Degenerative Neurological and Neuromuscular Disease

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REVIEW

Current Perspectives: Obesity and Neurodegeneration - Links and Risks

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Abstract: Obesity is increasing in prevalence across all age groups. Long-term obesity can lead to the development of metabolic and cardiovascular diseases through its effects on adipose, skeletal muscle, and liver tissue. Pathological mechanisms associated with obesity include immune response and inflammation as well as oxidative stress and consequent endothelial and mitochondrial dysfunction. Recent evidence links obesity to diminished brain health and neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Both AD and PD are associated with insulin resistance, an underlying syndrome of obesity. Despite these links, causative mechanism(s) resulting in neurodegenerative disease remain unclear. This review discusses relationships between obesity, AD, and PD, including clinical and preclinical findings. The review then briefly explores nonpharmacological directions for intervention.

Keywords: obesity, metabolism, Alzheimer's, Parkinson's, neurodegeneration

Introduction

Obesity is a disease of excessive fat accumulation and is defined by a body mass index (BMI) greater than or equal to 30kg/m^2. While obesity develops gradually and is traditionally seen in the older sedentary population, the disease is becoming more common in younger individuals.[1] The development of obesity is driven mostly by caloric excess from a "Western"-style diet.[2] Despite increasing evidence for the negative health effects of obesity,[3] the World Health Organization reported 13% of the world population to be obese in 2016 and since 1975 the prevalence of obesity has nearly tripled.[4] This has important implications for other chronic diseases that have been linked to metabolic dysregulation, including neurodegenerative diseases.

Research has identified both modifiable and nonmodifiable risk factors for obesity. Early twin studies report a heritability of 40–80% for BMI.[5] More recently, Genome-Wide Association Studies have identified 115 genetic loci, accounting for 2–3% of the variation in BMI. This suggests that approximately 20% of the variation in BMI may be due to genetic factors.[6] Socioeconomic factors such as education, income, and occupation may also contribute to obesity at both an individual and environmental level.[7–9] The literature is clear that weight reduction can be achieved by modifying lifestyle behaviors. Although weight loss can result from exercise alone,[10–12] exercise in combination with dietary programs lead to greater weight loss.[13–17] Sleep is also associated with obesity. Low sleep duration is associated with a greater incidence of obesity.[18–20] However, this relationship appears to be a "U shaped" function as obesity risk increases with long sleep duration.[21,22]

Obesity can negatively affect many systems throughout the body, most notably the cardiovascular system. Individuals with obesity have elevated blood pressure independent of adrenergic activity.[23] The observed hypertension in obese patients is due to an increase in stroke volume, which can lead to left ventricular hypertrophy.[24,25] Another adverse effect of obesity is disrupted hemodynamics. Individuals with obesity have elevated cholesterol and low-density lipoprotein levels,[26,27] which can impair vascular tone.[28] Cholesterol accumulation alone can also drive atherosclerotic plaque

Received: 1 August 2023
Accepted: 21 December 2023
Published: 3 January 2024

formation which can further damage endothelial cells from increased shear stress.[29,30] Concurrently, obesity has a negative impact on other organs such as the liver. Obesity is strongly linked to nonalcoholic fatty liver disease (NAFLD), with disease severity related to impaired glycemic status.[31,32] Direct relationships between the prevalence of type 2 diabetes (T2D) and BMI have been reported.[33] The overnutrition associated with obesity leads to chronically elevated insulin and inflammation, which can result in insulin resistance that precedes hyperglycemia.[34,35]

Obesity and related metabolic changes have been linked to impaired brain health and development of neurodegenerative disease. There is evidence that insulin resistance can develop not only in the periphery but also in the central nervous system (CNS).[36,37] Mechanisms linking metabolic dysfunction and neurodegeneration include insulin resistance and associated factors such as inflammation, immune response, oxidative stress, and mitochondrial dysfunction. The review summarizes obesity-related metabolic changes across tissue types that are linked to neurodegeneration as well as potential interventions.

Metabolic Changes Associated with Obesity

Total energy expenditure is defined as the daily amount of energy an individual expends and is a combination of basal metabolic rate, thermogenic effect of food, and physical activity.[38] Basal metabolic rate accounts for the majority of total energy expenditure, and variability amongst individuals depends primarily on their lean and fat mass composition. All cells require mitochondrial ATP production to sustain cellular function. Impaired nutrient delivery, uptake, and biogenesis can impair mitochondrial function. In healthy individuals, elevated glucose levels stimulate the release of insulin from the beta cells of the pancreas. Many cells utilize insulin-dependent glucose transports, such as Glucose Transporter Type 4 (GLUT4), to transport glucose from the blood into the cell. Elevated fatty acid levels in individuals with obesity can impair glucose metabolism and insulin production and result in beta cell loss.[39] Over time, skeletal muscle, adipose tissue, and liver become less responsive to elevated insulin, leading to detrimental effects in additional organs including the brain.[40] These tissue specific effects will be discussed in the following section.

