Obesity-induced Cognitive Impairment in Older Adults: a Microvascular Perspective

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Short title: Synergistic effects of aging and obesity on cognitive decline

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Abstract

Over two thirds of individuals aged 65 and older are obese or overweight in the United States. Epidemiological data show an association between the degree of adiposity and cognitive dysfunction in the elderly. In this review, the pathophysiological roles of microvascular mechanisms, including impaired endothelial function and neurovascular coupling responses, microvascular rarefaction and blood-brain barrier disruption in the genesis of cognitive impairment in geriatric obesity are considered. The potential contribution of adipose-derived factors and fundamental cellular and molecular mechanisms of senescence to exacerbated obesity-induced cerebromicrovascular impairment and cognitive decline in aging are discussed.

Keywords: aging, obesity, metabolic syndrome, senescence, cognition, endothelial dysfunction, neurovascular coupling, blood brain barrier, Nrf2

1. Introduction

Currently, over 35% of individuals aged 65 and older are obese (over 55% of black women) and if the current trend continues, nearly half of the elderly population in the U.S. will be obese by 2030 (302). In this age group, the prevalence of overweight is 78.4% for men and 68.6% for women(93). There is increasing evidence that obesity has deleterious effects on the brain and cognitive function(27, 115, 216, 217) (Figure 1). Importantly, several epidemiological studies, including the Framingham Heart Study, the Health, Aging and Body Composition (ABC) study, the Swedish Adoption/Twin Study of Aging and Baltimore Longitudinal Study on Aging suggest that aging and obesity exerts synergistic negative effects on cognition(69-71, 83, 114, 120, 121, 136, 310). Furthermore, the Whitehall II Study also shows that early midlife obesity is associated with lower executive function and lower MMSE (Mini Mental State Examination) and impaired memory, ability, and executive function later in life(223). In the last decade, significant progress has been made in this research field, and many new concepts have emerged that shed light on the cellular and molecular mechanism underlying obesity-induced cognitive impairment in the elderly. The current view is that obesity both promotes the development of vascular cognitive impairment (VCI)(110) (the most important form of Alzheimer's disease related dementia [ADRD]) and also increases the incidence of Alzheimer's disease (AD)(169).

There is increasing evidence that both aging and obesity causes structural and functional impairment in the cerebral microcirculation, which plays a crucial role in the pathogenesis of both VCI and AD. In this review, potential microvascular contributions to cognitive impairment associated with obesity in the elderly are discussed. Obesity-related alterations in three main regulatory paradigms involved in the regulation of cerebral blood flow (CBF): cerebral autoregulation, endothelium-mediated vasodilation and neurovascular coupling responses responsible for functional hyperemia. Pathophysiological consequences of cerebromicrovascular dysregulation in obesity are explored, including blood brain barrier (BBB) disruption, neuroinflammation, exacerbation of neurodegeneration, microvascular rarefaction and ischemic neuronal dysfunction and damage. In addition, potential obesity-related mechanisms such as adipose tissue dysfunction, hyperinsulinemia and altered gut-brain axis which may be causally linked to microvascular dysfunction are considered. Finally, the evidence for the causal role of cellular senescence in exacerbation of the deleterious effect of obesity on cerebrovascular function and cognition in aging is critically examined. Understanding the cellular mechanisms behind the synergistic interaction of aging and obesity on cognitive decline is important to develop effective interventions for prevention.

2. Links among aging, obesity and cognitive decline

2.1. Epidemiological studies

Several large-scale longitudinal and cross-sectional studies have contributed to our understanding on the negative interaction of aging and obesity on cognitive impairment(148). In the Health Aging and Body Composition Study (Health ABC study), over 3000 participants between the ages of 70 and 79 years were followed up for 8 years and the associations between baseline measures of overall and regional adiposity and change in cognitive function over time was examined. The results showed that higher measures of radiographically measured total fat mass and subcutaneous fat were associated with worsening cognitive function after 7 years (136). In the Framingham Heart study with participants of mean age around 66 years, the obese individuals demonstrated lower cognitive performance after controlling for other risk factor such as hypertension (83). The Baltimore Longitudinal Study on Aging (BLSA) conducted in over 1700 participants with a mean age of 55 years also reported that obesity indices (larger waist circumference and waist-hip ratio) were associated with poorer performance on cognitive tests over time (114). Similarly, the Neurological Diseases in Central Spain (NEDICES), a population-based cross-sectional study with ~2000 elderly subjects aged 65 years

or older showed that obese or overweight status was associated with the lowest quartiles of global cognitive functions (26). Studies conducted as part of the Women's Health Initiative (WHI) in elderly post-menopausal women also reported similar findings (139) suggesting that there are no gender differences in the observed negative interaction of aging and obesity on cognition. In addition, aged individuals with comorbidities associated with obesity such as hypertension, diabetes, hypercholesterolemia or sedentary life style showed greater decline in memory, dexterity and executive functions (82, 300, 310, 323). In particular, in older adults with central obesity, even modest degrees of hyperglycemia was shown to exacerbate cognitive decline(106). In older heart failure patients, cerebral hypoperfusion due to a decreased cardiac output and microvascular consequences of obesity interact to adversely influence cognitive function (5). Similar negative interaction have also been reported for patients with obstructive sleep apnea where obesity reduced the capacity for working memory relative to non-obese sleep apnea patients (233).

It should be noted that while in most clinical studies a strong association between obesity and cognitive decline is evident in mid-life, in late life there are important confounding factors, which may affect this association. In fact there are few studies that appear to suggest that obese older individuals may have certain health benefits(13, 157). Several theories have been put forward to explain this 'obesity paradox'(117). It is possible that the obesity paradox represents an artifact arising from biases in observational studies (e.g. inadequate adjustment for smoking, which cause weight loss and significantly increase risk for vascular diseases). Another important concern is reverse causation due to illness-induced weight loss. These potential hypotheses were further explored in the British Whitehall II stud where obesity at age 50 was a strong predictor of dementia but not at ages 60 or 70. Furthermore, incident dementia cases had higher BMIs up to 16 years before diagnosis but lower BMIs from 8 years before diagnosis(237). Evidence from longitudinal pre-clinical studies on aged mice fed a high fat diet support this concept, suggesting that weight loss due to chronic disease (e.g. cancer) predict a significant decline in performance on behavioral studies. It is also possible that an inherent selection bias in large scale clinical studies where the unhealthiest obese patients are naturally excluded by early mortality may also contribute to the obesity paradox(19). Further, analyses based on BMI measurements alone might be inaccurate as it neglects lean and fat tissue distribution. Central adiposity assessed by waist-to-hip ratio or waist circumference combined with measurements of body composition may be more consistent when determining the effects of obesity on cognition. To overcome the inherent limitations of clinical studies and to provide mechanical insight into the pathogenesis of cognitive decline associated with geriatric obesity several well-controlled pre-clinical studies were conducted on lean and obese animal models of aging. These studies provide strong support for the concept that aging exacerbates the deleterious effects of obesity on cognition (see below).

2.2. Preclinical studies

The deleterious effects of obesity on cognition and cerebral health have been well documented in rodent models(38, 246, 284-286, 298). For example, feeding a high-fat diet (HFD) for 4 to 6 months to mice results in impaired performance in the T-maze test(184), the Morris water maze test(166) as well as other behavioral tasks(38, 246, 285, 286). There are a number of studies extant which have investigated the interaction of aging and obesity on cognitive decline(284, 286, 298). Using mouse models with HFD induced obesity, several studies have demonstrated that advanced aging and diet-induced obesity exert synergistic deleterious effects on cognitive function and cerebral health(38, 246, 285, 286), extending the clinical observations. It is a strength of these studies that similar level of obesity can be induced both in young and aged mice using an identical chronic HFD feeding paradigm. Thus, it is possible to assess the influence of aging per se, independent of the duration or severity of obesity. Using this approach it was demonstrated that aging exacerbates HFD-induced decline in learning and memory function in mice(246) assessed in the elevated plus maze and Y-maze tests(286). Further, mid-life obesity was also associated with compromised visual recognition memory in novel

object recognition test in mice (212). Interestingly, there are data suggesting that females may be more at risk for mid-life obesity-induced VCID than males. A recent study reported that feeding a HFD to middle-aged female mice results in greater weight gain and glucose intolerance than in males and that greater visceral fat mass gain and increased systemic TNFα levels in females correlated with more pronounced spatial memory deficits in females as compared to males (225).

