Tucsek et al., 2014a).

Understanding additional mechanisms that contribute to the development of insulin resistance may have therapeutic potential for preventing or reversing obesity-associated endothelial dysfunction. Herein, we discuss the role of specific obesity-related mechanisms including inflammation, hyperinsulinemia/insulin resistance, and gut dysbiosis on endothelial function and cognitive impairment. Likely, obesity induces a feed-forward cycle among these various mechanisms, which ultimately culminates into endothelial cell dysfunction and consequently cognitive impairment (Figure 1). While other mechanisms such as oxidative stress, mitochondrial dysfunction, and neurotrophic factors are important, they have been extensively reviewed elsewhere (de Mello et al., 2018; Sripetchwandee et al., 2018), and thus will not be discussed here. We conclude our review with a summary of therapeutic strategies currently being investigated for alleviating the detrimental impacts of obesity-induced cognitive impairment. Understanding the impact of the relationship among these phenomena may help bring forward new therapeutic strategies to mitigate obesity-induced cognitive impairment.

The link between obesity and cognitive impairment

Clinical Studies

Clinical studies evaluating the link between obesity and cognitive impairment demonstrate inconsistent findings. Some support an association between obesity and cognitive impairment (Gunstad et al., 2010; Prickett et al., 2015; Wang et al., 2016a) while others fail to demonstrate a relationship(Reviewed in (Bischof and Park, 2015; Gunstad et al., 2010; Han et al., 2009). These inconsistent findings may be due to variations in study design. First, clinical studies may differ based on the population age, which consist of early life (4–18 years old), early to mid-life (19–65 years old), or mid-life to late-life (65+ years old) (Smith et al., 2011). Overall, studies suggest that early and mid-life obesity are associated with worse cognitive outcomes. Of these two population ages, mid-life obesity has the most adverse effects on cognition (Dye et al., 2017). In fact, lower scores on the Mini-Mental State Examination (MMSE) correlate with midlife obesity (Bischof and Park, 2015). Cognitive performance on tests involving visual memory, organization, executive function, attention and visuomotor speed was worse in individuals with central obesity in midlife (Wolf et al., 2007). A previous study reported that late-life obesity correlated with better performance on attention and executive function tasks (Gunstad et al., 2010); however, a recent study reported no association between late-life obesity and cognitive impairment (Deckers et al., 2017). Overall, these studies suggest that aging may play a role in obesity-related cognitive impairment; however, the mechanisms have not been elucidated.

In addition to cognitive deficits, recent data suggest that differences in brain structure in obese and non-obese populations are present. For example, volumes of brainstem and diencephalon reduction were noted in early adulthood obesity (Marques-Iturria et al., 2013). Likewise, lower cortical thickness was observed in the left superior frontal and right medial orbitofrontal cortex in a similar group of patients, which may provide some explanation about the association between obesity and cognitive dysfunction in obese individuals (Marques-Iturria et al., 2013). Others have demonstrated that populations with increased BMI display decreased global brain volume and gray-matter volume with decreased neural viability in both frontal and parietal cortices (Gazdzinski et al., 2008). Similarly, reductions in global white matter integrity (Verstynen et al., 2012) and atrophy of the temporal, frontal, occipital cortices, hippocampus, thalamus, and midbrain have also been noted in other populations with increased BMI (as reviewed in Shafer et al. (Shefer et al., 2013). Coinciding with these findings is the observation that a high BMI in midlife leads to declines in neuron and myelin viability (Gazdzinski et al., 2008) and may be associated with abnormalities in altered brain plasticity (Wang et al., 2016a). Collectively, these studies show that obesity may be a causal link for deleterious changes in brain structure. Additional studies are needed to confirm the aforementioned findings.

Second, clinical studies may use different indices for “obesity” designation. The majority of clinical studies use body mass index (BMI≥30 kg/m^2) as the obesity metric. Unfortunately, BMI does not account for alterations in body composition; hence, it inadequately correlates with adiposity. Central adiposity metrics, such as waist circumference (≥ 40 inches for men and ≥ 35 inches for women) or waist-hip ratio (≥ 1 for men and ≥ 0.8 for women), correlate

better with cognitive impairment (Han et al., 2009; Nilsson and Nilsson, 2009; Wang et al., 2016a).

Third, studies differ based on the cognitive test used to assess cognitive impairment. This stems from the fact that the term “impairment” is broad and involves multiple cognitive domains. Thus, it is difficult to assess every cognitive domain in a single study, which may lead to conflicting reports. Still, strong evidence from the extant literature suggest that obesity negatively impacts memory and is associated with poor performance on psychomotor, selective attention, decision making, and executive function tests (as reviewed in Dye et al. (Dye et al., 2017).

Finally, while many clinical studies report the presence or absence of comorbidities such as hypertension, hypercholesterolemia, diabetes, dyslipidemia, or hyperglycemia, some studies fail to adjust for comorbidities when assessing the link between obesity and cognitive deficiencies. A study by Singh-Manoux and colleagues demonstrated that obese individuals who were metabolically unhealthy had a faster rate of cognitive decline compared to obese individuals without metabolic abnormalities over a 10-year period (Singh-Manoux et al., 2012). While this study demonstrates obesity works synergistically with metabolic disorders to drive changes in cognition, the authors also showed that obesity in the absence of metabolic disorders increased the rate of global cognitive decline in comparison to the rate of decline in normal weight individuals (Singh-Manoux et al., 2012). These reports have since been confirmed by other groups as well (Ala Abu Saleh, 2015; Farah et al., 2016). Table 1 summarizes clinical studies from the past decade taking into consideration study population age, obesity metrics, cognitive test, and comorbidities for each of the specified studies. Given the great variability in clinical studies, it is difficult to evaluate potential mechanisms that drive obesity-related cognitive impairment. Preclinical animal models provide the opportunity to explore novel mechanisms underlying the pathogenesis of obesity-related cognitive impairment and to develop innovative therapies.

Preclinical Studies

The western diet has been regarded as playing a significant role in the obesity epidemic. In animal models, the diet is comprised of at least 40% of calories from fat and supplemented with a lesser amount of simple carbohydrates (Lesniewski et al., 2013). Diet-induced obesity tends to vary between laboratories, with some using both high-fat and high simple-carbohydrate concentrations, while others use one or the other. Western and high simple-carbohydrate diet models induce cognitive impairment and brain dysregulation in rodent models (Darling et al., 2013; Hsu et al., 2015; Jurdak and Kanarek, 2009; Kanoski and Davidson, 2011; Yeomans, 2017). This cognitive deficit is apparent despite either no change in weight reported or minimal changes compared to a high-fat diet (HFD) (Jurdak and Kanarek, 2009; Kanoski and Davidson, 2011). Standing alone, the HFD mouse model of obesity has clinical translatability (Aroor et al., 2018; Pulakat et al., 2011), and will be discussed here.

Similar to clinical studies, preclinical animal studies also suffer from the lack of consistency in study design. First, the age of HFD induction and the duration of feeding differs across preclinical studies. The impact of juvenile onset HFD feeding on cognitive performance has

been rigorously reviewed, with the vast majority of studies demonstrating a causative relationship (Del Olmo and Ruiz-Gayo, 2018; Noble and Kanoski, 2016). This has been corroborated in both the adult and aged mouse phenotypes (reviewed (Cordner and Tamashiro, 2015). Studies demonstrate cognitive impairment after two weeks (McLean et al., 2018; Sims-Robinson et al., 2016a), 9 days (Murray et al., 2009), and even as early as 3 days on a HFD (Thaler et al., 2012), indicating that the length of feeding does not appear to be a major factor.

Second, the percentage of fat used for HFD treatment varies among the preclinical studies. Typically, obesity is induced by feeding animals a diet containing 32-60% of calories from fat. Studies with diets consisting of ≥40% of kilocalories from fat report diet-induced cognitive impairment in both mice and rats (Fu et al., 2017; Underwood and Thompson, 2016; Wang et al., 2016b). In contrast, some studies demonstrate that HFD does not correlate with cognitive impairment (Kosari et al., 2012; Li et al., 2013; Mielke et al., 2006). The impact of HFD in preclinical models on cognitive function has been extensively reviewed (Cordner and Tamashiro, 2015).

Third, similar to clinical studies, preclinical studies differ in the type of cognitive test utilized to assess cognitive impairment. Studies demonstrate that diet-induced obesity reduces performance in Morris water maze (Cordner and Tamashiro, 2015; Gladding et al., 2018; Kasper et al., 2018; Sims-Robinson et al., 2016a; Spinelli et al., 2017), novel object recognition (Cordner and Tamashiro, 2015; Kadish et al., 2016; Sims-Robinson et al., 2016a; Sona et al., 2018), and Y-maze (Almeida-Suhett et al., 2017; Cordner and Tamashiro, 2015; Gladding et al., 2018; Labouesse et al., 2018; Martins et al., 2017; Sona et al., 2018). The Morris water maze, Y-maze, and Novel Object Recognition task are designed to test spatial, working, and recognition memory, respectively. Finally, HFD mice display multiple comorbidities such as hyperinsulinemia, glucose intolerance, and hypertension (Buettner et al., 2007; Oakes et al., 1997; Tschop and Heiman, 2001; Vincent et al., 2009) depending on the percentage of fat used and the duration of HFD feeding. Table 2 summarizes preclinical studies published from 2016-2019 comparing differences in the timeline of HFD feeding, percentage of fat in the experimental diet, cognitive test, and the presence of comorbidities. Despite the variability among preclinical studies, animal models provide the opportunity to explore the molecular mechanisms underlying obesity-related cognitive impairment.