Adipose Tissue

The most prominent manifestation of obesity is accumulation of adipose tissue. There are two primary types of adipose tissue with important differences in their distribution patterns, their function, and their metabolic properties. White adipose tissue is located throughout the body, where it stores lipids and regulates circulating fatty acid levels.[41] White adipose is distributed in two anatomically distinct regions: subcutaneous adipose lies beneath the skin and visceral adipose (ie abdominal fat) surrounds internal organs. While only accounting for ~10% of total fat mass, visceral fat is more strongly associated with cardiovascular risk than subcutaneous fat.[42–44] Brown adipose tissue is distinctly different due to its role in maintaining body temperature, which can profoundly affect energy expenditure.[45] Brown adipose tissue distribution is more limited and is most active during the early years of life.[46] Brown adipose activity is lower in males whose BMI is greater than 25 compared to males with lower BMI.[47] The thermogenic properties of brown adipose tissue results in greater energy consumption and may prevent obesity by lowering plasma glucose and lipids, thus improving glucose homeostasis.[48]

In addition, the increased adipose tissue seen in obese individuals may stimulate the release of fatty acids into the plasma.[49] Elevated fatty acids can accumulate in skeletal muscle which may cause insulin resistance in skeletal muscle and liver.[50] Hyperglycemia stimulates the glycolytic pathway and the Krebs cycle, leading to a heightened influx of electron carriers into the mitochondria. This, in turn, results in the production of free radicals in the form of superoxide.[51] Furthermore, elevated fatty acids can generate superoxide, thus increasing oxidative stress.[52]

Skeletal Muscle

Skeletal muscle accounts for about 40% of total body weight and is a metabolically active tissue that plays a significant role in energy homeostasis.[53,54] Skeletal muscle consists of distinct fiber types, classified generally as Type I (slow-twitch) fibers, and Type II (fast-twitch) fibers. Although these two fiber types can be further divided into subtypes, this review will focus broadly on Type I and Type II muscle fibers. Type I fibers have a greater oxidative potential than Type II fibers[55] due to their greater mitochondrial density.[56] The composition of skeletal muscle varies across muscle groups,

with Type I fibers predominating in anti-gravity muscles and Type II fibers predominating in muscles involved in fast movements. Physical exercise can promote skeletal muscle hypertrophy, while physical inactivity and various diseases such as cancer and diabetes can cause muscle atrophy.[57] Although the greater body weight associated with obesity may lead to muscle hypertrophy, strength per body mass is lower in obesity.[58] Defining muscle quality as grip strength divided by lean mass, Raghupathy et al reported that individuals with obesity, particularly women, may have greater muscle mass but their muscle quality is lower.[59] Grip strength is a noninvasive biomarker that may indicate an individual's health status.[60] Grip strength is inversely correlated with blood glucose levels.[61,62]

Sarcopenia, which is the loss of muscle mass and strength, is associated with aging and is a risk factor for cognitive decline.[63] Sarcopenia can begin as early as age twenty-five[64] and progresses thereafter.[65] The association between sarcopenia and obesity is complex but it does increase the risk of disability, morbidity, and mortality.[66] Interestingly, obesity in the elderly is considered a risk factor for sarcopenia when defined by body fat percentage, but protective when defined by BMI.[67] Due to the decreased muscle and bone mass in the elderly compared to young, these different outcome measures should be assessed.[68] Skeletal muscle plays a major role in metabolism, so sarcopenia can profoundly impact these processes, leading to pathologies such as oxidative stress, inflammation, and insulin resistance.[69]

Skeletal muscle energy production is fiber type specific. Type I fibers use oxidative metabolism and Type II fibers rely primarily on glycolytic metabolism.[70] Type I fibers have a greater expression of proteins that transport, phosphorylate, and oxidize glucose compared to Type II fibers, suggesting that glucose uptake and metabolism is greater in Type I fibers.[71] Skeletal muscle from individuals with obesity is characterized by insulin signaling deficits that lead to impaired glucose metabolism.[72–74] While the exact mechanism remains unclear, chronic overnutrition likely stresses insulin signaling, resulting in decreased glucose uptake in skeletal muscle. Greater blood glucose resulting from decreased uptake in muscle results in increased liver glucose and impaired liver insulin resistance.[40] Obesity is associated with a reduced percentage of Type I fibers and an increased percentage of Type II fibers.[75] Given that glucose trafficking and utilization is greater in Type I fibers, this selective decrease may further exacerbate insulin signaling deficits. In addition, obesity is accompanied by greater lipid deposits in skeletal muscle, greater lipid oxidation, and lower glycemic oxidation.[76–78] These alterations require greater metabolic flexibility. The failure to adequately meet these energy demands can trigger autophagy[79] and potentially contribute to the development of neurodegenerative disease.[80]

Liver

The liver plays a central role in metabolism by synthesizing, storing, and releasing lipids and glucose.[81] In the healthy insulin sensitive state, insulin decreases gluconeogenesis (glucose production) in the liver.[82] The most common liver disease is NAFLD,[83] which is associated with obesity.[84] The hyperinsulinemia and hyperglycemia that accompany insulin resistance result in an imbalance favoring fat storage in the liver, which can progress to NAFLD.[85] NAFLD begins as low-grade localized inflammation, but obesity and insulin resistance can exacerbate this inflammation and cause it to spread systemically, affecting multiple organ systems including the brain.[86] While the CNS is generally protected from systemic circulation, cytokines and chemokines can cross the blood brain barrier and have been implicated in cognitive impairment.[87]