3. Microvascular mechanisms contributing to cognitive impairment

The high metabolic demands of the brain are met by a dense microcirculatory network that is estimated to span approximately 600 km in total length in humans. The cerebral microcirculation ensures appropriate distribution of oxygen, glucose and other nutrients to the neural tissue and it is also responsible for washout of metabolic by-products, maintenance of the ionic milieu, formation of the blood brain barrier (BBB) and regulation of transport of various substances across it. Thus, microvascular health plays a critical role in the maintenance of normal neuronal and cognitive function(62, 63, 68, 90, 101, 133, 134, 142, 144, 146, 168, 254, 255, 270, 306). Cerebromicrovascular dysfunction and microvascular damage has been increasingly recognized as key contributors to age- and obesity associated cognitive impairment. Clinical studies show that obesity promotes dysregulation of cerebral blood flow (Figures 2 and 3), which directly relates to cognitive decline(5, 28, 87, 130, 173, 231, 308). Experimental studies extend the clinical findings and provide mechanistic insight into the synergistic effects of obesity and aging on cerebromicrovascular function. Here we provide an overview of the specific pathogenic roles of endothelial dysfunction, neurovascular impairment, microvascular rarefaction and blood brain barrier disruption in the pathogenesis of VCI associated with geriatric obesity (Figure 4).

3.1. Endothelial dysfunction and neurovascular uncoupling

Microvascular endothelial cells play a critical role in CBF regulation through the production of a variety of vasoactive mediators including the gasotransmitter nitric oxide (NO)(278). Endothelium-dependent, NO-mediated microvascular dilation contributes to the maintenance of resting CBF as studies show that acute blockade of NO synthase decreases CBF and results in cerebral hypoperfusion(74, 278). Aging and obesity-associated endothelial dysfunction, characterized by decreased NO bioavailability, has been shown to cause cerebral hypoperfusion leading to cognitive decline (222, 273). In addition to NO, endothelial cells also produce other vasoactive mediators including endothelin-1 as well as vasoactive arachidonic acid metabolites including prostacyclin, 20-HETE and thromboxanes. Age-related impairment in endothelial NO production may also affect prostacyclin-mediated vasodilatory responses in older humans in the peripheral circulation(195). Further, obesity is also associated with diminished synthesis of PGI_2 which contributes to impaired peripheral vasodilatory responses in rodent models(123). There is initial preclinical evidence that interaction of obesity and aging also alter synthesis of vasoactive arachidonic acid metabolites in the brain(298).

One of the important mechanisms that contribute to endothelial dysfunction in aging and obesity is oxidative stress(66, 214, 262, 264, 267, 277, 278, 281, 286, 293, 306). Both aging and obesity are associated with increased production of mitochondrial superoxide production mediated in part by increased expression of NADPH oxidases in the brain vasculature and also in the other organs(67, 171, 208, 209, 280). Importantly, obesity and aging have synergistic effects on endothelial oxidative stress and up-regulation of NADPH oxidase expression(286). Increased levels of superoxide derived from NADPH oxidases and mitochondrial sources react with endothelium-derived NO to form peroxynitrite, thus decreasing the bioavailability of NO in aging and obesity (31, 67, 104).

In addition to increased obesity-related free radical production, decreased anti-oxidant defense mechanisms also contribute to increased oxidative stress in aging(102, 265, 289, 291, 293). Nuclear

factor-erythroid 2-related factor 2 (Nrf2) is an evolutionarily conserved transcription factor which regulates the expression of anti-oxidative and anti-inflammatory genes in the vasculature(293). Previous studies demonstrated that aging is associated with impaired Nrf2 signaling in the vasculature, which in turn increases the sensitivity to oxidative stress-induced vascular damage (290). Accordingly, Nrf2 deficient mice exhibit increased HFD/obesity-related vascular oxidative stress, which exacerbates endothelial dysfunction(265, 288, 295).

Emerging evidence suggests a crucial role for endothelial NO production in neurovascular coupling responses (NVC)(50, 75, 261, 264, 265, 267, 269, 277, 279). NVC ("functional hyperemia") is a vital homeostatic mechanism involved in moment-to-moment adjustment of regional blood flow to the energetic demands of neurons during periods of intense neuronal activity(262) (Figure 5). Functional hyperemia not only ensures adequate supply of oxygen and glucose to astrocytes and neurons but also effectively clears the metabolic by-products of neuronal activity. NVC depend on an orchestrated interplay between neurons, astrocytes, endothelial cells and smooth muscle cells culminating in coupling of increased blood flow to neuronal activity(262). Pharmacological inhibition of NVC significantly impairs learning and memory in mice highlighting the importance of normal NVC in the maintenance of cognitive functions (269). It is significant that obesity results in neurovascular uncoupling (Figure 5), which effect is exacerbated in aging, promoting cognitive decline(163, 286). Importantly, treatment with apocynin, a NADPH oxidase inhibitor, improves endothelium-dependent NVC in aged obese mice suggesting a critical role for increased oxidative stress in neurovascular dysfunction(286). Further evidence for this concept is provided by studies demonstrating that Nrf2 dysfunction also exacerbates obesity-induced neurovascular uncoupling and cognitive impairment, mimicking the aging phenotype(266). In addition to Nrf2, previous studies also provide evidence that insulin-like growth factor-1 (IGF-1) mediated pathways exert multifaceted cerebromicrovascular protective effects, which act to preserve endothelial vasodilation and NVC(10, 90, 103, 243, 263, 268, 277, 282). Aging results in decreased levels of circulating IGF-1(20, 35, 105, 263)). Mouse models of genetic IGF-1 deficiency were shown to exhibit accelerated neurovascular aging phenotype, characterized by neurovascular uncoupling, impaired endothelial NO production and cognitive impairment(277). IGF-1 receptors are abundantly expressed in different cells of the neurovascular unit including endothelial cells, astrocytes and smooth muscle cells. There is now evidence that cell-type specific depletion of IGF-1 receptors in endothelial cells mimic several aspects of age-related neurovascular uncoupling (Tarantini, Csiszar and Ungvari 2020, manuscript in preparation). Importantly, previous studies also show that genetic IGF-1 deficiency also exacerbates obesity-induced endothelial dysfunction Lewis dwarf rats(14), mimicking the aging phenotype.