Molecular mechanisms contributing to obesity-induced cognitive impairment

Several mechanisms play a role in obesity-related cognitive impairment (Dye et al., 2017; Kanoski and Davidson, 2011; Miller and Spencer, 2014; Noble and Kanoski, 2016). Vascular contributions to cognitive impairment has been increasingly recognized in both preclinical and clinical studies (Akiguchi and Yamamoto, 2010; Fulop et al., 2018; Khan et al., 2018; Toth et al., 2017). HFD is associated with decreased vascular integrity in the brain of rodent models (de Aquino et al., 2018; Fu et al., 2017; Kalyan-Masih et al., 2016). Furthermore, BBB integrity is compromised following HFD (Freeman and Granholm, 2012; Kanoski et al., 2010). The BBB plays a fundamental role in maintaining brain homeostasis.

Given that endothelial cells are one of the major cell types that form the BBB, obesity driven endothelial dysfunction contributes to BBB impairment through several mechanisms (Wardlaw et al., 2013). Hence, understanding the potential impact of obesity on endothelial cell function may be a key factor reversing obesity-associated cognitive impairment.

BBB breakdown precedes and activates neuroinflammation and neurodegeneration. Evidence from studies in aged animal models of obesity suggest that chronic HFD leads to enhanced plasma-derived IgG leakage into the hippocampal perivascular space (Tucsek et al., 2014a). Similarly, these authors showed that aged-mice fed a HFD for 24 months had decreased hippocampal microvascular density accompanied by impairments in hippocampal-dependent cognitive function compared to mice on a normal chow diet (Tucsek et al., 2014b). These studies suggest that increased neuroinflammation may induce declines in microvascular integrity leading to cognitive decline and that these changes are compounded with increasing age. Several mechanisms contribute to obesity-induced BBB breakdown and its deleterious cerebrovascular effects.

One mechanism of obesity mediated BBB breakdown is through disruption of tight junctions at the level of the endothelium (Zlokovic, 2008). Obese type 2 diabetic mice display declines in tight junction proteins Zonula occluden-1 (ZO-1) and claudin-12 (Salameh et al., 2019). Interestingly, treatment with the mitochondrial carbonic anhydrase inhibitor, topiramate, improved tight junction protein expression and restored BBB integrity in these animals (Salameh et al., 2019). Likewise, increases in thrombin induced pericyte activation led to declines in ZO-1 and occludin but not claudin-5 in a HFD mouse model (Machida et al., 2017). Collectively, these studies suggest that obesity may induce tight junction disruption leading to BBB breakdown.

In addition, infiltration of serum-derived substances into the hippocampal space allows for microglial activation and subsequent reductions in endothelial cell tight junction protein expression in obesity (Sumi et al., 2010)(Shigemoto-Mogami et al., 2018). Long chain saturated fatty acids derived from chronic HFD intake facilitate activation of microglia to promote chronic neuroinflammation (Dalvi et al., 2017; Fritsche, 2015; Thaler et al., 2012), which contributes to cognitive impairment (Kahn and Flier, 2000; Thaler et al., 2012). HFD aged mice also display exacerbated activation of microglia associated with impaired hippocampal learning and memory deficits (Valcarcel-Ares et al., 2019). Accordingly, Bocarsly et al. reported that diet-induced obesity led to reductions in dendritic spines as well as altered microglial morphology within the prefrontal cortex, a phenomenon accompanied by deficits in prefrontal cortex-dependent cognitive tasks (Bocarsly et al., 2015). Interestingly, pharmacological inhibition of microglia activation in obese mice was shown to be protective against cognitive degradation as a result of improvements in BBB integrity (Cope et al., 2018). Additional mechanisms underlying obesity-induced initiation of BBB breakdown will be described below.

Systemic Inflammation

Chronic consumption of a “western diet” promotes systemic inflammation. Although there are various sources of inflammation with HFD consumption, the main source stems from white adipose tissue hypertrophy and dysfunction. Migrant macrophages homing to

hypertrophic adipose tissue adopt an atypical pro-inflammatory phenotype (Ghanim et al., 2004). Notably, multiple adipose tissue macrophage (ATM) subsets exist in obese adipose tissue. These populations have distinct functions, express specific markers, and have specific tissue distributions not typical of M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes (Coats et al., 2017; Gordon, 2003; Kratz et al., 2014; Xu et al., 2013). Instead, obese ATMs reflect a distinct metabolically active group of surface expression markers induced by free fatty acids, high glucose, and hyperinsulinemia (Kratz et al., 2014), which subsequently drive adipocyte hypertrophy (Lumeng et al., 2007; Weisberg et al., 2003). In mice, both resident and recruited ATMs make up about 50% of adipose tissue cells in obese animals compared to 10% in lean animals (Guilherme et al., 2008; Weisberg et al., 2003). Upon activation, ATMs produce pro-inflammatory cytokines including Interleukin (IL)-6 and tumor necrosis factor (TNF)-α.

Interleukin-6 (IL-6)—IL-6 is produced by ATMs and has pleiotropic effects on inflammation, the immune response, and vascular function (Roytblat et al., 2000; Yasukawa et al., 1987). Accumulating evidence suggest that IL-6 is a major inflammatory cytokine that increases with adipocyte hypertrophy in obesity (Almuraikhy et al., 2016). Clinical studies in obese patients demonstrate that IL-6 and IL-6 receptor expression are upregulated in subcutaneous adipose tissue from patients with increased BMI and percentage body fat compared to lean subjects (Mohamed-Ali et al., 1997; Sindhu et al., 2015). IL-6 is purportedly a better correlate of obesity and insulin resistance compared to other cytokines, however there are conflicting reports about IL-6 that make its role in obesity-induced pathophysiology unclear. Administration of Tocilizumab, the anti-IL-6 drug, reduced systemic inflammation but led to metabolic syndrome and weight gain (Febbraio et al., 2010), and IL-6 knockout mice demonstrate overt obesity onset, insulin resistance, and M1 macrophage polarization (Matthews et al., 2010; Mauer et al., 2014; Wallenius et al., 2002). As such, it has become increasingly evident that IL-6 in the CNS plays a critical role in modulating body weight and metabolism through signaling in the CNS (Fernandez-Gayol et al., 2019; Timper et al., 2017). Although IL-6 appears beneficial for modulating weight via CNS signaling, its chronic systemic presence in obesity may be linked to detrimental effects on cognition.

Accumulating evidence suggest that obesity-induced systemic inflammation is associated with poorer cognitive outcomes. IL-6 is known to disrupt neural circuitry responsible for cognitive functioning and task completion (Vallieres et al., 1997), inhibit neurogenesis (Monje et al., 2003), decrease synaptic plasticity (Poluektova et al., 2005), and impede learning and memory performance (Braida et al., 2004) in mice. Reports on the impact of IL-6 on cognitive decline in obesity have been inconsistent with some supporting a role for IL-6 in cognitive decline (Donzis and Tronson, 2014; Lai et al., 2017; Lampe et al., 2019; Palta et al., 2015; Singh-Manoux et al., 2014; Weaver et al., 2002; Yaffe et al., 2003) and others failing to demonstrate a role for IL-6 in cognitive decline (as reviewed in Donzis and Tronson, 2014). A longitudinal study in the Whitehall II cohort found that mid-life IL-6 plasma concentrations were predictive of cognitive decline (Singh-Manoux et al., 2014). Despite these positive associations, a recent study suggest that IL-6 is not associated with

cognition (Wennberg et al., 2018). It is well established that IL-6 negatively impacts vascular function, which can have long-term deleterious impacts on the BBB.

An overwhelming body of evidence suggest that IL-6 has deleterious impacts on endothelial cells (Hartman and Frishman, 2014; Schwingshackl and Hoffmann, 2014). Although the endothelium does not express the membrane IL-6 receptor, IL-6 is secreted from endothelial cells and has various direct and indirect effects on the endothelium (Hou et al., 2008). One study demonstrated that IL-6 significantly impaired endothelial colony forming cell outgrowth, which was restored after inhibition of the IL-6 receptor (Shahrivari et al., 2017). Experimental overexpression of IL-6 in the brains of mice leads to BBB permeability and neuroinflammation, while IL-6 knockout mice have preserved BBB function despite an enhanced inflammatory response (Paul et al., 2003). IL-6 BBB dysfunction are likely caused by signaling at the cellular level, as IL-6 suppresses endothelial NO expression and bioavailability (Saura et al., 2006). IL-6 also works in concert with TNF-α to disrupt adherens/tight junction expression and increased permeability through suppression of tight junctions in brain microvascular endothelial cells (Rochfort et al., 2016; Rochfort and Cummins, 2015).