Early studies by Stanhope et al linked the consumption of fructose-sweetened beverages to the development of NAFLD.[88] Over the past 30 years, total sugar consumption (ie sucrose and high-fructose corn syrup) has increased by about 15%.[89] Although commonly compared to glucose, fructose differs in that it decreases liver ATP levels and increases liver de novo lipogenesis.[90] Uric acid is a byproduct of fructose metabolism and accumulates in visceral fat in individuals with obesity.[91] While common in the "Western Diet", fructose can also be elevated indirectly. The Polyol pathway, better known as the aldose reductase pathway, is a two-step pathway that converts glucose to fructose with sorbitol as an intermediate. Uric acid can activate aldose reductase, further promoting the development of NAFLD.[92] Furthermore, correlations between beta-amyloid load and inflammation in individuals with mild cognitive impairment have been observed.[93] Microglia can release pro-inflammatory cytokines upon activation and contribute to neuroinflammation.[94] Aldose reductase has been linked to inflammation and using BV-2 cells, Song et al reported aldose reductase inhibitors reduce the beta-amyloid stimulated production of TNF-α in microglia.[95] In addition, a prospective study reported individuals with the highest consumption of fructose were at a greater risk of dementia compared to those

who reported no fructose intake.[96] Further research into the role fructose and aldose reductase have in metabolism and neurodegenerative diseases is warranted.

Brain Metabolism

The brain is the most metabolically active organ of the body, consuming 20% of available glucose and oxygen at rest.[97,98] Neural activation causes rapid changes to local brain blood flow.[99] To maintain adequate global brain blood perfusion and removal of waste products, baroreceptors and chemoreceptors continuously monitor and adapt to changes in blood pressure and chemicals such as CO2.[100,101]

Although similar in some ways, the brain has unique mechanisms to maintain metabolic needs compared to the periphery. The blood-brain barrier is a specialized layer of endothelial cells supported by astrocytes and pericytes that limits the permeability of blood-borne substances into the CNS.[102] Unlike other tissues, neurons and astrocytes primarily use insulin-independent transporters to transport glucose across this barrier. Another difference between central and peripheral metabolism is their preferred energy substrates. While peripheral tissues can leverage fatty acids as alternative fuel substrates, the CNS is more limited. When less glucose is available, such as times of starvation or exercise, the brain becomes more reliant on ketones[103] or lactate.[104] Finally, the brain uses a unique and localized glucose transport system. GLUT1 is primarily localized to endothelial cells and the perivascular endfeet of astrocytes.[105] Both GLUT3 and GLUT4 are located on neurons, with localization of GLUT4 corresponding to insulin receptor expression.[106–109] GLUT5 is primarily located on microglia.[110] Additional research into the intersection between peripheral and central glucose metabolism and its role in aging and neurodegeneration is ongoing and warranted. In addition to the mechanisms reviewed in this section, obesity is associated with reduced cerebral perfusion[111–113] and individuals with obesity exhibit cortical thinning even in the absence of cognitive impairment.[114]

Potential Mechanisms for Links Between Obesity and Brain Health

Our focus of the review so far has covered defining obesity, risk factors associated with obesity, and the effects of obesity in various tissues. We will now shift our attention to how these changes interact with mechanisms that link insulin resistance to the two most common neurodegenerative diseases, AD and PD.

Insulin Resistance

Insulin resistance is defined as the impaired response of the body to insulin. Insulin secreted from the pancreas circulates throughout the body and binds to cell surface receptors, initiating a signaling cascade. Insulin resistance can occur when any step along the signaling pathway is disrupted. Mechanisms that cause insulin resistance are not clearly understood and beyond the scope of this review. As mentioned earlier, elevated fatty acids can suppress insulin stimulated glucose uptake in skeletal muscle and liver. I insulin-dependent GLUT is predominately expressed in these tissues. However, insulin resistance is also observed in cells that primarily express insulin-independent GLUT such as the endothelial cells in that comprise the blood-brain barrier.

Plasma glucose is commonly elevated in obesity and is associated with reduced cerebral glucose uptake.[115] In cognitively impaired individuals, increased glucose levels in serum were associated with attenuated regional cerebral glucose metabolism.[116] In addition, our group reported that individuals whose fasting glucose levels increased over one year also had greater brain atrophy and increased cerebral amyloid accumulation compared to individuals whose fasting plasma glucose levels decreased over the same amount of time.[117]

During an immune response, blood flow and leukocytes are increased to eliminate a pathogen. Toll-like receptors (TLR) expressed on the surface of innate immune cells recognize pathogen associated molecular patterns. When a pathogen associated molecular pattern binds to a TLR, cytokines, such as IL-6 and TNF-α are released to recruit immune cells. These inflammatory cytokines are chronically elevated in obesity,[118] and chronic inflammation is believed to contribute to insulin resistance.[119]

Although IL-6 is well known for its role in immune and inflammatory responses, it has recently gained more recognition for its acute effect on metabolism.[120] Increased release of IL-6 from adipose tissue occurs 60 minutes post-exercise in healthy adults.[121] When healthy adults were infused with IL-6, lipolysis increased without changes in

catecholamines, glucagon, or insulin, and the infusion did not cause hypertriglyceridemia.[122] In a randomized controlled trial that included exercise and the IL-6 receptor antagonist tocilizumab, reduced visceral fat mass was observed in the exercise alone group but not in the group that exercised and received tocilizumab.[123] Cumulatively, these studies show the important acute role IL-6 has in prevention of adiposity. The chronically increased levels of IL-6 seen in individuals with obesity may reflect a shift in whole body preference to fatty acid metabolism, resulting in glucose sparing. Glucose is stored in the form of glycogen and is primarily found in skeletal muscle but is also found abundantly in the liver. Thus, changes in metabolic signaling may cause insulin resistance and NAFLD, two diseases commonly present in obesity.