3.2. Microvascular rarefaction

Microvascular rarefaction, manifested by a decline in capillary density, contributes to cognitive impairment through a decline in CBF, reducing metabolic support for neurons(48, 278). Previous studies demonstrate that obesity results in decreased capillary density in the cortex and hippocampus and this effect is exacerbated in aging(48, 187, 244, 286). Importantly, the extent of obesity-induced capillary rarefaction in the hippocampus is directly correlated to the extent of cognitive impairment(286) providing additional evidence for the close association between dysregulation of CBF and neuronal dysfunction. It is also possible that co-morbidities associated with obesity, such as hypertension, play also a pathogenic role in worsening capillary rarefaction observed with aging (263). The mechanisms underlying cerebromicrovascular rarefaction in aging and obesity may include impaired endothelial NO bioavailability(48, 96-98), loss of pericytes(286), increased endothelial apoptosis(124, 152), decreased levels of pro-angiogenic factors (e.g. VEGF(299), IGF-1(20, 35, 105, 147, 263)) and impaired endothelial angiogenic processes(64, 65, 263, 286, 292, 294, 297). Overexpression of VEGF in vivo in the aged rodent brain or in vitro VEGF treatment of cultured primary microvascular endothelial cells

derived from aged rats result in impaired angiogenic responses, consistent with the concept that aging results in endothelial resistance to angiogenic stimuli(292). Aging-induced impairment of endothelial angiogenic processes and resistance to VEGF have been attributed to decreased expression of VEGF receptors (12), dysregulation of angiogenic miRNA expression(294), impaired SIRT1 activation(64, 143) and impaired Nrf2 signaling(297). Further studies are warranted to determine how diet-induced obesity impacts these synergistic mechanisms in the cerebral microcirculation.

3.3. Blood brain barrier damage and neuroinflammation

Blood-brain barrier (BBB) is a specialized structure formed by endothelial cells of cerebral microvessels, pericyte, astrocyte end-feet and basal membrane in the central nervous system. This heavily restricted barrier maintains CNS homeostasis by facilitating transport of essential nutrient molecules, regulating ion balance and preventing the influx of serum derived factors into the brain parenchyma(254-256). The integrity of BBB is critical for the maintenance of proper neuronal function (72). BBB leakage or increased permeability is commonly associated with cognitive impairment under various pathological conditions including but not limited to AD, diabetes, stroke and traumatic brain injury (181, 254-256). In fact, a recent study reported increased BBB permeability as an early biomarker for cognitive dysfunction in humans independent of the presence of AD related biomarkers like Aβ and/or tau in the hippocampus(190).

Both aging and obesity promote BBB disruption (181), and our studies demonstrate that their effects are synergistic(265, 285, 298). The mechanisms underlying exacerbated obesity-induced BBB damage in aging are likely multifaceted. First, alterations in the expression of tight junction and adherens junction proteins including occludin, claudins and cadherins might impair BBB integrity(286). Additionally, both aging and obesity are likely to result in post-translational modifications, including phosphorylation, palmitoylation, glycosylation, acetylation and methylation of tight junction proteins, which may affect their stability and proper cellular localization(248). Pericytes are also critical structural component of BBB and pericyte deficient *Pdgfrβ*$^{-/-}$ mice have increased BBB permeability (9). In that regard it is significant that aged obese mice have less pericyte coverage in the cerebral microvessels than younger ones(284). Lastly, cells forming the BBB have a high metabolic rate, consistent with the high energy demands for active ATP-dependent transporters. Proteomic analysis from freshly isolated cerebral microvessels indicate that several proteins important for cellular energy metabolism are downregulated in diet-induced obesity (207) suggesting that impaired energy metabolism in the endothelial cells could also potentially contribute to BBB disruption. There is strong evidence that age-related decline in cellular NAD+ levels and uncoupling of the mitochondrial electron transport chain contribute importantly to impaired energy metabolism of cerebromicrovascular endothelial cells(66, 142, 144, 146, 264, 267, 270). While the precise mechanisms that contribute to the hypometabolic state of microvascular endothelial cells observed in obesity are not known, decreases in circulating levels of adiponectin (high molecular weight form), a hormone known to stimulate energy metabolism through AMPK pathway, could potentially play a role(205, 258).

One of the major consequences of BBB breakdown is leakage of plasma constituents including IgG, thrombin and fibrinogen into the brain parenchyma(285). Increased infiltration of plasma proteins through the BBB promotes neuroinflammation mediated through activation of resident immune cells, especially microglia(285). For example, interaction of IgG with Fc gamma receptors (FcγR) results in microglia activation(100) leading to secretion of pro-inflammatory cytokines, chemokines and reactive oxygen species. There is evidence demonstrating synergistic interaction of aging and HFD-induced obesity to exacerbate leakage of IgG and promote microglia activation in the mouse hippocampus (285, 298). Activated microglia may also cause further BBB damage, thus driving a vicious cycle of neuroinflammation (234). Chronic unresolved inflammation in obesity adversely affects neuronal function related to cognition(58, 108, 111, 118, 132). Increased presence of activated microglia in the

hippocampi of obese aged mice is associated with exacerbated impairment of long-term potentiation (LTP) of excitatory synaptic transmission, an important cellular correlate for learning and memory(298). It is significant that Nrf2 deficient mice exhibit exacerbated HFD/obesity-related BBB disruption, neuroinflammation and LTP impairment in the hippocampi, mimicking the aging phenotype(266).

4. Obesity-related factors that contribute to cerebromicrovascular impairment

The cellular mechanisms underlying the increased susceptibility of the elderly to obesity-induced cerebromicrovascular impairment and cognitive decline are likely multifaceted. Here we discuss the potential role of adipose tissue inflammation, altered adipokine secretion, insulin resistance and alterations of the gut-brain axis.

4.1. Adipose tissue dysfunction

Once considered an inert fat storage organ, adipose tissue is now recognized as an active endocrine organ that secretes a variety of adipokines, which can act both at peripheral and central sites. Excessive accumulation of fat in obesity is associated with adipose tissue dysfunction. This results in dysregulated secretion of adipokines including pro-inflammatory cytokines and chemokines rendering the adipose tissue as a major contributor to systemic inflammation. Emerging studies suggest that the crosstalk between adipose tissue and the brain plays a key role in the increased vulnerability of obese elderly patients for cognitive impairment. In this section, we discuss potential adipose tissue-related mechanisms that can affect cerebral microcirculation and cognition.

4.1.1. Heightened inflammatory status of the adipose tissue promotes systemic inflammation

Obesity is associated with low grade inflammation within the adipose tissue (including increased infiltration and activation of macrophages, pro-inflammatory changes in the cellular secretome), which results in elevated levels of circulating pro-inflammatory mediators(89, 122, 198, 230, 253). Based on the observations from clinical studies investigating the effects of weight loss strategies on systemic inflammation (95, 197), it can be inferred that adipose tissue dysfunction and its heightened inflammatory status contribute significantly to systemic inflammation in obesity. In particular, inflammatory cytokines and neuroinflammation(58, 61, 84, 94, 140, 141, 150, 170, 178, 183, 193, 200, 226, 240, 246, 265, 274, 283, 284, 298) have an important role in impaired neuronal function and the pathogenesis of both VCI and AD(46, 52, 119, 159, 194, 232).

Adipose tissue is capable of handling excess energy intake by expansion of existing adipocytes (hypertrophy) and also through adipogenesis where the progenitor cells proliferate and differentiate to generate new adipocytes (hyperplasia). Inadequate expansion of adipocytes results in hypertrophied adipocytes which tilts the secretory profile of adipocytes favoring inflammation (59). With long term obesity, this is followed by infiltration of immune cells in the adipose tissue, most notably macrophages, CD8+ T cells, mast cells, and B cells. Obesity is also known to alter the polarization of adipose tissue macrophages from anti-inflammatory M2 to pro-inflammatory M1 phenotype leading to persistent unresolved inflammation(47). Activated macrophages and inflamed adipocytes secrete a variety of cytokines and chemokines such as IL-6 and TNF-α, which enter the circulation and lead to systemic inflammation. Additionally, toll-like receptors (e.g. TLR4) are abundantly expressed both on adipocytes and macrophages. When stimulated by circulating bacterial breakdown products (see discussion of the "leaky gut" below) in these cells multiple inflammatory signal transduction cascades are activated promoting the secretion of a range of inflammatory cytokines and acute phase proteins. There is strong evidence that aging exacerbates obesity-induced inflammation in the adipose tissue(15, 249, 284, 286, 298, 311), which contributes to the development of several secondary diseases such as the metabolic syndrome, insulin resistance, type 2 diabetes mellitus and hypertension. The heightened inflammatory status of the adipose tissue and the consequential increases in circulating cytokines are also thought to play a critical role in exacerbation of VCI and AD in older obese individuals.