TNF-α—TNF-α is constitutively produced by ATMs in dysfunctional adipose tissue of obese subjects and acts as a potential mediator of insulin resistance (Cawthorn and Sethi, 2008; Hotamisligil et al., 1993) through activation of phosphatases, which impair insulin signaling (Nieto-Vazquez et al., 2008). Impaired insulin signaling contributes to increased adiposity (Zhou and Rui, 2013). A recent study in obese hemodialysis patients showed that TNF-α was associated with abdominal obesity (Beberashvili et al., 2019). It is particularly noteworthy that genetic ablation of the TNF-α receptor 1 makes mice resistant to diet-induced obesity (Romanatto et al., 2009).

Under normal physiological conditions, constitutive production of hippocampal TNF-α modulates synaptic strength (Beattie et al., 2002), and elevated hippocampal levels in HFD mice correlate with cognitive impairment (Jeon et al., 2012; Ma et al., 2018). Evidence that cognitive impairment is mitigated through suppression of systemic TNF-α concentrations within the hippocampus points to a role for TNF-α in modulating cognitive decline (Grundy et al., 2014; Labrousse et al., 2012). Despite these findings, there are conflicting reports about the role of TNF-α on cognition. An independent study in FIFD mice failed to demonstrate a correlation between TNF-α and cognitive function (Boitard et al., 2014). Despite these findings, a recent study reported that administration of infliximab, a TNF-α inhibitor impermeable to the BBB, improves pathology in transgenic Alzheimer's disease mice, a model commonly associated with cognitive impairment (Paouri et al., 2017).

TNF-α may modulate cognitive function through its effects on the micro vasculature and endothelium. Small vessels excised from obese patient perivascular tissue are less responsive to endothelium-dependent relaxation, a mechanism likely due to TNF-α-induced endogenous oxidative stress signaling (Virdis et al., 2011). This same group demonstrated that small arteries in perivascular adipose tissue produce TNF-α and oxidative stress in excess, leading to loss of vasorelaxation (Virdis et al., 2015). Infliximab administration leads to improvements in vascular reactivity to acetylcholine, a vasodilator, in obese subjects with

metabolic syndrome (El Assar et al., 2013; Tesauro et al., 2008). Small arteries dissected from the visceral fat of obese patients display suppressed endothelial dependent relaxation in response to acetylcholine; however, aberrant response was mitigated by infliximab (Virdis et al., 2011). Similar findings have been observed in rodent models of obesity and/or models with an inflammatory phenotype. HFD consumption increases TNF-α in both the femoral artery and corpus cavernosum of rats (Sponton et al., 2017). Isolated mesenteric vascular beds from HFD mice displayed improvements in insulin-mediated vasodilation upon treatment with infliximab (da Costa et al., 2016). Collectively, this evidence points to role for TNF-α in mediating microvascular damage in obesity.

As previously stated, damage to the microvasculature in the periphery ultimately leads to changes in vascular structures of the CNS. While this evidence points to a role for TNF-α in obesity-related endothelial dysfunction in the periphery, TNF-α mediated endothelial dysfunction also occurs at the BBB (Deli et al., 1995). TNF-α increases permeability of human brain microvascular endothelial cells (Didier et al., 2003). Thus, it's no surprise that TNF-α modulates disruption of BBB integrity. The administration of the TNF-α inhibitor, etanercept, restores BBB integrity and cognition in mice (Cheng et al., 2018). Overall, these data suggest a role for inflammation in obesity-related cognitive impairment. Inadvertently, chronic low-grade inflammation, often observed in obesity, have been implicated in the pathogenesis of hyperinsulinemia and insulin resistance (Esser et al., 2014).

Hyperinsulinemia

CNS insulin receptor signaling is important for synaptic plasticity, neuronal survival, learning and memory, etc. (see Chiu and Cline (2010) for a comprehensive review). Diet-induced obesity leads to hyperinsulinemia and is associated with impaired CNS insulin signaling (Hussain et al., 2019; Petrov et al., 2015; Sims-Robinson et al., 2016a); however, the mechanisms are not known. Impaired CNS insulin signaling is typically attributed to diet-induced CNS insulin receptor resistance (Hussain et al., 2019; Kim et al., 2011a; Kim et al., 2011b; Petrov et al., 2015; Sims-Robinson et al., 2016b). Alternatively, impaired CNS insulin signaling may be due to a deficiency of insulin in the CNS. Hyperinsulinemia and diet-induced obesity are associated with decreased CNS insulin levels (Begg et al., 2013; Israel et al., 1993; Kaiyala K. J., 2000). CNS insulin must be transported via receptor-mediated transport through the BBB from the periphery (Banks et al., 1997; Banks et al., 2012).

Although limited, evidence from the literature support the notion that CNS insulin transport is mediated by the insulin receptor (Banks, 2004; Banks et al., 1997; Banks et al., 2012; King and Johnson, 1985). Insulin uptake in bovine aortic endothelial cells requires normal insulin signaling (Wang et al., 2013; Wang et al., 2008). Furthermore, these studies demonstrate that ablating insulin receptor function reduces insulin uptake. High concentrations of insulin receptors are reported in brain capillaries (Blumling Iii and Silva, 2012; Pardridge, 2008; Pardridge and Boado, 2012). Although these studies suggests that the insulin receptor is involved in receptor-mediated uptake in endothelial cells, it is worth noting that a recent study demonstrated that insulin can enter the CNS through non-insulin receptor mediated processes (Rhea et al., 2018). Overall, impaired CNS insulin receptor

signaling coupled with the reduced CNS insulin transport provides a potential mechanism underlying obesity-related cognitive impairment.

Obesity is associated with lower cerebrospinal fluid (CSF) insulin, a measure of CNS insulin levels (Kern et al., 2006; Kullmann et al., 2016). Interestingly, reduced CSF insulin concentrations are also observed in patients with mild cognitive impairment (Craft et al., 1998; Gil-Bea et al., 2010). This is associated with an decrease in underlying brain insulin sensitization (Sims-Robinson et al., 2010), observed through aberrant signaling of the insulin receptor (Kim et al., 2012) in both the hypothalamus (Ono, 2019) and hippocampus (Pratchayasakul et al., 2011; Sims-Robinson et al., 2016a). Insulin dysregulation in the hippocampus have been directly implicated in impaired memory processes such as synaptic plasticity (McNay et al., 2010; Spinelli et al., 2017; Spolcova et al., 2014; Suarez et al., 2019). Impaired insulin sensing in the hypothalamus is linked to decreased glucose sensing, which may eventually lead to a feed forward cycle in the obesity pathology (Chen et al., 2017; Ono, 2019; Weissmann et al., 2014).

Intravenous insulin has been shown to improve cognition in healthy subjects (Craft et al., 1999; Craft et al., 1996; Kern et al., 2001), however, this is not a viable treatment option for cognitive impairment due to secondary complications such as hypoglycemia (Morris and Burns, 2012). Intranasal insulin has been offered as a way of directly increasing CNS insulin concentrations, while avoiding altering systemic glucose and insulin levels (Claxton et al., 2015; Craft et al., 2012; Reger et al., 2006). CNS insulin receptors are highly expressed in areas of the brain important for memory consolidation and executive functioning such as the hippocampus (Baskin et al., 1983; Hill et al., 1986), and are specifically concentrated at the synapses (Laron, 2009). Hence, it is not surprising that intranasal insulin improves memory in cognitively normal humans (Benedict et al., 2004; Benedict et al., 2007). Additional studies are warranted to explore the potential role of CNS insulin signaling and transport on obesity-related cognitive impairment.

Hyperinsulinemia and insulin resistance are linked to decreased BBB integrity (Arnold et al., 2018) and endothelial cell dysfunction (Muniyappa and Sowers, 2013). Insulin is known to have a direct vasodilatory effect, mediated through the stimulation of NO production in endothelial cells (Kuboki et al., 2000) via protein kinase B (Akt) activation (Muniyappa and Sowers, 2013). Hence, hyperinsulinemia impairs vascular tone. HFD animals exhibit impaired neurovascular coupling (Tarantini et al., 2018) as well as diminished insulin-mediated BBB responses, microvascular perfusion, and cognitive decline (de Aquino et al., 2018; Fu et al., 2017). Interestingly, some studies suggest that insulin sensitizers such as metformin and pioglitazone may confer beneficial effects on endothelial function (Muniyappa and Sowers, 2013; Naka et al., 2011; Radenkovic, 2014). These findings taken together suggest that obesity coupled with hyperinsulinemia may have detrimental effects on endothelial function. While the inflammation and hyperinsulinemia connection is grounded in the literature, a mounting body of evidence suggest that the gut microbiome may play a role in modulating hyperinsulinemia and obesity’s impact on cognition.