TNF-α is a proinflammatory cytokine that can activate nuclear factor-kappa B (NF-kB) and may lead to insulin resistance.[124] NF-kB is negatively correlated with lipoprotein lipase activity, which can lead to an accumulation of triglycerides.[125] Peroxisome proliferator activated receptors (PPARs) are a set of nuclear receptors that can exert anti-inflammatory effects. Remels and others showed that PPAR activation, specifically the subtype PPARγ, can suppress cytokine induced NF-kB activity in skeletal muscle.[126] Anti-TNF-α-drugs (eg infliximab, etanercept) are currently used to treat inflammatory diseases such as Crohn's Disease, rheumatoid arthritis and plaque psoriasis. Initial results from the use of these drugs to treat insulin resistance in obesity have been mixed. Following 32 weeks of infliximab treatment, insulin sensitivity did not improve in obese men.[127] Likewise, four weeks of etanercept treatment did not affect insulin sensitivity in obese individuals.[128] However, when administered to participants with obesity for six months, etanercept improved fasting glucose levels compared to placebo.[129]

Microbiota Shift

The discovery of Helicobacter pylori as a cause of stomach ulcers ushered a new focus on the role of endogenous microbes in disease.[130] This new perspective led to efforts to identify all microbes that colonize the human body. Bacteroidetes constitute the most abundant bacteria in the human gut. While their relationship with humans is viewed as symbiotic, microbiota can also produce harmful products such as neurotoxins and immunotoxins. Nondigestible carbohydrates ingested by humans can be used by microbiota via fermentation, resulting in beneficial byproducts such as vitamins (vitamin K, vitamin B components) and short chain fatty acids (ie acetate, butyrate and propionate).[131,132] Short chain fatty acids can be used as an energy source but also play a major role in regulating immune cells such as macrophages.[133] Although one recent study reported that obese adults have more Firmicutes and fewer Bacteroidetes than normal-weight and lean adults,[134] another study reported no such difference.[135] To the best our knowledge no studies have explored the relative time course of microbiota shift and development of obesity.

Metformin is commonly prescribed to individuals with T2D because it lowers hepatic glucose production and decreases intestinal glucose absorption. Recent research suggests that some of the effects of Metformin may result from its ability to alter the gut microbiota of patients with T2D.[136] Transplantation of human gut microbiota from obese individuals to germ free mice was reported to induce vascular dysfunction and impair glucose tolerance compared to germ free mice transplanted with gut microbiota from a lean individual.[137] This study aligns with the microbiota shift hypothesis and the relative differences in Firmicutes and Bacteroidetes in individuals with obesity compared to lean individuals. Vrieze et al completed a hyperinsulinemic-euglycemic clamp before and after six weeks of fecal microbiota transplantation from a lean donor and found that insulin sensitivity was improved by the procedure in metabolically impaired individuals.[138] While the same group observed similar findings in a different study, the effects were no longer present at 18 weeks.[139]

The production of short chain fatty acids may improve glucose metabolism via glucagon-like peptide 1 (GLP-1).[140] GLP-1 can increase insulin levels and can to increase glucose disposal through an insulin-independent mechanism.[141] This may explain why early life obesity is a risk factor for neurodegeneration while late life obesity can be protective. Long-term effects of early life obesity on the pancreas results in beta cell failure, decreased insulin secretion, and metabolic dysfunction. Pancreatic function is likely intact in individuals who increase adiposity later in life. When these insulin-sensitive individuals experience dysbiosis, the production of short chain fatty acids leads to synthesis of GLP-1 and their body is still sensitive to insulin-dependent pathways.

The short chain fatty acids act on two G-protein coupled receptors, FFAR2 and FFAR3, that bind GLP-1 and peptide YY (PYY), respectively.[142] Our group has reported that individuals diagnosed with AD have a greater early response to

GLP-1 and PYY during a mixed-meal test. Further analysis revealed that PYY was associated with decreased brain volume in the cognitively healthy group but not in the AD group. The elevated metabolic response may be elicited to compensate for reduced receptor density in the brain.[143]

Oxidative Stress

Oxidative stress is elevated in obesity.[42] Oxidative stress is a condition where the production of reactive oxygen species (ROS) outweighs the body's ability to detoxify these products.[144] While ROS play a physiological role in metabolic signaling,[145] they can also cause damage to lipids, proteins and DNA.[146] One major source of ROS production is through oxidative metabolism in mitochondria. During oxidative phosphorylation electrons interact with oxygen and produce ROS such as superoxide, mostly at complex I and III.[147] The overproduction of ROS has been shown to cause cellular damage which can lead to mitochondrial dysfunction.[148] While the etiology remains unclear, PD and AD are both associated with mitochondrial dysfunction, which may result from oxidative stress.[149,150]