Studies have shown a causal link between systemic inflammation and cognitive impairment (167). Circulating inflammatory mediators can affect cerebromicrovascular function and cognition through several mechanisms. First, they promote microvascular oxidative stress and endothelial dysfunction, induced endothelial activation and impair cellular energy metabolism. Further, circulating cytokines have also been demonstrated to disrupt BBB function by modifying tight junction structures (327), inducing endothelial apoptosis (44) and glycocalyx degradation on the apical endothelium (307). Cytokines like IL6, TNFα, IL-1β and IL-1α can selectively cross BBB using active transport systems (21, 23, 116) and activate resident glial cells to foster neuroinflammation and cognitive decline.

4.1.2. Altered adipokine secretion

In addition to cytokines, dysregulation in the secretion and signaling of other adipokines (leptin, adiponectin and resistin) has also been implicated in the pathogenesis of neurovascular diseases(204).

Leptin is a peptide hormone secreted in proportion to white adipose tissue mass. Originally the effect of leptin was only considered in the hypothalamus where it is involved in the regulation of central control of food intake and energy homeostasis. However, identification of the leptin receptor (LepR) on endothelial cells and LepR mediated transport mechanisms at the BBB (22, 76) suggests that leptin can also affect the microcirculation and thereby potentially modulate microvascular contributions to cognitive decline. However, the vascular (and cognitive) effects of leptin signaling are likely complex. On endothelial cells, leptin has been shown to upregulate endothelin-1, as well as to stimulate the expression of adhesion molecules and induce oxidative stress(271). There are also studies showing that leptin induces hypertension and/or endothelial dysfunction(92, 128, 129, 151, 155). Leptin-deficient and whole-body leptin receptor-deficient mice are protected from neointimal hyperplasia in response to arterial wall injury(25). Clinical studies show that high leptin levels predict acute cardiovascular events, coronary restenosis and stroke(25). Yet, LepR deficiency causes cognitive impairment in Zucker rats and db/db mice(164) and endothelial specific LepR deficiency was reported to associate with poor vascular outcomes(127). Studies show that leptin responsiveness decreases with aging and obesity which may be related to defective leptin transport across BBB, downregulation of LepRs and/or impaired leptin signaling downstream of LepRs (73, 188). Leptin resistance is associated with high circulating levels of leptin both in aging and obesity(229). Studies investigating the direct effects of leptin resistance on the cerebral microvessels are warranted.

Resistin is a pro-inflammatory adipokine, which promotes insulin resistance(250) and atherosclerosis(204, 221, 303). Elevated resistin level is associated with an increased risk of ischemic stroke(32, 79, 137, 153, 218, 303). Resistin was shown to increase permeability in a cell culture-based blood-brain barrier model(312). Resistin has also been causally linked to endothelial dysfunction(219, 227) Yet, its role in dysregulation of CBF and NVC responses, BBB disruption and cognitive decline(180) remains elusive.

Adiponectin is an adipokine produced primarily in adipose tissue, that circulates at high concentrations and modulates metabolic processes, including glucose regulation and fatty acid oxidation and confers potent anti-inflammatory effects(126, 156, 318-320). It acts as an insulin-sensitizing hormone in muscle and liver(126). Through these actions it ameliorates diabetes and prolongs lifespan in mouse models of type 2 diabetes (e.g. db/db mice on high fat diet)(201). Adiponectin activates the AMPK (AMP-activated protein kinase) - PGC1α (Peroxisome proliferator activated receptor gamma coactivator 1 alpha) axis in cells(318). Importantly, aging and obesity associate with decreased adiponectin levels(179, 258). Decreased adiponectin levels have also been observed in elderly patients with neurocognitive disorders (109). In contrast, the anti-aging dietary regimen caloric restriction increases circulating adiponectin levels in experimental animals(78, 154, 179, 196, 235, 315, 328). Adiponectin was shown to confer multifaceted neuroprotective and vasoprotective effects(8, 154, 235, 319). Adiponectin receptors (AdipoR1 and AdipoR2) are expressed in the hippocampus and other brain

regions and adiponectin was shown to promote synaptic transmission and memory function (29, 304). Accordingly, AdipoRon, a small molecule pan-adiponectin receptor agonist has been also shown to modulate hippocampal synaptic transmission (324) and attenuate neuroinflammation (326).

Adiponectin also exerts diverse endothelial protective effects. It was shown to protect endothelial cells against high glucose and oxidized LDL-induced oxidative stress (185, 206), increase the production of NO^{1179} (51) and maintain capillarity and microvascular blood flow(260). The pan-adiponectin receptor agonist AdipoRon was shown to improve endothelial function(55). Adiponectin was also reported to inhibit atherogenesis(319) and to modulate inflammatory processes in cerebromicrovascular endothelial cells(247). Further, several studies established a critical role of adiponectin in anti-aging vascular effects of caloric restriction(154, 235). Exercise training and weight loss were also shown to increase adiponectin levels, which associate with improvement of microvascular endothelial function(60, 210). Whether therapies targeting adiponectin signaling can exert similar improvements in brain microvascular function in obese elderly patients remains to be determined.

4.2. Insulin resistance

Obesity is commonly associated with hyperinsulinemia and insulin resistance, a prerequisite for prediabetes and type 2 diabetes(257). Clinical studies have shown that diabetes or prediabetes accelerates the progression from mild cognitive impairment to dementia(57, 83, 287, 314), with age and the duration of diabetes being the major risk factors (172).

Intact insulin signaling in the brain is important for normal cognitive functions. High fat diet-induced obesity has been shown to induce insulin resistance in the hippocampus (99, 131), a region known to regulate learning and memory. Preclinical studies have shown that hippocampal specific insulin resistance impairs spatial learning and neuroplasticity without affecting peripheral glucose homeostasis (112), suggesting insulin resistance in the brain could contribute to obesity-induced cognitive dysfunction. While the exact mechanisms underlying obesity-induced insulin resistance in the hippocampus are not known, reduced receptor mediated transport of insulin across BBB or reduced expression of insulin receptors in the hippocampus could play a role (24, 138). In addition to its direct actions on neurons, insulin signaling can also modulate cognitive functions through its actions on the brain microvasculature. Under insulin sensitive states, insulin activates eNOS to produce NO through the phosphatidyl inositol (PI)-3-kinase-Akt signaling pathway resulting in increased tissue perfusion and subsequent augmentation of glucose disposal (77, 186). Obesity-induced insulin resistance in the hippocampal microvessels led to decreased insulin-mediated microvascular perfusion and eNOS expression in the hippocampus (99). In insulin resistant obese Zucker rats, treatment with insulin sensitizing agents like metformin and rosiglitazone was reported to improve endothelial NO mediation(36) and partially rescue cerebral microvascular rarefaction (48). Considering that BBB damage precedes cognitive dysfunction in obesity (259, 317), insulin resistance in the cerebromicrovascular endothelial cells as a causative factor for BBB damage and cognitive decline in obesity needs to be investigated.