Gut Microbiome

The gut microbiome is an aggregate of more than 100 trillion microorganisms, including bacteria, viruses, fungi and protozoa (Gill et al., 2006). The microbiome is essential for microbiota-gut-brain bidirectional communication (Rhee et al., 2009). The two most prominent bacterial divisions in the gut include gram positive Firmicutes and gram negative Bacteroidetes, which make up 90% of all phylogenetic types. Changes to food and environment have drastically altered the microbiome (Gomez, 2017). Disturbance in gut homeostasis is often due to loss of beneficial bacterial, overgrowth of harmful bacterial, or loss in microbial diversity also known as gut dysbiosis (DeGruttola et al., 2016). This is particularly true in obesity; the obese gut in mice and humans has an increased Firmicutes/Bacteroidetes (F/B) ratio compared to lean controls (Angelakis et al., 2012; Furet et al., 2010; Kong et al., 2013), leading to greater adiposity (Turnbaugh et al., 2006). Higher F/B ratios have been linked to numerous disease processes (Flint et al., 2007; Ley et al., 2006) likely through changes in body-weight, inflammation, insulin sensitivity, and behavior (Allen et al., 2017; Liang et al., 2018). Furthermore, there is evidence suggesting a decline in overall bacterial diversity in obese individuals (Yun et al., 2017). While some controversy exists whether gut dysbiosis impacts obesity, (Sze and Schloss, 2016; Sze and Schloss, 2017), animal models provide more direct approaches at studying the phenomenon. Fecal transplant from obese mice to germ-free mice leads to the development of obesity (Backhed et al., 2007; Turnbaugh et al., 2008). Interestingly, the opposite effect can occur with fecal transplants from lean to obese mice (Sun et al., 2018). Collectively, these studies suggest that gut dysbiosis may be both a result and potentiator of obesity. Mechanisms underlying the role of gut dysbiosis in obesity and obesity-induced cognitive impairment have been reviewed elsewhere (Cuevas-Sierra et al., 2019; Noble et al., 2017).

Gut microbiota homeostasis promotes optimal brain development and cognitive functioning (Diaz Heijtz et al., 2011) Clinical and preclinical evidence suggests that obesity-induced changes in the gut microbiome may play a role in the development of cognitive dysfunction. Patients with dementia have a higher F/B ratio compared to non-demented patients (Saji et al., 2019), and elderly adults with increased F/B ratios have poorer immediate and delayed recall scores (Manderino et al., 2017). This is also the case preclinically. Obese mice demonstrating an increase in F/B ratios and a decline in gut microbiota diversity had impaired recognition and spatial memory (Zhang et al., 2018). In line with this finding is the discovery that administration of antibiotics in DIO mice led to improved insulin signaling in the brain and improved anxiety and depression associated with cognitive functioning(Soto et al., 2018) Moreover, aged normal weight mice with obese-type gut microbiota displayed BBB dysfunction, reduced CBF and deteriorations in cognition (Hoffman et al., 2017). Similarly, a recent discovery by Bruce-Keller et al demonstrated that mice with obese-type gut microbiota displayed neurocognitive and behavioral disruptions in the absence of obesity (Bruce-Keller et al., 2015). Interestingly, rats subjected to a western diet had alterations in hippocampal genes important for neuroplasticity; however, these abnormalities were reversed with probiotic treatment (Beilharz et al., 2018). Notably, the authors reported that probiotic administration led to increases in *Streptococcus* and *Lactobacillus* in the gut (Beilharz et al., 2018).

Diet-induced obesity models that exhibit gut microbiome imbalance and cognitive impairment also demonstrate reduced tight junction proteins (Zhang et al., 2018). There appears to be a role for vascular dysfunction in mediating these effects (Braniste et al., 2014). Microbiome diversity is inversely correlated with arterial stiffness (Li et al., 2017), and obese-type gut microbiota induces BBB dysfunction and reduced CBF (Hoffman et al., 2017). Interestingly, intestinal microbiota modulates the expression of BBB tight junction proteins (Kelly et al., 2015).

One mechanism by which alterations in the microbiome promotes cognitive dysfunction is through increasing BBB permeability (Braniste et al., 2014). The BBB is comprised of a tightly sealed monolayer of brain endothelial cells connected at a junctional complex by tight junction and adherens junction proteins (Hawkins and Davis, 2005). Diet-induced obesity models that exhibit alterations within the microbiome and cognitive impairment demonstrated reduced tight junction proteins in the BBB (Kelly et al., 2015). One mechanism through which microbial gut imbalance may lead to reduced tight junction proteins at the BBB is through diminished short chain fatty acids (SCFAs) typically produced during dietary fiber fermentation (Pryde et al., 2002). SCFAs modulate tight junction formation through enhancing the expression of tight junction proteins within the prefrontal cortex and hippocampus of the brain of germ-free adult mice (Braniste et al., 2014). Macrovascular changes also impact cognitive decline. It is well established that declines in central artery elasticity negatively impacts cognitive function (Palta et al., 2019). Interestingly, a recent study showed that gut microbial diversity is inversely associated with central artery stiffness in women, even after adjusting for insulin resistance and other cardiovascular disease risk factors (Menni et al., 2018). Likewise, antibiotic treatment in aged mice reversed endothelial dysfunction and arterial stiffening through attenuation of inflammation and oxidative stress (Brunt et al., 2019). Taken together, these studies suggest that gut dysbiosis may lead to changes in vascular structure or BBB integrity that are detrimental for cognitive function. Additional studies are needed in obese preclinical models and patients to further confirm these findings.

Therapeutic strategies

Dietary Interventions

Diets are often characterized by the macronutrient, which includes fats, proteins, and carbohydrates, that is primarily providing the source of energy for the body. Given the role of fatty acids in the development of insulin resistance (Thomas and Pfeiffer, 2012), it is generally assumed that reducing the dietary intake of fat will be beneficial for improving insulin resistance; however, such diets are often difficult to maintain. The Mediterranean diet is not comprised of a fat-restriction, but rather consists of fruits, vegetables, legumes, cereals, and olive oil. The Mediterranean diet has beneficial effects on insulin resistance, diabetes risk and overall cardiovascular health (Kastorini et al., 2011; Riserus et al., 2009). Similarly, the ketogenic diet, a low carbohydrate diet with fat as the primary energy source, improves glycemic control and insulin sensitivity (Forsythe et al., 2008).

Several previous studies have highlighted the role of diet on inflammation associated with obesity (Bullo et al., 2007; Calder et al., 2011; Galland, 2010; Lee et al., 2013). The

Mediterranean diet exerts anti-inflammatory effects by decreasing inflammatory cytokines including IL-6 and TNF-α (Calder et al., 2011; Casas et al., 2014; Casas et al., 2016; Hu et al., 1997; Mena et al., 2009; Urpi-Sarda et al., 2012). The ketogenic diet is associated with a reduction in inflammatory markers including but not limited to TNF-α (Forsythe et al., 2008; Ruskin et al., 2009). Cross sectional studies have demonstrated a link between carbohydrates and inflammatory cytokines (Du et al., 2008; Levitan et al., 2008; Pischon et al., 2005; Qi et al., 2006a; Qi et al., 2006b). It is clear that diet has impacts on neuroinflammation. However, conflicting reports exist regarding the role of diet modification on gliosis.

The composition of the gut microbiota is largely dependent upon diet (Finegold and Rolfe, 1983; Graf et al., 2015; Hayashi et al., 2002; Mueller et al., 2006). A change from a high-fat, low fiber diet to a low-fat high-fiber diet leads to marked changes in the microbiota within 24 hours (Wu et al., 2011). Western style diets alter the gut microbiota resulting in a decrease in bacterial diversity (Wu et al., 2011). Whereas, elevated levels of Bacteriodetes are observed in individuals adhering to the Mediterranean diet (Gutierrez-Diaz et al., 2016). Likewise, in obese patients with severe metabolic disease, consumption of a Mediterranean diet or a low fat diet reversed gut dysbiosis (Haro et al., 2017). Unfortunately, the validity and reproducibility of studies focused on the impact of diet on gut microbiota in humans is challenging since most investigators rely on self-reporting of dietary habits. Animal models, however, have provided some useful information. Diet modification from an ad libitum low fat diet to caloric restriction in young rats reduced the F/B ratio (Tanca et al., 2018). A recent study in monkeys compared the changes in gut microbiota following a western and Mediterranean-type diets (Nagpal et al., 2018). Similar to previous studies, alterations in the gut microbiota were observed (Carmody et al., 2015; David et al., 2014; De Filippo et al., 2010; Hale et al., 2018; Nagpal et al., 2018). Whether improved outcomes due to dietary intervention is facilitated through alterations in the microbiome is not well understood.

In the past decade, lifestyle modifications have emerged as an alternative strategy to reduce the risk of cognitive impairment (Daviglus et al., 2010). A recent review provides a comprehensive report of randomized controlled trials published from 2014–2016 exploring the efficacy of various nutritional interventions on preventing the onset of cognitive disorders and dementia (Agosti, 2018). The Mediterranean diet is one of the most studied dietary interventions to protect against cognitive decline. According to observational studies, the Mediterranean diet is associated with a reduced risk of cognitive impairment, mild cognitive impairment, and Alzheimer's disease (Lourida et al., 2013; Psaltopoulou et al., 2013; Singh et al., 2014; Solfrizzi et al., 2017). A randomized controlled trial demonstrated that subjects randomly assigned to the Mediterranean diet supplemented with extra virgin olive oil performed better on episodic memory and attention tasks compared with the control group. Furthermore, the Mediterranean diet subjects demonstrated a significant improvement in frontal and global cognition (Valls-Pedret et al., 2015). Despite the positive effects from observational studies, more interventional studies are needed to validate these findings.