Endothelial cell vascular tone is regulated by the release of nitric oxide (NO).[151] NO can also act as an antioxidant by reacting with superoxide to form peroxynitrite.[152] ROS can uncouple endothelial nitric oxide synthase, thus lowering NO bioavailability which may further contribute to ROS production.[153] In addition, cytokines associated with insulin resistance (ie IL-6 and TNF-α) can compromise NO bioavailability and cause endothelial dysfunction.[154] Reduced NO disrupts endothelial-dependent vasodilation, leading to cardiovascular diseases such as atherosclerosis.[155] Venturelli et al reported lower NO bioavailability and peripheral circulation in the aging population with further reductions seen in AD.[156]

ROS can damage oligodendrocytes and lead to myelin loss in the CNS.[157] The degradation of gray matter volume, specifically in the hippocampus in AD and substantia nigra in PD, is a hallmark feature. However, white matter abnormalities are also associated with AD and PD and may even precede changes seen in gray matter.[158,159] Recent studies have used magnetic resonance imaging to quantify myelin water fraction to provide a surrogate measure of myelin content. Obesity[160] and common comorbidities such as hypertension[161] and metabolic syndrome[162] have been associated with lower myelin content in the brain. Together, these findings suggest that obesity-related ROS production can disrupt endothelial cell function and decrease white matter integrity. Further research is needed to determine interactions between endothelial and mitochondrial dysfunction and their effects on neurodegenerative diseases.

Emerging Links Between Obesity and Neurodegenerative Diseases

Introduction to Risk Factors for AD and PD

We have discussed the links between obesity and neurodegeneration so far. In both AD and PD, overlapping risk factors such as age,[163] T2D,[164,165] and depression[166,167] have been observed. Insulin resistance can play a role, both directly and indirectly, as highlighted throughout the review. However, the complexity of these diseases extends beyond insulin resistance. Understanding these links and risk factors should pave the way for optimal preventative and therapeutic treatments. Although they share some risk factors, neurodegenerative diseases such as AD and PD also have specific risk factors. A major risk factor for AD is the apolipoprotein Epsilon-4 allele (*APOE*4).[168] Apolipoprotein E (apoE) is a protein that mediates lipid transport and is known for regulating CNS lipid metabolism,[169] and *APOE*4 carriers have been shown to express lower levels of apoE.[170] In *APOE4* carriers, *APOE* promotes Aβ production and reduces clearance.[171] In addition, the *APOE*4 allele is associated with lower cerebral myelin content in otherwise healthy older individuals.[172] *APOE*2 carriers, who have a lower risk for AD, exhibited significantly greater cerebral myelin. For PD, family history, dyspepsia, and exposure to toxins (ie pesticides, oils and metals) have been shown to be a risk factors.[173] Interestingly, α-synuclein has been linked to demyelination in multisystem atrophy, a rare form of parkinsonism.[174] The Lewy bodies that are found in PD substantia nigra express α-synuclein[175] and mutations in α-synuclein were the first form of familial PD discovered.[176] Because the α-synuclein histopathology differs between multisystem atrophy and PD[177] disease mechanisms likely also differ for this protein. It is possible that multiple influences from genetic and lifestyle factors to myelin content may link risk for AD, PD, and potentially other neurodegenerative diseases. Further research is needed to determine these temporal and functional relationships.

Obesity and Alzheimer's Disease

As relationships between obesity and brain health have become apparent, preclinical studies support a link between obesity and AD.[178–180] With few exceptions, these studies report that diet-induced obesity worsens cognitive performance and increases AD-like peripheral biomarkers and histological makers in the brain. Early studies hypothesized a primary role for altered cholesterol metabolism in AD. These studies reported greater cortical and hippocampal Aβ accumulation in rabbits and transgenic mice (PSAPP model of AD) fed high cholesterol or high fat/high cholesterol diets.[181,182] These findings were extended to memory deficits and markers of diminished cortical and hippocampal cholinergic function in non-transgenic rodents fed a high cholesterol or high fat/high cholesterol diet.[183,184] Using Tg2576 mice, Ho et al found that the spatial memory deficits and Aβ pathology present in this model of AD are exacerbated following the onset of high-fat diet-induced insulin resistance.[185] The lack of elevated cholesterol in the insulin-resistant mice led the group to conclude that impaired insulin signaling is a key mechanism linking diet-induced obesity and AD. Similar effects following streptozotocin (STZ)-induced insulin depletion in the APP/PS1 transgenic mouse model of AD support this conclusion.[186]

Recently, the Hascup lab focused on the effects of a high fat diet on extracellular glutamate dynamics and phenotypic markers in the AβPP/PS1 mouse model of AD.[187] Using enzyme-coated multisite electrode arrays, the group reported that a high fat diet exacerbated cognitive impairment and further elevated basal extracellular levels and stimulus-evoked glutamate release in the hippocampus of AβPP/PS1 mice. The insulin-resistant, high fat-fed AβPP/PS1 exhibited greater vesicular glutamate 1 transporter and glial fibrillary acidic protein density in the hippocampal regions where glutamate dynamics were affected.