4.3. Altered gut-brain axis (dysbiosis)

The gut microbiome, with an estimated 100 trillion microrganisms, has emerged as an important contributor to cognitive health. A change in the composition of the gut microbiome due to loss of beneficial bacteria or overgrowth of harmful bacteria leading to an overall decrease in microbial diversity is called dysbiosis. Both aging and obesity are associated with a dysbiotic microbiome(39, 165, 238). Specifically, increased levels of Firmicutes (F) and decreased levels of Bacteroides (B) phylum bacteria have been reported both in obesity and aging (175, 220, 272). More importantly, these changes in the microbiome are linked with impaired CBF, BBB impairment and cognitive dysfunction (43, 175). Clinical studies show that dementia patients have a higher F/B ratio (224) and elderly patients with

similar dysbiotic microbiome perform poor in cognitive tests (176). Similarly in preclinical studies, obese mice with poor microbial diversity exhibited impaired spatial memory (325) and fecal/cecal transplantation from high fat diet fed mice to germ free mice resulted in selective disruptions in exploratory, cognitive, and stereotypical behavior in the absence of obesity (37). These studies suggest that dysbiosis could contribute to obesity and/or aging-induced cognitive dysfunction.

One of the major mechanisms by which dysbiotic gut microbiota may impact cognition is through promoting BBB impairment. Brainste et al showed that germ free mice (both during the intrauterine and the postnatal period) had increased BBB permeability with reduced expression of the tight junction proteins, occludin and claudin-5 (34). Exposure of germ free mice to normal microbiota reversed the above mentioned adverse effects on BBB (34) suggesting gut microbiota-brain communication is essential for normal development and maintenance of BBB function. Although there are correlational studies connecting gut microbiome perturbations and obesity and aging-induced BBB dysfunction and cognitive decline (43, 175), the direct cause-effect relationship needs further investigation. Dysbiosis can also indirectly affect cognition through promoting systemic inflammation. Rodent studies have shown that intake of western diet compromises the gut barrier by decreasing the level of tight junction protein ZO-1and transepithelial resistance in the colon (160). The resulting leaky gut makes it easier for the entry of bacteria derived lipopolysaccharide (LPS) in to the circulation leading to endotoxemia and systemic inflammation (43). In addition, dysbiosis also results in decreased production of beneficial short chain fatty acids (SCFAs) such as acetate, propionate and butyrate by microbial fermentation of indigestible carbohydrates. Obesity is associated with decreased plasma levels of SCFAs (199), which are known to have anti-inflammatory and immune-modulatory effects. Especially, sodium butyrate has been shown to improve cognitive function by increasing BDNF levels in the brain (322). It is also highly possible that butyrate can modulate the aging process due to its epigenetic actions by inhibition of histone deacetylase activity (296).

5. Cellular senescence: a potential mechanism for accelerated vascular aging in obesity

Cellular senescence is a cell-autonomous aging process characterized by irreversible cell cycle arrest, expression of a senescence-associated secretory phenotype (SASP), heterochromatin foci and increased expression of cell cycle inhibitors like p16. Senescent cells accumulate in various tissues of the body including the brain during aging and have been implicated in the pathogenesis of age-related diseases (16, 17, 41, 42, 53, 54, 61, 102, 145, 162, 293, 301). One of the major mechanisms through which senescent cells contribute to aging and age-related diseases is through SASP where the secretome containing pro-inflammatory mediators and matrix degrading proteases detrimentally affect the tissue microenvironment impairing normal tissue function and rejuvenation. Elimination of senescent cells that expresses p16 protein has been recently reported to improve lifespan and health span in rodents (11, 18, 91, 211, 313), consistent with the notion that senescent cells drive organismal aging.

Emerging evidence suggest that cellular senescence in the vascular cells could mediate aging and obesity-induced vascular pathologies. Primary cerebrovascular endothelial cells and pericytes isolated from aged mice had higher SA-β gal activity and increased expression of cell cycle inhibitors, p16 and p21 when compared to young mice (321). BulbR1 (H/H) mice, which exhibit an increased number of senescent endothelial cells and pericytes demonstrated less coverage of tight junction proteins in the cortical microvessels and a compromised BBB integrity (321). Metabolic factors that have relevance for obesity and the metabolic syndrome, including high glucose levels, oxidized low-density lipoproteins and advanced glycation end products, have been reported to induce premature senescence in endothelial cells (40, 174, 236). We have recently demonstrated that obesity increases expression of senescence markers in the mouse cerebral circulation and this effects is exacerbated by genetic depletion of Nrf2(266). Further, Nrf2 deficiency accelerates age-associated induction of senescence and inflammation in the hippocampus (102). These studies point to a potential role for accelerated vascular

senescence in the brain contributing to the adverse interaction of aging and obesity in the pathogenesis of VCI. It is important to better understand the mechanisms by which metabolic factors in obesity might induce premature senescence in the vasculature. Further studies elucidating the cell types that become senescent in aging and obesity in the cerebral vasculature will provide crucial details on the cellular mechanisms involved in senescence-mediated cognitive aging. Identification of senescent cells by assessing their transcriptomic profile (single cell RNA sequencing (145)), by flow cytometry(316) or by immunohistology should be attempted in obese aged animals. The effects of senolytic treatments in these models should also be tested(316).

6. Intervention strategies

6.1. Exercise

Several studies have documented the beneficial effects of exercise on age and obesity-dependent neurovascular dysfunction, cerebral blood flow and cognition. In older obese/overweight individuals, a morning bout of moderate-intensity exercise, with subsequent light-intensity walking breaks from sitting, improved cerebral blood flow measured by transcranial Doppler (305). In another study, 4 month high intensity interval training improved cerebral oxygen extraction along with positive cognitive outcomes including improved short-term and verbal memory, attention and processing speed in middle-aged obese patients(80). In addition, three separate meta-analyses of longitudinal studies have reported that physical activity delays or prevents late-life cognitive decline and dementia (30, 45, 241). Some studies have also compared the effects of different types of exercise on microvascular and cognitive outcomes in aging. Acute aerobic, but not resistance training was shown to improve attention and working memory in aged individuals (81). Similarly, moderate aerobic exercise for 24 weeks improved vasomotor organization, attention and concentration in healthy aged subjects (3). In another study, a supervised aerobic intervention for 6 months also improved fluency and resting cerebral blood flow in healthy low-active middle-aged and older adults in the Brain in Motion (BIM) study (113). Several other studies also overwhelmingly support the positive effects of aerobic exercise on cerebral blood flow and cognitive outcomes in older individuals (2, 49, 149). Interestingly, exercise was able to confer similar cognitive benefits either alone or in combination with dietary intervention in obese elderly patients (189). While the majority of studies suggest that exercise benefits obese older adults, some studies did not find any association of physical activity and the prevalence of cognitive impairment in the elderly (86, 239). The presence of co-morbidities like diabetes may likely contribute to the observed inconsistency in the positive effect of exercise in obese elderly individuals (85).

Preclinical studies have provided additional evidence elucidating microvascular mechanisms contributing to exercise mediated beneficial cognitive outcomes in aging and obesity. Voluntary wheel running for 6 months in mid-life reduced BBB permeability, increased microvessel pericyte coverage, reduced microglial activation and preserved basement membrane in the microvasculature of APOE deficient mice (245). Six weeks of voluntary wheel running also appears to increase capillarization and VEGF levels in the hippocampus of middle-aged mice (161). Chronic physical activity after the onset of obesity also improved insulin-mediated vasodilation in the cerebral vessels in middle-aged rats(202). These aforementioned exercise-induced microvascular protective effects likely can be attributed, at least in part, to reduced systemic inflammatory status. Results from the Health ABC and NHANESIII studies show that self-reported physical activity is associated with reduced levels of circulating IL6, TNFα and C-reactive protein (CRP) levels, and this association is independent of both BMI and waist-to-hip ratio in older adults (1, 56). Although the existing evidence supports the concept that exercise improves cognition via exerting microvascular protective effects, additional studies are needed to completely understand the circulating mediators and the exact cellular and molecular mechanisms involved in its effects on neurovascular coupling and brain capillarization, especially in obese elderly individuals.