In 2011, the American Heart Association established the "Life's Simple 7," for achieving ideal cardiovascular health. The Life's Simple 7 definition of an ideal cardiovascular diet includes a diet rich in fruits and vegetables, oily fish, fiber, and low in sodium which is

similar to the Mediterranean diet (Sacco, 2011). In a large clinical trial known as the EVIDENT study, participants who had a high Mediterranean Diet adherence score had higher arterial elasticity (Garcia-Hermoso et al., 2018). Likewise, in a randomized controlled trial, adherence to the Mediterranean diet for 1.5 years improved endothelial function, as measured by flow mediated dilation, in diabetic and pre-diabetic patients compared to a low-fat diet alone (Torres-Pena et al., 2018). These changes in endothelial function may be due to increases in serum NO and declines in endothelin-1 (Storniolo et al., 2017) and reactive oxygen species production (Carnevale et al., 2014; Giordano et al., 2012). Subsequent reports suggest that the Mediterranean diet reduces endothelial cell damage and improves the regenerative capacity of endothelial progenitor and circulating progenitor cells (Cesari et al., 2018; Marin et al., 2011). Conversely, carotid atherosclerosis patients on a modified Mediterranean diet for 20 weeks did not demonstrate improvements in internal carotid or large basal cerebral artery blood flow or cognitive function (Droste et al., 2014). The benefits of the diet were likely masked by statin use in two-thirds of the study population as statins improve NO bioavailability and increase CBF (Droste et al., 2014). The impacts of the ketogenic diet on the vascular function are not as well understood and additional studies are needed to understand its impact in cardiovascular health.

Bariatric Surgery

Decades of obesity research indicates that lifestyle interventions including diet and exercise, are not effective for helping severely obese individuals. The National Institutes of Health (NIH) established guidelines, which specify that obese individuals with a BMI≥35 with comorbidities or BMI≥40 without comorbidities are ideal candidates for weight loss surgery, known bariatric surgery. Bariatric surgery has emerged as an effective therapy for these individuals yielding sustained reductions in weight (Adams et al., 2007; Buchwald et al., 2004; Gloy et al., 2013; Maggard et al., 2005; Maggard-Gibbons et al., 2013; O'Brien et al., 2013; Padwal et al., 2011; Picot et al., 2009; Sjostrom, 2013; Sjostrom et al., 2007). Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB) and biliopancreatic diversion with duodenal switch represents the three most commonly types of bariatric surgeries(Buchwald and Oien, 2013). An analysis of various randomized controlled trials (Arterburn and Courcoulas, 2014) revealed that bariatric surgical procedures results in greater average weight loss of (~57 pounds) compared with non-surgical options (Dixon et al., 2008; Ikramuddin et al., 2013; Ikramuddin and Livingston, 2013; Mingrone et al., 2012; O'Brien et al., 2006; Schauer et al., 2012).

The impact of bariatric surgery on insulin resistance has been extensively reviewed (Rao et al., 2012). A reduction in fasting glucose and insulin levels as well as improvements in insulin sensitivity are reported within 3 months following bariatric surgery (Leichman et al., 2008). Some argue that weight loss is responsible for the improvements in glucose metabolism and insulin resistance following bariatric surgery (Adami et al., 2004; Castagneto et al., 1994; Pereira et al., 2003; Summers, 2002). Others suggest that the reversal of insulin resistance occurs prior to the manifestation of substantial weight loss (Leichman et al., 2008; Rubino et al., 2010; Schauer et al., 2003; Sugerman et al., 2003)..

Given that obesity is characterized as a state of chronic inflammation, the anti -inflammatory changes observed with weight loss play a significant role in overall health (Cottam et al., 2004). TNF-α is the most frequent cytokine assessed following bariatric surgery due to its strong associated with insulin resistance (Moller, 2000). Reports on the impact of RYGB surgery on TNF-α are contradictory demonstrating either no change (Catalan et al., 2007; Sams et al., 2016), an increase (Illan-Gomez et al., 2012), or a decrease (Miller et al., 2011). The latter clinical study is consistent with preclinical studies, which reveal a decrease in TNF-α levels in adipose tissue at 9 weeks post-surgery in rats (Rideout et al., 2010). In contrast to RYGB, the reports of TNF-α following LAGB are relatively consistent with multiple groups demonstrating no change in serum levels of TNF-α (Kopp et al., 2003; Laimer et al., 2002) and a decrease in subcutaneous adipose tissue (Moschen et al., 2010). The reports for IL-6 levels following RYGB surgery are also inconsistent demonstrating either an increase (Illan-Gomez et al., 2012), or a decrease (Lindegaard et al., 2015). Similar to RYGB, the serum levels of IL-6 also varied across different studies following LAGB with either no change (Laimer et al., 2002; Moschen et al., 2010) or a decrease (Samaras et al., 2013). Taken together, these studies suggest that the surgical procedure, post-surgical time point, and tissue evaluated contribute to the inconsistencies in the field regarding the potential role of inflammation.

Comprehensive data exploring the impact of bariatric surgery on the microbiome has been extensively reviewed (Ulker and Yildiran, 2019). Bariatric surgery increased microbial richness. Previous studies observed an increase in microbial diversity and altered microbial composition in both man (Furet et al., 2010; Graessler et al., 2013; Kong et al., 2013; Zhang et al., 2009) and rodents (Li et al., 2011; Liou et al., 2013). Studies suggest that these changes in the microbiota may be independent of weight loss or caloric restriction and are maintained up to 9 years post-surgery (Liou et al., 2013; Tremaroli et al., 2015). Furthermore, colonization of germ-free mice with fecal material from RYGB mice resulted in weight loss and reduced adiposity, suggesting that RYGB-associated microbiota can improve host metabolism (Liou et al., 2013; Tremaroli et al., 2015). Overall, these studies suggest that bariatric surgery leads to alterations in the microbiota.

Severely obese patients seeking bariatric surgery have poorer baseline cognition compared to healthy weight controls (Prickett et al., 2018). The Longitudinal Assessment of Bariatric Surgery (LABS) project is a multi-site, prospective longitudinal examination of the safety and efficacy of bariatric surgery and the impact on cognitive function. Improvements in multiple cognitive domains following surgery persisted for several years. Executive function and memory performance remained at this improved level however, attention scores declines in participants that regained a substantial amount of weight (Alosco et al., 2014a; Alosco et al., 2014b; Gunstad et al., 2011; Miller et al., 2013). Overall, these data suggest that bariatric surgery improves obesity-related cognitive impairment.

Severely obese patients experience various structural adaptations in the arteries over time that lead to increases in blood pressure and subsequent changes in arterial stiffening. While still limited, studies assessing the long-term impact of bariatric surgery on vascular disease outcomes are underway. A recent study revealed that morbidly obese patients who underwent LAGB experienced weight reduction but did not exhibit improvements in

endothelial function and arterial stiffness after 4-years (Galkine et al., 2018). Conversely, a study in 16 morbidly obese subjects undergoing bariatric surgery demonstrated that study participants had improvements in retinal microvascular health after 4 years but not in large arterial stiffness (Streese et al., 2019). Still, others demonstrated that laparoscopic sleeve gastrectomy improved insulin mediated microvascular function in morbidly obese patients with insulin resistance or diabetes (Ministrini et al., 2018). Nevertheless, improvements in endothelial function and arterial stiffness post-bariatric surgery may be due to surgery-induced reversal of underlying chronic conditions including sleep apnea (de Assuncao Machado et al., 2018), high levels of subcutaneous adipose tissue (Backdahl et al., 2018), insulin resistance and inflammation (Vazquez et al., 2005) that are common amongst obese patients. Accordingly, studies revealed that markers of inflammation and endothelial function including ICAM-1, E-selectin, and P-selectin were improved following RYGB surgery (Stolberg et al., 2018; Vazquez et al., 2005; Yadav et al., 2017) but, these studies failed to assess changes at the blood vessel level. Moreover, studies examining the impacts of bariatric surgery on changes at the level of the blood brain barrier are missing. Additional studies are needed to fully understanding the role of bariatric surgery in improving vascular dysfunction in obesity.

Exercise

Structured exercise training improves cardiometabolic health indices (Campbell et al., 2015; Stefanov et al., 2013; Umpierre et al., 2011). Adolescent girls on a prescriptive resistance and aerobic exercise training 12 week intervention display 50% lower plasma insulin concentrations at the end of the intervention period (Bharath et al., 2018). Likewise, combined resistance and aerobic exercise significantly reduces homeostatic model assessment of insulin resistance (HOMA-IR) and blood pressure parallel to body fat in obese adolescent girls (Son et al., 2017). Obese adults with type 2 diabetes demonstrate improved glycemic control with supervised exercise training, but this effect is not sustained with unsupervised training (Gajanand et al., 2019). Likewise, running wheel exercise training for 6 weeks led to significant declines in fasting blood glucose levels in mice and HbA_{1c} in HFD rats (Mehta et al., 2018). Voluntary exercise in HFD mice also led to improved insulin sensitivity (Fjaere et al., 2019). Collectively, these studies suggest that supervised, prescriptive exercise training is an effective intervention for obesity-induced cardiometabolic risk factors.