As mentioned previously, elevated cytokines can activate NF-KB. Studies have shown that inhibition of NF-KB can improve insulin resistance, suggesting its importance in the development of inflammation-induced insulin resistance.[188,189] In the CNS, reactive microglia are associated with neuroinflammation and tauopathy and may be a result of activated NF-KB. Microglial NF-KB signaling has been shown to drive tauopathy in PS19 mice.[190] Sandhu et al recently reported that friedelin, a molecule with antioxidant and anti-inflammatory properties, reversed scopolamine-induced memory dysfunction. In addition to its anticholinergic properties, scopolamine is known to activate neuroinflammatory markers such as NF-KB. Friedelin reduced NF-KB in this study.[191]

There is growing evidence that midlife obesity is a risk factor for AD and dementia, but that this relationship does not hold in late life.[192–194] It is unclear the degree to which this is modulated by survival bias, as excess body weight and obesity have been linked to premature mortality.[195] In addition, other factors such as changes in substrate metabolism throughout the body, and tissue-specific changes, such as loss of lean mass may contribute. Finally, there is evidence that BMI instability is related to neuropathological markers of AD and related dementias, suggesting that cycles of weight loss and regain may also be a contributing factor.[196] In midlife, it has also been observed that individuals with elevated amyloid in addition to hypertension or obesity experienced faster cognitive decline compared to individuals with elevated amyloid or cardiovascular risk factors alone.[197]

A meta-analysis of whole brain studies showed that individuals with obesity have abnormalities in gray matter volume.[198] White matter is also reduced in individuals with elevated BMI.[199,200] These alterations in brain structure can predispose an individual to neurodegenerative diseases such as PD and AD, and potentially contribute to peripheral neurodegeneration as seen in multiple sclerosis (MS) and diabetic neuropathy.

Women are at a greater risk of developing AD compared to men, regardless of their *APOE* allele.[201] Gustafson et al, conducted a study to measure anthropometrics, neuropsychiatric assessment, and brain atrophy with computerized tomography (CT) and repeated measurements after 24 years. This study found that obesity may contribute to temporal atrophy in women.[202] It is important to understand the association between early adulthood obesity and menopausal symptoms to possibly identify why women are at a greater risk of developing AD. The onset of menopause tends to occur at a later age in obese women.[203] Studies have reported that perimenopausal and postmenopausal women experience greater changes in brain volume. One study reported that perimenopausal women have greater reductions in grey matter volume.[204] Similarly, perimenopausal and postmenopausal women have greater reductions in hippocampal volume

compared to premenopausal women.[205] However, Franz et al have reported similar results in men after following them for 40 years.[206] While this relationship has been shown for decades, the mechanism remains unclear.

More recently, metabolic, and cerebrovascular dysfunction have been shown to be potential mediators that link obesity to cognitive decline.[207] An additional molecule of interest in obesity is leptin. Leptin is a hormone that is released from adipose tissue that regulates energy balance by inhibiting hunger. Leptin has been reported to be strongly correlated to BMI.[208,209] Both changes in leptin levels and alterations in leptin signaling may be relevant to the link between obesity and brain health. Leptin can cross the blood-brain barrier.[210] In addition to its pro-satiety effect, leptin also has a role in hippocampal neurogenesis.[211] Narita et al reported a positive relationship between plasma leptin levels and gray matter volume in the right hippocampus in elderly individuals free from metabolic syndrome and dementia.[212] Genetic mutations in leptin receptors and defects in the pathway that synthesize leptin can occur in obesity resulting in "leptin resistance".[213] While the mechanism is unclear, the impaired signaling of leptin may lead to structural changes in the hippocampus. Witte et al reported individuals with mild cognitive impairment have lower serum leptin levels compared to healthy controls. While no association between leptin and memory performance was observed, higher leptin levels did correlate with larger right hippocampus volume.[214]

Obesity and Parkinson's Disease

The motor symptoms of PD result from degeneration of dopamine neurons that project from the midbrain substantia nigra to the caudate nucleus and putamen (collectively, striatum) in the forebrain. Clinical diagnosis usually occurs with the onset of motor symptoms, which emerge only after substantial nigrostriatal dopamine loss. In fact, the preclinical phase of PD (which is often accompanied by autonomic and affective dysfunction) can last more than 20 years.[215] Although many contributing factors have been linked to PD, we will focus on obesity-related factors in the following section.

Evidence supporting a relationship between peripheral glucose dysregulation and nigrostriatal dopamine function initially came from studies using streptozotocin (STZ) to destroy pancreas insulin-producing beta cells in a rat model of Type 1 diabetes.[216] These studies report lower midbrain and striatal tissue dopamine content[217] and lower measures of dopamine turnover in the striatum in STZ-treated rats.[218] The dopamine turnover measure correlated with blood glucose levels in the latter study. Unlike Type 1 diabetes, obesity is accompanied by both hyperglycemia and hyperinsulinemia prior to the onset of insulin resistance and eventual T2D. Dopamine signaling is affected not only by DA content and release, but also by postsynaptic DA receptors, where the intercellular signal is propagated, and presynaptic DA transporters, where DA is taken up for recycling and to terminate the signal. Evidence from in vitro and in vivo studies report that insulin can affect both postsynaptic DA receptor and presynaptic DA transporter expression and function.[219,220]

Preclinical studies using the MPTP and 6-hydroxydopamine (6-OHDA) neurotoxin models of PD report enhanced neurotoxicity in rodent models of diet-induced obesity. In 2005, Choi et al reported that mice fed a high-fat diet for 8 weeks exhibited greater striatal DA depletion and lower TH levels in the substantia nigra following a low dose of MPTP in mice.[221] We extended this study in 2010 to the 6-OHDA rat model and reported greater striatal DA depletion in high fat-fed than chow-fed animals.[222] The high fat-fed rats in our 6-OHDA study exhibited hyperglycemia and hyperinsulinemia, and DA depletion in the striatum and the substantia nigra correlated significantly with HOMA-IR values and epididymal fat mass. Preclinical studies conducted by others using these toxin models have replicated and extended these findings.[223,224]

Preclinical studies also reveal that obesogenic diets facilitate disease processes in mice harboring PD-related α-synuclein mutations. In a study using A53T mice, a high calorie diet exacerbated autonomic dysfunction that occurs in early disease stage in these animals.[225] This effect, which was manifested as an elevated resting heart rate, was ameliorated by intermittent energy restriction. These findings were extended to motor decline and mortality in the A30P α-synuclein mouse model of PD. When fed a high-fat diet, these mice became insulin-resistant and exhibited earlier motor decline and death than their standard chow-fed counterparts.[226] Histology revealed greater α-synuclein aggregation in the brainstem of the obese mice.