6.2 Dietary interventions

Weight loss mediated through various forms of dietary interventions including calorie restriction (CR), intermittent fasting and consumption of a Mediterranean diet have inconsistent cognitive outcomes in the obese elderly population. Three months of 30% CR increased verbal memory scores which correlated with reduced body weight, fasting insulin and CRP levels in overweight aged subjects (309) and the same is true for patients with mild cognitive impairment (MCI) (125). Importantly, improved cognition was observed only during the negative energy phase of CR which is no longer sustained during the subsequent weight maintenance phase (215). However, some studies report that weight loss by CR alone was not sufficient to improve cognition, unless combined with exercise(88, 213). This could be due to the adverse side effects of CR including decrease in muscle mass which adversely affects the overall glucose metabolism and negates the positive effects of weight loss on cognition. Hence, intermittent fasting (various dietary regimen with alternating fasting and non-fasting cycles) has emerged as a better alternative to CR as it has been shown to improve cognition in the obese elderly (203) without adverse side effects (7). Previous studies demonstrated that CR in aged rodents increases Nrf2 activity , increases the angiogenic potential and reduces the cellular and mitochondrial oxidative stress in cerebromicrovascular endothelial cells (64) and these changes at the level of microvasculature are at least in part mediated through circulating factors (65). Additional studies are needed to understand the source and the microvascular impact of these circulating factors in the context of VCI.

Changes in diet composition including Mediterranean diet rich in olive oil or the ketogenic diet low in carbohydrate and high in fat have also been shown to affect cognition positively in the elderly population (33, 275). Especially, adherence to the Mediterranean diet improved endothelial function marked by increases in flow-mediated dilation (275), increases in serum NO, decline in ROS and endothelin-1 production (252) and improves the regenerative capacity of endothelial progenitor cells (276). However, most of the above-mentioned studies focused on the peripheral vasculature and the effects of diet composition on cerebral microvasculature are far from clear.

6.3 Other non-lifestyle interventions

While diet and exercise seem effective in overweight or moderately obese individuals, lifestyle interventions are not amenable for severely obese patients. Bariatric surgery is a popular non-lifestyle intervention for obese subjects with a BMI≥40 to yield sustained weight reductions. Results from the Longitudinal Assessment of Bariatric Surgery project demonstrated improved executive and memory performance and was maintained 2-3 years after surgery-induced weight loss, while this effect was lost in the subset of participants who regained weight (4, 6). As seen with other weight loss strategies, bariatric surgery mediated cognitive improvements are associated with improved metabolic outcomes and reduced systemic inflammation (251), which could affect brain microvasculature to impact cognition.

In women, the role of estrogen in modulation of vascular function and cognition should not be overlooked(182). Surgical menopause in women ≤45 years of age through bilateral oophorectomy significantly affects cognitive performance(107) (158). In contrast, estrogen replacement through hormone replacement therapy in older women was shown to improve cognitive test scores, especially when started early during the post-menopausal period (177).The protective role of estrogen on endothelial function has been extensively studied and reviewed elsewhere (242).

7. Perspectives

It is becoming increasingly accepted that microvascular mechanisms could play a critical role in aging-induced and obesity-related cognitive impairment. Rescuing microvascular function for treatment and prevention of cognitive decline is a promising approach as the cerebral vasculature and the

neurovascular unit are more accessible targets for pharmacological and non-pharmacological (e.g. dietary, exercise) interventions than non-vascular cells in the brain. Further translational studies are warranted to test the cerebromicrovascular and cognitive protective effects of combinations of various exercise protocols, dietary regimens and anti-aging pharmacological interventions in obese older adults at risk for VCI.

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Figure legends

Figure 1. Obesity in aging promotes cognitive impairment and dementia. A) Prevalence of dementia by BMI status, across age categories. Note that obesity in aging is associated with a significant increase in the prevalence of dementia. Figure is reprinted with permission from reference (192). B) Obesity is associated with impaired cognitive performance (lower Rapid Visual Information Processing [RVIP] accuracy score) in older participants of the Oklahoma Longitudinal Study on Aging (>60 years old). The RVIP task (Cambridge Neuropsychological Test Automated Battery [CANTAB] battery of tests) a sensitive serial discrimination task where task performance reflects visual sustained attention (vigilance) and working memory capabilities. fMRI studies show that frontal, parietal and cerebellar regions are activated during the task. Older individuals exhibit a decreased performance on the RVIP task(191), which is further exacerbated by obesity. Data are replotted from reference(62). * indicates significant difference between the 2 groups.

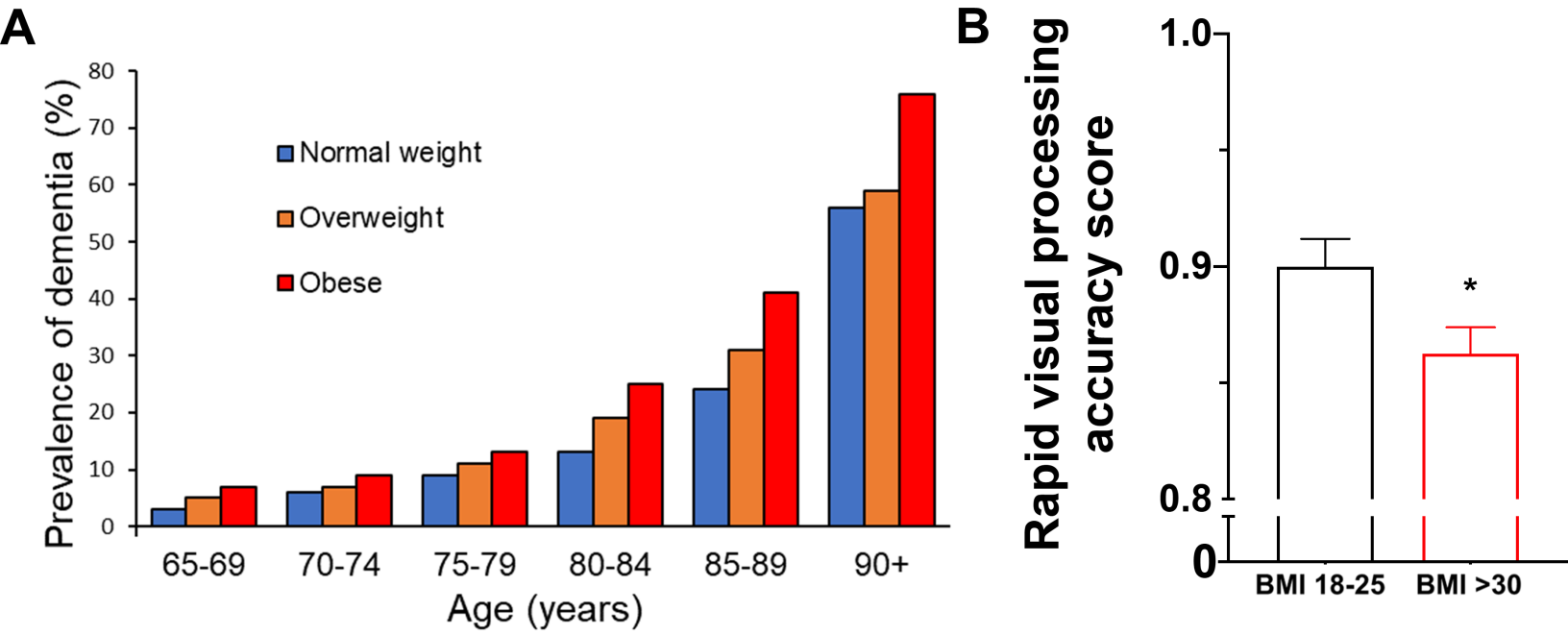
Figure 2. Cerebral blood flow is decreased in obese subjects. Panels A show the relationship between body mass index (BMI) and age-adjusted mean baseline blood flow velocities (BFV) in right and left middle cerebral artery (□MCAR, ■MCAL). Panel B shows that mean BFV in MCAR ($p=0.017$) and MCAL ($p=0.0002$) are higher for normal weight (BMI<25 kg/m2) than overweight (BMI 25–30 kg/m2) and obese subjects (BMI>30 kg/m2). Panels C and D show the average cerebrovascular resistance (CVR in □MCAR and ■MCAL during baseline and head-up tilt (mean±SE). The figures are reprinted with permission from reference(231).