Adipose tissue hypertrophy leads to increased macrophage infiltration and activation yielding increases in inflammatory cytokine production including IL-6 and TNF-α (Bjorntorp et al., 1971a; Bjorntorp et al., 1971b; Drolet et al., 2008). Interestingly, completion of a 3 week high intensity interval training (HIIT) program increased IL-6 in obese adults while a 3 week moderate-intensity continuous training (MICT) exercise intervention lead to cytokine suppression (Vella et al., 2017a; Vella et al., 2017b). A conflicting study in obese elderly adults demonstrated elevated levels of IL-6 following a prescriptive MICT program (Pedrinolla et al., 2018). HFD rodents undergoing an 8 week endurance training displayed reductions in TNF-α, and IL-6 (Rocha-Rodrigues et al., 2017). Combined aerobic and resistance training for 8-weeks in obese subjects leads to reductions in TNF-α (Jin et al., 2018). Moreover, a 24 week HIIT yields suppression of TNF-α in

obese adolescents (Tenorio et al., 2018). TNF-α levels are reduced in HFD mice following wheel running and treadmill exercise (Bradley et al., 2008; Kim and Yi, 2015). Overall, these studies support a role for exercise in modulating TNF-α in clinical and experimental models of obesity.

Exercise reportedly increases the diversity of the gut microbiome (Clarke et al., 2014). Interestingly, obese women exposed only to an endurance exercise intervention for 6 weeks display inert taxonomic modifications in the gut microbiome (Munukka et al., 2018). BMI and exercise frequency purportedly dictate gut microbiota diversity (Bai et al., 2018). For example, two independent studies report that HFD mice experience a shift in microbiota composition with wheel running exercise (Evans et al., 2014; Schipke et al., 2019). Notably, a 6-week HIIT treatment in HFD mice led to increased microbiome diversity and F/B ratio in the fecal microbiota and distal gut (Denou et al., 2016). Conversely, a recent report demonstrated that low-to-moderate exercise training program was not effective in reversing HFD induced changes in the microbiome of mice (Ribeiro et al., 2019). Taken together, these studies suggest that exercise may modulate changes in the microbiome; however, additional human studies are warranted to clarify the role of exercise in modulating the gut microbiome.

The effectiveness of exercise on improving cognitive function in obese patients is inconsistent (Espeland et al., 2017a; Espeland et al., 2017b; Smith et al., 2010) but there is substantially more evidence supporting a role for the benefits of exercise. For example, a 4-month high intensity training (HIT) program improves short-term and verbal memory along with attention and processing speed in middle-age obese patients (Drigny et al., 2014). Results from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial demonstrated that a 2-year diet and structural exercise intervention improves processing speed and executive function amongst overweight, elderly subjects compared controls (Ngandu et al., 2015). Interestingly, the benefits of exercise alone and exercise in combination with diet provided similar improvements in cognition amongst frail, obese elderly patients (Napoli et al., 2014). These findings are in line with studies in preclinical models. An early preclinical study demonstrated that HFD-induced cognitive deficits in hippocampal-dependent memory improved with both voluntary running wheel or forced treadmill exercise training in Sprague-Dawley (Noble et al., 2014). Moreover, Jeong et al. revealed that treadmill exercise training in HFD rats improves memory restoration (Jeong and Kang, 2018). While aerobic interval training in HFD mice demonstrated improvements in spatial learning and memory (Shi et al., 2018). Collectively, these studies suggest that exercise training has beneficial effects on obesity-associated cognitive function in both clinical and preclinical studies.

The majority of studies examining the therapeutic capacity of exercise on arterial de-stiffening and vascular function in obesity support a role for increased physical activity in limiting obesity-induced damage to the vasculature. A recent study examining the effectiveness of a low-volume, HIT training program in obese individuals showed that skeletal muscle capillarization increased while aortic pulse wave velocity (PWV), a measure of aortic stiffness downstream of endothelial dysfunction, decreased in obese individuals (Scott et al., 2019). Interestingly, acute maximal exercise increased carotid-femoral fPWV in

obese individuals, which may reflect underlying preclinical vascular disease in obesity (Bunsawat et al., 2017). Still, others have demonstrated that in populations with metabolic syndrome, an 8-week supervised training program lead to significant improvements in vascular stiffness and subsequent improvements in metabolic disease and fitness (Slivovskaja et al., 2018). Consistent with this finding is the discovery that exercise training effectively de-stiffened the central arteries in obese men independent of weight loss and dietary modification (Maeda et al., 2015).

In animal models of diet-induced obesity, exercise prevented cerebrovascular damage despite increases in weight gain (Graham et al., 2019). Similarly, exercise prevented diastolic dysfunction likely due to declines in oxidative stress and improved mitochondrial architecture (Bostick et al., 2017). In addition, chronic exercise therapy in obese rats led to restoration of insulin-mediated vasodilation as well as improvements and skeletal muscle and cerebral microcirculation (Olver et al., 2017). Additional studies are needed to fully understand mechanisms responsible for exercise-induced changes at the vascular level in obese populations.

Conclusions and perspectives

Obesity is a global pandemic that is still on the rise in developing countries. The interconnected relationship between early- to mid-life obesity and cognitive impairment makes the public health and economic implications of this issue urgent. Thus, understanding mechanistic pathways at the intersection of these diseases is important for guiding the development of therapeutic strategies that prevent and/or reverse disease. The framework presented in this review is based on our current knowledge of how aberrant endothelial function in obesity drives changes in the brain that may culminate into cognitive impairment. Presently, factors associated with obesity including hyperinsulinemia/insulin resistance, inflammation, and disruption at the microbiota-gut-brain axis appear to orchestrate pathophysiologic insults at the level of the endothelium. Endothelial dysfunction is an early event in the manifestation of cognitive impairment and dementia. Establishing a clinical tool that will detect endothelial dysfunction may be useful for assessing cognitive impairment risk. Given that endothelial dysfunction promotes premature arterial stiffening, measuring arterial stiffness may be promising. This can be accomplished by measuring carotid-femoral pulse wave velocity (cfPWV), which inversely correlates with cognitive function (Triantafyllidi et al., 2009). Additional studies are needed to understand the clinical utility of cfPWV in predicting cognitive impairment risk associated with obesity.

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Abbreviations

ATM	Adipose tissue macrophage
BBB	blood brain barrier
BMI	body mass index
cfPWV	carotid-femoral pulse wave velocity
CNS	central nervous system
CSF	cerebral spinal fluid
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
F/B	Firmicutes/Bacteroidetes
HFD	high-fat diet
HIIT	high intensity interval training
HOMA-IR	homeostatic model assessment of insulin resistance
IL	interleukin
LAGB	laparoscopic adjustable gastric banding
LABS	Longitudinal Assessment of Bariatric Surgery
MICT	moderate-intensity continuous training
NIH	National Institutes of Health
NO	nitric oxide
PI3k	phosphoinositide 3-kinase
Akt	protein kinase b
RYGB	Roux-en-Y gastric bypass
TNF	tumor necrosis factor
VCID	vascular contributions to cognitive impairment and dementia

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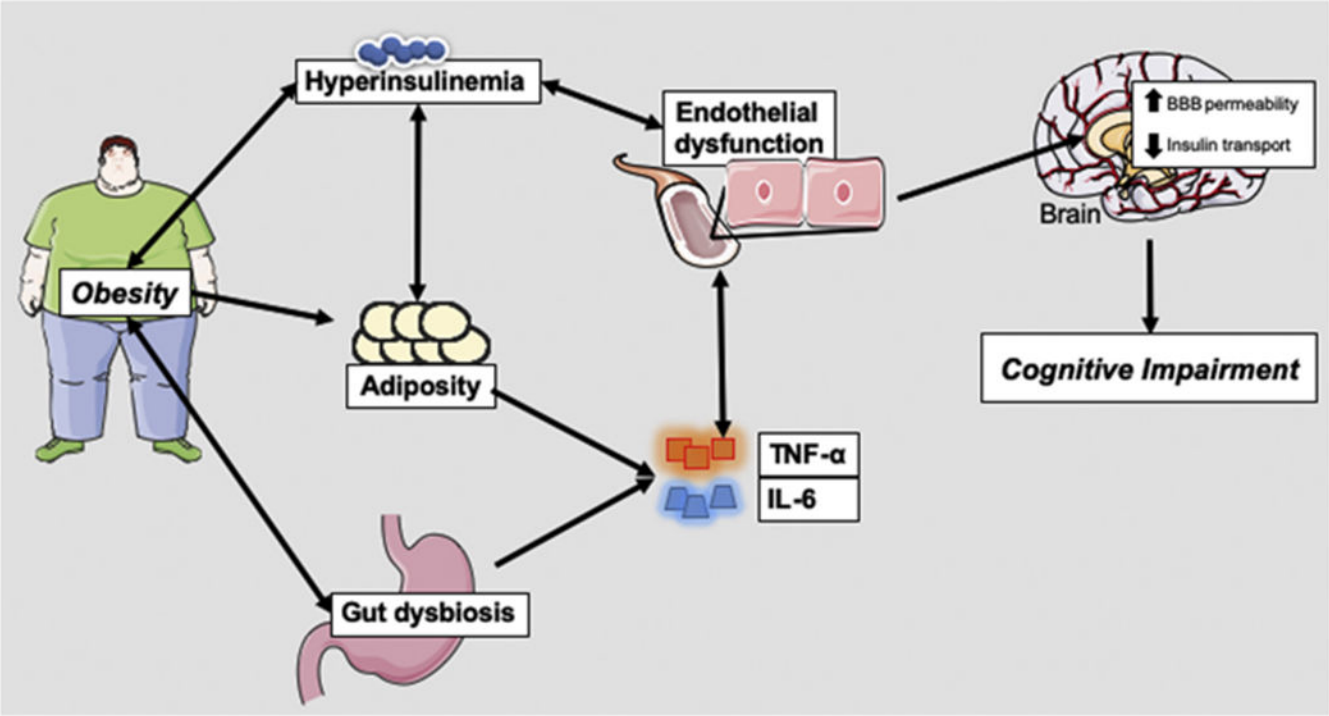

Figure 1. Obesity induces cognitive decline.