To explore obesity-related mechanisms that might occur during a preclinical period in PD, we tested the effects of a high fat diet on DA release dynamics in non-lesioned, young adult rats. We reported that after a 12-week high-fat diet, insulin-resistant young adult rats exhibited significantly blunted DA release in the striatum compared to insulin-sensitive rats fed normal chow.[227] The amplitude of DA released was significantly negatively correlated with the HOMA-IR measurement of insulin resistance. Extracellular DA clearance was also prolonged in this group. Despite being 7-months-old, their DA release and clearance dynamics resembled those measured previously in senescent 24-month-old rats.[228] Iron content was greater in the high fat group and proteins related to iron metabolism differed significantly between the two diet groups. Iron content in the substantia nigra iron increases with aging and with PD, where it is involved in generating highly reactive free radical species and promotes DA auto-oxidation.[229]

We followed this study with one to determine whether adopting a "healthier" diet reverses neural vulnerability following a high-fat diet.[230] After feeding two groups of rats a high-fat diet for 3 months, we switched one of the groups to normal chow while the other group continued with the high-fat diet. We included a control group that was fed normal chow throughout the study. Although systemic insulin resistance and protein markers of mitochondrial and proteasomal dysfunction in the striatum were lower in the group that was switched to normal chow, nigrostriatal DA depletion was similar between the two high-fat diet groups.

PD is the second most common neurodegenerative disorder with an incidence rate of every 17 per 100,000 individuals per year.[231] Similar to AD, increasing age is positively correlated to PD incidence. However, unique to PD is the high prevalence and incidence of PD in areas where herbicides and pesticides are commonly used.[232] The association between pesticide use and PD has been confirmed in population-based control studies.[233] Pesticides are believed to promote oxidative stress which can lead to mitochondrial dysfunction, thus paralleling the findings previously mentioned in preclinical studies.

Emerging Directions for Interventions

There are no cures for AD and PD and current treatments are limited to symptom management. Drugs like donepezil and levodopa can respectively enhance acetylcholine and dopamine function, but both lose efficacy with disease progression. Likewise, deep brain stimulation in PD can improve symptoms but does not alter disease course. Newly developed monoclonal antibodies, such as lecanemab do exist and may show a potential option for treatment of AD, they come with a steep annual cost that will place barriers on who can receive treatment. Therefore, the focus of this review will be on nonpharmacological interventions.

Dietary Intervention

Given the link between metabolic dysfunction in obesity and neurodegeneration, dietary interventions are a logical approach. In a mouse model of pre-diabetes, alternate day fasting attenuated ROS production and reduced peripheral nerve damage.[234] Clinical studies in aging volunteers report salutary effects of long-term dietary interventions on brain health.[235,236] In older adults free from metabolic disorder and memory impairments, participants assigned to a 30% reduced calorie diet for 3 months exhibited improved memory scores compared to the control diet group.[237] Similarly, calorically restricted postmenopausal with obesity exhibited improved memory function as well as increased gray matter volume in the inferior frontal gyrus and hippocampus as well as enhanced functional connectivity in the hippocampus compared to a control group.[238]

A ketogenic diet essentially eliminates carbohydrates (<20g/day) while increasing caloric intake from fat and protein. With general fasting or a ketogenic diet, ketones such as beta-hydroxybutyrate are produced by the liver and are used as an alternative fuel source.[239] In a single-phase, assessor-blinded, two-period randomized crossover trial, participants diagnosed with AD (n=26) were randomized into a ketogenic diet (29% protein, 6% carbohydrates and 58% fat) or a low fat diet (19% protein, 62% carbohydrates and 11% fat) for 12 weeks. After a 10-week washout period, participants completed the alternate diet for an additional 12 weeks. Although cognitive function was not affected by diet, activities of daily living and quality of life were significantly improved by the ketogenic diet. The ketogenic diet also resulted in greater weight loss and resulted in mostly favorable effects on cardiovascular risk factors.[240] In a double-blinded placebo-controlled study, participants diagnosed with AD (n=20) ingested a ketogenic formula after an overnight fast.

Initial cognitive performance was not affected by the ketogenic supplement despite elevated circulating ketones[241] Repeated testing in participants in the ketogenic group revealed improved performance in immediate and delayed memory tasks at week 8 compared to baseline. In a recent randomized controlled trial (n=47), participants diagnosed with PD underwent ketogenic or low fat diet intervention for 8 weeks.[242] Although motor and nonmotor symptoms were improved in both diet groups, the ketogenic urinary problems, pain, fatigue, daytime sleepiness, and cognitive impairment were lower in the ketogenic group.