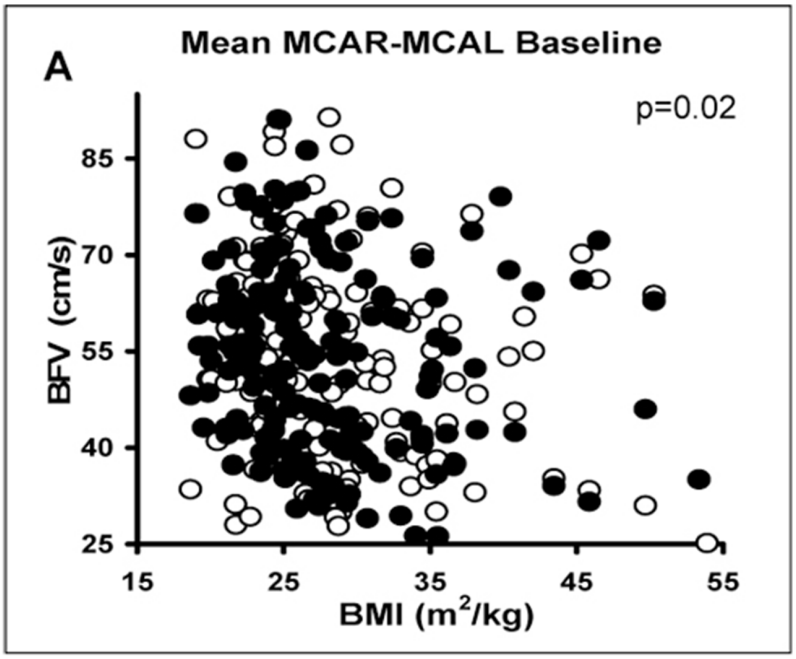
Figure 3. Obesity and the metabolic syndrome impair CBF. A) CBF is decreased proportional to the number of metabolic syndrome factors (including abdominal obesity, triglycerides, HDL-cholesterol, blood pressure, and fasting glucose) present in an individual. Lower CBF was reported to most robustly associate with abdominal obesity, and only to a lesser extent with triglycerides and fasting glucose(28). B) Participants with metabolic syndrome and obesity show significantly lower CBF in large portions of the cortical surface of the frontal and parietal lobes, and the lateral and superior portions of the temporal and occipital lobes (yellow: voxel-wise results at $p < 0.05$, FEW corrected, controlling for age, sex, and reference cluster. Resting CBF assessments were made using background-suppressed pseudo-continuous arterial spin labeled (pcASL) MRI. The figures are reprinted with permission from reference(28).

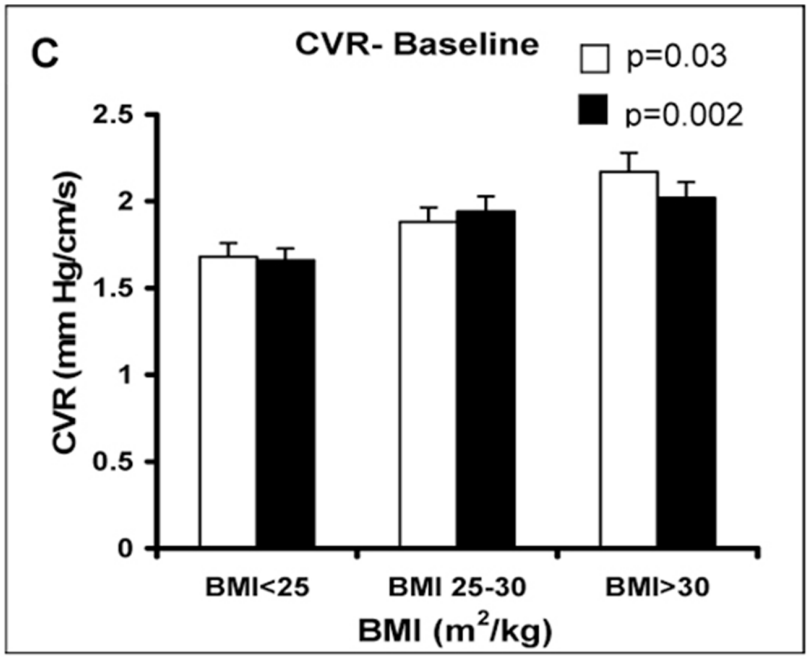
Figure 4. Proposed scheme for cerebromicrovascular contributions to obesity-induced cognitive decline in older adults. Excessive accumulation of fat in obesity is associated with adipose tissue dysfunction and low grade inflammation, which results in altered secretion of adipokines and pro-inflammatory cytokines. These circulating factors mediate the crosstalk between adipose tissue and the brain by impairing the cerebral microcirculation. In aging heightened inflammatory status of the adipose tissue promotes increased systemic inflammation, which – together with age-related impairment of cellular stress resilience pathways - play a key role in the increased vulnerability of obese elderly patients for cognitive impairment. Functional and structural impairment of the cerebral microcirculation results in endothelial dysfunction, neurovascular dysfunction and microvascular rarefaction, all of which contribute to a significant decline in cerebral blood flow. Microvascular inflammation and disruption of the blood brain barrier exacerbate neuroinflammation. Obesity is also associated with dysbiosis. Age-related breakdown of the intestinal barrier promotes the leakage of bacterial breakdown products to the

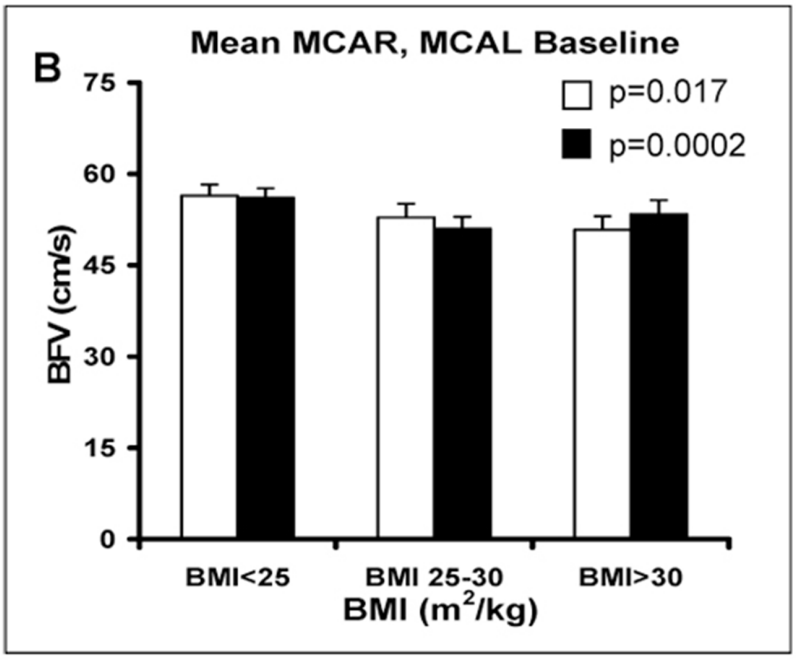
circulation, exacerbating microvascular inflammation and blood brain barrier dysfunction (PAMPs: Pathogen-Associated Molecular Patterns). The resulting ischemic and inflammatory foci play a role in the pathogenesis of cognitive impairment. The model predicts that the aforementioned obesity-related structural and functional cerebromicrovascular alterations synergize to promote cognitive impairment in high risk older adults.