Schematic illustrating how the consequences of obesity (hyperinsulinemia, adiposity, and gut dysbiosis) results in the production of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). This culminates into endothelial dysfunction, which leads to increased cytokine influx, increased blood brain barrier (BBB) permeability, and reduced insulin transport in the brain. This feed forward cycle of insults ultimately contribute to cognitive impairment.

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Table 1.

Impacts of obesity on cognition across the lifespan

Authors	Population	Age range (mean, sd)	N	Study Design	Obesity Indices	Areas of cognitive functioning assessed (measures)	Findings (abbreviated)	Risk Factors Considered (adjusted for?)
(Davis and Cooper, 2011)	*Early life, obese*	7-11 years (9.3±1.1)	170	Cross-sectional cohort study	BMI, WC, X-ray adiposity	executive function (cognitive assessment system)	[−]:executive function and obesity	none
(Jansen et al., 2011)	*Early life, healthy weight and overweight*	Overweight (10±0.9), healthy weight(9.9±0.7)	32	Cross-sectional study	BMI	perceptual reasoning (Colored Progressive Matrices test); perception and movement (Chronometric mental rotation test)	[−]: perception and movement, perceptual reasoning and obesity	none
(Schwartz et al., 2013)	*Early life, obese*	12-18 years; males (14.9±1.8); females (15.1±1.9)	911	Cross-sectional retrospective cohort study	Visceral fat (MRI), total body fat	processing speed (automatic and controlled detection speed, symbol sear, coding); interference (Stroop Color-Word Test) Ruff 2 & 7 Selective Attention Test); working memory(Self-Ordered Pointing Task); visuospatial memory(Dot location Learning); verbal memory(Stories subtests of the Children's Memory Scale); cognitive flexibility (Semantic and Phonemic fluency); all domains (WISC-III)	[−]: processing speed, working memory, resistance to interference, cognitive flexibility and visceral fat [+]: processing speed, verbal memory and total body fat	none
(Verdejo-Garcia et al., 2010)	*Early life, healthy and overweight*	13-16 years; overweight/obese (14.3± 1.2); healthy (15.3±0.9)	61	Cross-sectional	BMI	anxiety and impulsivity(Impulsive behavior scale, sensitivity to punishment and reward questionnaire); mental flexibility (Letter-number sequencing, TMTB); reasoning (Analogical reasoning similarities); planning (zoo map); interference(Stroop test); flexibility (Five Digit Test, TMTA); self-regulation (revised-strategy application test R-SAT); decision making (Iowa Gambling Test)	[-]:Inhibition, flexibility, decision making, flexibility and BMI [ø]: working memory, planning, memory and BMI	none
(Lokken et al., 2009)	*Early life, obese*	13-19 years (15.9± 1.7)	25	Cross-sectional retrospective cohort study	BMI	reading ability(Wde Range achievement test); intelligence (Wechsler Abbreviate Scale of Intelligence); global cognition (Computerized Cognitive Test Battery); verbal fluency and memory(Digitspan, Verbal Interference); attention (Continuous performance task, Switching of Attention); visuospatial (Mask task); Impulsivity(Go-No Go test)	[−]: attention, executive function and obesity	Hypertension, Type 2 diabetes (no)
(Fergenbaum et al., 2009)	*Early- Mid-life, healthy, overweight, obese*	19-65 years	207	Cross-sectional	BMI, WC	executive function (Clock Drawing Test), visual attention and task switching (TMTA/B)	[−]: cognitive performance and obesity/increased waist circumference;	Metabolic syndrome, dyslipidemia, insulin resistance, hypertension diabetes (yes)

Authors	Population	Age range (mean, sd)	N	Study Design	Obesity Indices	Areas of cognitive functioning assessed (measures)	Findings (abbreviated)	Risk Factors Considered (adjusted for?)
							[ø]: cognitive performance and overweight or healthy weight	
(Gunstad et al., 2010)	*Mid- late life, overweight*	19-93 (55± 16.9)	1,703	Cross-sectional and longitudinal, prospective cohort study	BMI, WHR, weight	global cognition (MMSE);working memory (WAIS-R); visual attention/ cognitive flexibility (TMTA/B); verbal learning, fluency and memory(California Verbal Learning Test, Letter Fluency, Boston Naming Test,); Memory (Prospective Memory Test Benton Visual Retention Test, Blessed Information-Memory-Concentration test); visuo-spatial (Card Rotations)	[−]: global cognitive performance, attention, memory, verbal fluency, and BMI, WC, or WHC [+]: visuospatial/ TMTB and BMI, WC, or WHC	Type 2 diabetes/glucose intolerance, hypertension (yes)
(Deckers et al., 2017)	*Early-late life, obese*	24-81 years (58± 15)	1,823	Longitudinal cohort study	BMI, WC	verbal learning and memory (Visual Verbal Learning Test); executive function (Concept Shifting Test); processing speed (Letter Digit Substitution Test)	[−]: memory, executive function processing speed and obesity	Hypertension, type 2 diabetes, cardiovascular disease, depressive symptoms (no)
(Nilsson and Nilsson, 2009)	*Early, Mid-late, Late life, normal weight, overweight*	35-55 years (47.0±6.0); 60-70 years	3,526	Cross-sectional, prospective cohort study	BMI, WHR	word comprehension task, global cognition (MMSE); memory(prospective memory test), free recall test, immediate free recall test, cued test, name-stem completion task, name recognition task, fluency test	[−]: semantic memory and oven/weight; [+]: spatial ability and middle-aged overweight [ø]: episodic memory and overweight after adjusting for CVD risk	Hypertension, diabetes, stroke (no)
(Singh-Manoux et al., 2012)	*Early to Mid-life, metabolically normal, abnormal obese*	39-63 years (49.7±9.1)	6,401	Longitudinal cohort, prospective study	BMI	reasoning (Alice Heim 4-I); memory(20-word free recall test); verbal fluency (phonemic and semantic)	[−]: cognitive performance over time and metabolically abnormal obesity	Hypertension, cholesterol, diabetes, dyslipidemia, and hyperglycemia (yes)
(Wolf et al., 2007)	*Early-Late life, obese*	40-69 years (52±7.9)	1,814	Longitudinal cohort, prospective study	BMI, WHR	Executive function (neuropsychological test battery), Visual attention (TMTB, HVOT, Visual Reproductions test immediate and delayed recall)verbal and working memory (Paired Associates test immediate and delayed recall, logical memory test immediate and delayed recall)	[−] executive function, visuomotor skills	Hypertension (yes)
(Rochette et al., 2016)	*Mid-late life, obese*	(43±11.2)	171	Longitudinal prospective study	BMI	global cognition (Neurocognitive battery); language (verbal list recognition); verbal memory (dig it span forward, digit span backwards); Attention (sustained attention) Verbal Fluency (switching of attention-digits); interference (verbal interference-word);	[−]: cognitive performance and severe obesity	Hypertension, diabetes (no)

Authors	Population	Age range (mean, sd)	N	Study Design	Obesity Indices	Areas of cognitive functioning assessed (measures)	Findings (abbreviated)	Risk Factors Considered (adjusted for?)
						verbal fluency (letter fluency, animal fluency); task switching (switching of attention); executive function (maze errors and maze overrun errors)		
(Debette et al., 2011)	*Early - Mid-life, obese*	(54±9)	1,352	Longitudinal cohort, prospective study	BMI, WC, WHR	global cognitive function/executive function (Neuropsychological test battery); working visual memory(delayed recall component of the Visual Reproductions test, Logical Memory subtest from the Wechsler Memory Scale); visual attention/ cognitive flexibility; (Visual Reproductions test, TMTB and A)	[−]:executive function and mid-life obesity	Hypertension, diabetes, hypercholesterolemia (no)
(Sabia et al., 2009)	*Mid-life, healthy underweight overweight, obese*	(60.8±5.9)	5,131	Cross-sectional and longitudinal, prospective cohort study	BMI	global cognition (30-item MMSE); memory (20-word free recall test); reasoning (Alice Heim 4-I); verbal fluency test	[−]: cognitive performance over time and overweight or obesity [−]:MMSE, memory, executive function over time and obesity or underweight	diabetes, hypertension, cholesterol, coronary heart disease, stroke, glucose tolerance test(yes)
(Han et al., 2009)	*Mid- Late life, obese*	63-89 years (70±5.05)	2,767	Longitudinal, cross-sectional, prospective	BMI, WC, WHR, PBF	Global cognitive function (NA: CERAD-K)	[−] global cognitive function	Hypertension, diabetes, high cholesterol (yes)
(Benito-Leon et al., 2013)	*Mid - Late life, obese*	(74.9±5.5)	1,949	Cross sectional cohort, prospective study	BMI	global cognition (37-item version of MMSE), attention (easier form of TMTA), verbal learning and memory(Naming Test); immediate memory(immediate free recall); verbal and working memory(delayed recall, story recall, immediate logical memory, delayed logical memory); verbal fluency (Word Accentuation Test, Verbal fluency)	[−]: global cognition, attention, verbal fluency, memory and overweight/obesity	diabetes, hypertension, high cholesterol, dementia (yes)

Studies in table come from previous reviews Smith et al., 2011; Benito-Leon et al 2013; Bischof et al., 2015; Wang et al., 2016; Dye et al., 2017. AH4-I, Alice Heim 4-I; IMC, Blessed Information-Memory-Concentration test; MMSE, Mini-Mental State Exam; neuropsychological assessment CERAD-K, Consortium to Establish a Registry for Alzheimer's Disease, Korean; R-SAT, revised-strategy application test; TMT, Trail making test; WAIS-R, Wechsler Adult Intelligence Scale Revised; WISC, Wechsler Intelligence Scale for Children; HVOT, Hooper Visual Organization Test BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; Ø indicates null findings. (−) indicates inverse correlation between weight and speafic area of cognitive functioning. (+) indicates positive correlation between weight and area of cognitive functioning.