Exercise

Exercise can improve cardiovascular health and metabolic function and can increase neuroplasticity.[243–245] It has become evident that things that benefit the heart also benefit the brain. Guidelines from the American Academy of Sports Medicine recommend at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity, and at least two days of resistance exercise each week.[246] Goodpaster et al reported lower muscle glycogen oxidation during exercise in individuals with obesity compared to their lean counterparts.[247] This suggests that exercise protocols should be customized based on individual metabolic profiles rather than general guidelines. In a pilot study, we tested the effects of 150 minutes aerobic exercise in individuals who were at least 55 years old, sedentary, and diagnosed with probable AD or MCI. After 26 weeks the exercise group showed improved memory performance and reduced hippocampal atrophy compared to the stretching and toning control group.[248] Individuals with neurodegenerative disease are likely to be physically inactive due to changes in coordination, fatigue, and mood. In these populations, exercise is accompanied by risk of injury. A meta-analysis of exercise interventions in patients with chronic brain disorders, (such as PD, MS and AD) addressed the safety of exercising these populations. The meta-analysis found that that 83.3% of the studies reported no effect of physical injuries on completion of the exercise intervention.[249] Exercise decreased symptoms of depressive symptoms and had a positive effect on cognition.[249] It should be noted that the intensity of exercise was classified as “high” in only 18 of the 122 studies included in the meta-analysis. A randomized control trial tested the feasibility of exercising individuals with PD at various intensities, with target heart rates at 60–65% of maximum heart rate in the moderate intensity group and 80–85% maximum in the high intensity group. Participants in both exercise groups were able to meet their exercise intensity 4 times a week for 6 months.[250]

A recent study reported that exercise influences gut microbiota in obesity. In a group of insulin resistant individuals with an average BMI of 29.3, two weeks of aerobic exercise training reduced levels TNF-α and decreased the Firmicute/Bacteroidetes ratio by increasing the level of Bacteroidetes. While exercise had no effect on intestinal glucose uptake, HbA1c and body fat percentage were decreased in both exercise groups.[251] While this study demonstrates that exercise-mediated improvement in glucose uptake and body fat are accompanied by alterations in gut microbiota, follow up studies with these participants are necessary to link these effects to neurological outcomes.

Brain-derived neurotrophic factor (BDNF) plays an important role in neurogenesis, synaptic plasticity, and memory function.[252] A recent study reported that 12 weeks of probiotic supplements increased circulating BDNF levels, improved mental flexibility, and decreased stress in older adults.[253] BDNF is increased by exercise and may contribute to learning and memory due to its expression in the hippocampus.[254] In C57BL/6 mice, exercise reversed memory impairments and attenuated chronic stress-induced BDNF expression. These effects were diminished when the mice were injected with the AMPK inhibitor compound C. This suggests that exercise may protect against stress induced memory impairments by upregulating hippocampal AMPK-mediated BDNF induction.[255] In a recent study of physically inactive but cognitively healthy middle-aged adults at risk for AD (eg family history, *APOE*4), participants were randomly assigned to an exercise group or usual activity group. Although the chronic (26 weeks) exercise protocol did not affect BDNF, the myokine Cathepsin B was elevated with exercise and correlated with cognitive function. BDNF did correlate with metabolites however, suggesting a role for role for metabolic factors in BDNF regulation.[256] Further analysis of metabolomics did show close correlation to BDNF.

Sleep

As mentioned earlier, sleep is a modifiable risk factor for obesity. Lack of sleep can reduce endogenous antioxidant production, leading to activation of cytokines.[257] Obesity is associated with a greater risk for sleep disorders such as

insomnia, sleep apnea, and restless leg syndrome.[258] Sleep deprivation has been shown to increase AB production overnight in humans.[259] Although the immediate negative effects of sleep deprivation on cognitive function are well known, the consequences of long-term sleep deprivation remain unknown.[260–262] In the 3xTgAD mouse model of AD, sleep restriction for 6 weeks worsened memory loss and resulted in greater Aβ and pTau accumulation in the cortex compared to controls.[263] Recent research has shown that improving sleep duration and quality results in decreased appetite and greater loss of fat mass in overweight participants.[264] These results occurred by extending sleep duration by ~1.2 hours.

Conclusions

Taken together, these studies suggest that through various mechanisms, obesity and its sequelae can impair CNS cellular function and lower the threshold for neuropathology or degeneration that accompany symptoms of neurodegenerative diseases such as AD and PD. Obesity is a complex disease influenced by numerous factors. These include energy expenditure, mitochondrial dysfunction, insulin resistance, adipose tissue accumulation, skeletal muscle alterations, liver involvement, gut microbiota dysregulation, inflammation, and oxidative stress. These factors contribute to metabolic dysfunction and increase the risk of developing chronic diseases, including neurodegenerative conditions such as AD and PD.

We are just beginning to understand the significant connection between metabolic dysfunction and neurodegeneration. Targeted dietary interventions, along with exercise, offer promising avenues for managing obesity-related cognitive, motor, and affective symptoms in neurodegenerative diseases. Future research into these mechanisms will afford opportunities to not only optimize population-based guidelines, but to also implement personalized strategies to combat the negative impact of obesity on brain health.

Funding

Supported by R01 AG062548 and R01 AG081304.

Disclosure

The authors report no conflicts of interest in this work.

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