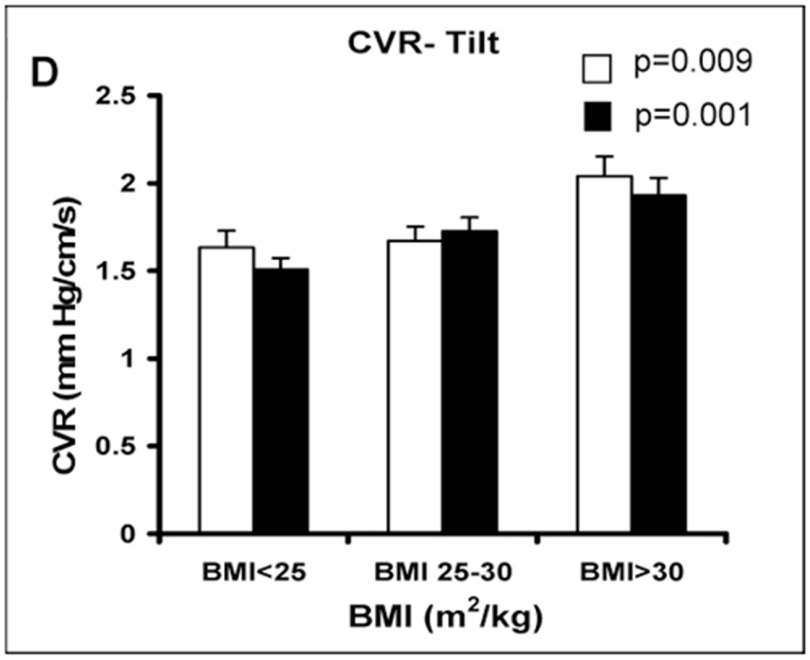
Figure 5. Obesity impairs neurovascular coupling responses. Panel A: Obesity impairs neurovascular coupling in mice. Representative pseudocolour laser speckle flowmetry maps of baseline CBF (upper panels) and CBF changes in the whisker barrel field relative to baseline during contralateral whisker stimulation (lower panels, right oval, 30 s, 5 Hz) in standard diet-fed lean and high fat diet-fed obese mice. Color bar represents CBF as percent change from baseline. Panel B shows the time-course of CBF changes after the start of contralateral whisker stimulation (horizontal bars). Summary data are shown in panel C. Data are mean±S.E.M. (n=6-8 in each group), *P<0.05 vs. lean control; $^{\#}$P<0.05 vs. untreated. (one-way ANOVA with post-hoc Tukey's tests). Panel D-E: Obesity impairs neurovascular coupling in older humans. Neurovascular coupling responses were assessed by functional Near-Infrared Spectroscopy (fNIRS) during a finger-tapping task in normal weight (BMI 18-25, n=10) and obese (BMI>30, n=10) older adults (>65 years of age). Data were analyzed using the Brain AnalyzIR toolbox(228) based on a General Linear Model (GLM) approach. Task-related changes in oxygenated hemoglobin (HbO) concentration (calculated using the Beer-Lambert law(135)) was used as an index of functional hyperemia. The design matrix included boxcar regressors for each stimulation, and a canonical hemodynamic response function was used to identify activated cortical regions. Beta-weights, scaling the predictors, were then used for group level statistics, where a *t*-contrast of [BMI 18-25]-[BMI >30] was applied (*p<0.05). In panel D solid lines represent statistically significant difference between groups in task-evoked neurovascular coupling responses in the area and vicinity of the left primary motor cortex, evidenced by the increased HbO concentration observed in the normal weight older adult group when compared to their obese counterparts. Bar graphs (panel E) represent calculated changes in HbO. Note that neurovascular responses, that show an age-related decline even in older adults, are inverted obese older adults. Position of fNIRS light sources (s14, s15) and light detectors (d13, d15 and d16) are shown in panel D. Data are re-plotted from previously published studies(63, 265).











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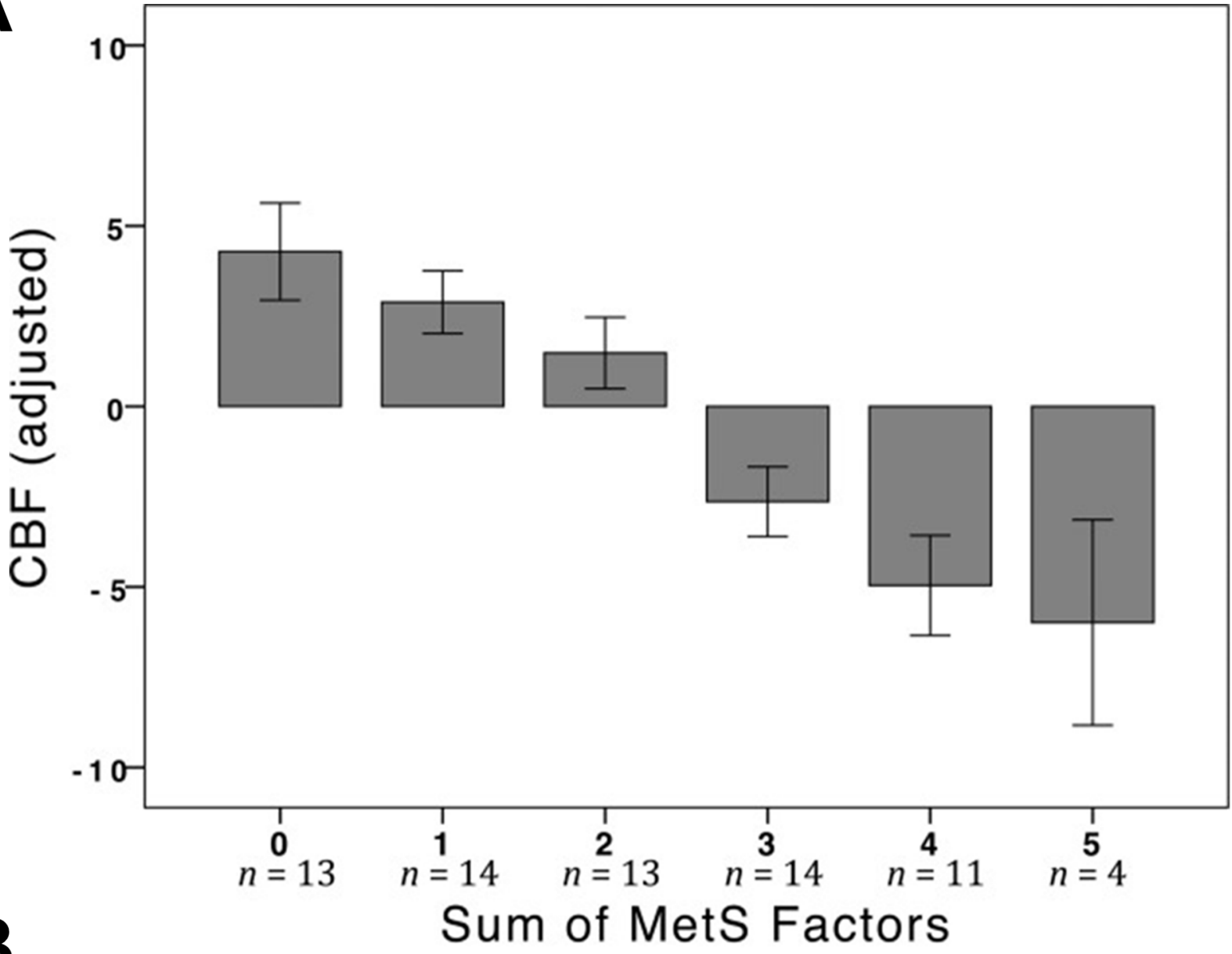

B

Error bars: +/- 1 SE