Table 2.

Animal models of obesity-induced cognitive impairment.

Author	Animal Background	Age Of High-Fat Feeding Specific HFD	Behavioral Task And Phenotype	Risk Factors Considered	Findings (Abbreviated)
(MARTINS ET AL., 2017)	C57BL6×129SV	From 2–14 months of age CD - 58G7, Test Diets HFD-58G9, Test Diets; 60% calories from lard	Novel Smell recognition test Y-Maze spontaneous alternation Significant impairment at 14 months in Y-maze performance in HFD group	Insulin concentrations	Fewer hippocampal synapses at 8 months in HFD group
(GLADDING ET AL., 2018)	C57BL/6J	From 4-16 months of age CD - Specialty Feeds; 7% fat w/w HFD - Specialty Feeds; 21 % fat w/w from safflower oil and clarified butter/ghee	Morris Water Maze Y-Maze Less time in the target quadrant in MWM and fewer novel arm entries in Y-maze in HFD group	Insulin sensitivity, Glucose tolerance, Leptin, hippocampal inflammation	Intrahippocampal insulin infusion alleviated behavioral deficits in HFD group
(VINUESA ET AL., 2018)	C57BL/6J	From 3-9 weeks of age CD - Gepsa Feeds; 2.5 kcal/g energy/pellet, 3.6% fat HFD - Gepsa Feeds; 3.9 kcal/g energy / pellet, 21.6% fat: monounsaturated fatty acids (44.7%), saturated fatty acids (29.8%) and polyunsaturated fatty acids (20.9%)	Elevated Plus Maze, Novel Object Location Recognition test Impaired novel object location recognition, no significant difference in EPM performance in HFD group	Pancreatic insulin, inflammation, DG neurogenic capacity	Inflammation changes in the hippocampus, decreased DG capacity, dendritic spine morphology alterations in HFD group
(SONA ET AL., 2018)	C57BL/6J	From 4-20 weeks of age CD – D12450 Research Diets; 10 kcal % fat HFD – D12492 Research Diets; 60 kcal % fat from lard	Two-way active avoidance, Y-maze test, passive avoidance, Object Recognition Impaired performance in novel recognition, Y-maze, and avoidance tests in HFD group	Glucose tolerance	Decrease in expression of both BDNF and GRP40 in HFD group
(LABOUESSE ET AL., 2018)	C57BL/6N	From 4-12 weeks of age CD-SSNIFF Diets; 10 kcal % fat HFD - SSNIFF Diets; 60 kcal % fat from lard	Y-maze Impaired Y-maze function in HFD group	None	Reduced miRNA associated with axon guidance and cognition, down regulation of axon guidance genes in HFD group
(SPINELLI ET AL., 2017)	C57BL/6	From 4-10 weeks of age CD – Mucedola, Italy; unreported HFD - Mucedola, Italy; unreported	MWM Impaired MWM performance in HFD group	Hippocampal insulin resistance	Impaired synaptic plasticity and insulin resistance in HFD group
(KASPER ET AL., 2018)	C57B1/6J	From 12-22 weeks of age CD - Teklad 7912; 17 kcal % fat HFD - D12492 Research Diets; 60 kcal % fat from lard	MWM Impaired MWM performance in HFD group	Peripheral insulin resistance	None
(ALMEIDA-SUHETT ET AL., 2017)	C57BL/6J	From 5 to 21 weeks of age CD – Harlan Teklad Global diet 2018 HFD-TD.06414, Harlan Laboratories; 60 kcal % fat from lard	Open field, elevated zero maze, Y-maze, forced swim test Increased anxiety behavior in open field and elevated zero maze, impaired cognitive	Glucose tolerance, IL-1B in hippocampus, amygdala, frontal cortex, and hypothalamus	Increased IL-1B in hippocampus and amygdala in HFD group

Author	Animal Background	Age Of High-Fat Feeding Specific HFD	Behavioral Task And Phenotype	Risk Factors Considered	Findings (Abbreviated)
			performance in y-maze, increased depressive behavior in forced swim in HFD group		
(KADISH ET AL., 2016)	C57BI/6	From 2-8 months of age CD – NIH.31 diet, Harlan Teklan HFD - TD.120084, Harlan Teklan; 41 kcal % fat, source unlisted, High-protein diet-TD.120083 High-carbohydrate diet- TD.120082	Open field, zero maze, social recognition, water maze* *not MWM* Impaired social recognition and water maze performance in HFD group	Body composition, hippocampal inflammation	Increased body fat percentage and total weight in HFD group. No change in hippocampal inflammation
(SIMS-ROBINSON ET AL., 2016)	C57BL/6J	From 4-12 weeks of age for dietary reversal and 4-20 weeks of age for HFD group CD – D12450B, Research Diets; 10 kcal % from fat HFD – D05090701, Research Diets; 54% kcal % fat from lard	NOR, MWM Impaired NOR and MWM after 16 weeks HFD group, recovered in the dietary reversal group	Glucose Tolerance, hippocampal insulin signaling	Impaired hippocampal insulin signaling in HFD group, recovered in the dietary reversal group
(MCLEAN ET AL., 2018)	C57BI/6J	From 12-14 weeks of age CD - D12450B, Research Diets; 10 kcal % from fat HFD – D12492 Research Diets; 60 kcal % fat from lard	NOR, object context task Impaired NOR and object context task	Glucose Tolerance	Impaired glucose tolerance in HFD mice, reversed in dietary reversal group
(SOONTORNNIYOMKIJ ET AL., 2016)	C57BL/6	From 5-10 and 15-20 months of age CD - 8604 Teklad; Harlan Laboratories HFD – D12492 Research Diets; 60 kcal % fat from lard	Novel place recognition task	Liver and hippocampal glutamine synthase immunoreactivity	Higher glutamine synthase activity in liver of HFD mice, higher glutamine synthase activity in the hippocampus of aged HFD mice.
(UNDERWOOD AND THOMPSON, 2016)	Long Evans	From 3-18 weeks of age CD – Open Source Diets; 14 kcal % fat HFD –Open Source Diets; 58 kcal % fat, augmented with coconut oil and casein protein	Spatial Object Recognition Impaired spatial memory in both sexes in HFD groups	Blood glucose, Glucose-tolerance testing, insulin tolerance testing, plasma corticosterone, leptin, and estradiol	Males became obese (not females)on HFD. HFD augmented corticosterone. HFD induced changes to insulin and glucose tolerance in males.
(WANG ET AL., 2016)	Sprague-Dawley	From 4-20 weeks of age CD – 8062, Chengdu Dossy Biological Technology Co. Ltd. HFD –Chengdu Dossy Biological Technology Co. Ltd.; 40 kcal % fat (unlisted source)	MWM, Object recognition task, open field Impaired object recognition, impaired reference and working memory(MWM) in the HFD group	Lipid levels (TC, LDL, TG, HDL)	TC, LDL, TG were significantly increased in the HFD group
(FU ET AL., 2017)	Sprague Dawley	From 2-10 months of age CD - protein 28 kcal %, carbohydrate 60 kcal %, and fat 12 kcal %) HFD – D12492 Research Diets; 60 kcal % fat from lard	Spontaneous alternation behavior, Novel Object Recognition Increased spontaneous alternation, impaired NOR for the HFD group.	Glucose Tolerance, euglycemic-hyperinsulinemic clamping, Heart rate, blood pressure, hippocampal microvascular perfusion	Impaired microvascular perfusion in hippocampus, impaired insulin signaling in HFD group

ABREVIATIONS: BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF); CONTROL DIET (CD); FREE FATTY ACID RECEPTOR 1 (GPR40); HIGH DENSITY LIPOPROTEIN (HDL); HIGH-FAT DIET (HFD); INTERLEUKIN (IL); LOW DENSITY LIPOPROTEIN (LDL) MORIS WATER MAZE (MWM); NOVEL OBJECT RECOGNITION (NOR); TOTAL CHOLESTEROL (TC); TRIGLYCERIDES (TG)