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Neurological Consequences of Obesity

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Abstract

Obesity, primarily a consequence of poor dietary choices and an increased sedentary lifestyle, has become a global pandemic that brings with it enormous medical, social, and economic challenges. Not only does obesity increase the risk of cardiovascular disease and certain cancers, but it is also recognized as a key driver of other metabolic syndrome (MetS) components. These components include insulin resistance, hyperglycemia with prediabetes or type 2 diabetes, dyslipidemia, and hypertension, and are underlying contributors to systemic metabolic dysfunction. More recently, obesity and diet-induced metabolic dysfunction have been identified as risk factors for the development of a wide variety of neurological disorders in both the central and peripheral nervous systems. An abundance of literature has shown that obesity is associated with mild cognitive impairment and altered hippocampal structure and function, and there is a robust correlation between obesity and Alzheimer's type dementia. Similarly, many reports show that both the autonomic and somatic components of the peripheral nervous system are impacted by obesity. The autonomic nervous system, under control of the hypothalamus, displays altered catabolic and anabolic processes in obese individuals attributed to sympathetic-parasympathetic imbalances. A close association also exists between obesity and polyneuropathy, a complication most commonly found in prediabetic and diabetic patients, and is likely secondary to a combination of obesity-induced dyslipidemia with hyperglycemia. This review will outline the pathophysiological development of obesity and dyslipidemia, discuss the adverse impact of these conditions on the

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Review criteria

We searched Pubmed and Google Scholar for articles published in English up to July 2016 and examined original articles and review articles. The following terms were used in various combinations: "obesity", "dyslipidemia", "adipose", "adipocyte", "inflammation", "brain", "Alzheimer's disease", "cognitive impairment", "hypothalamus", "hippocampus", "high fat diet", "high fat diet", "autonomic nervous system", "peripheral nervous system", "peripheral neuropathy", "lifestyle intervention", "exercise" and "bariatric surgery". We used our judgment to select articles to provide a summary of the causes of neurological complications of obesity rather than aiming to provide an exhaustive list of all research.

Contributors

All authors contributed equally to the concept and design of the Review. ELF had full access to all the data and had final responsibility for the decision to submit for publication. POB and LMH completed the literature search. POB and LMH drafted and, with ELF, finalized the Review. BBC and ELF provided critical review of the manuscript. POB created the figures. All authors have approved the final version.

Conflicts of Interest

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nervous system, and provide evidence for lipotoxicity and metabolic inflammation as the drivers underlying the neurological consequences of obesity. In addition, this review will examine the benefits of lifestyle and surgical interventions in obesity-induced neurological disorders.

Introduction

Recent data estimate that roughly 2.1 billion individuals are overweight or obese.[1] Although genetic background does predispose certain individuals/ethnicities to developing obesity,[2] the current pandemic that promotes weight gain is largely driven by an environment which arose in developed Western countries in the latter part of the 20th century.[3] This obesogenic environment is attributable to a number of factors, including the overconsumption of processed, affordable, heavily marketed, highly palatable, energy-dense foods combined with an increased sedentary lifestyle. Though there are indications that the exponential rise of obesity has plateaued in developed countries, numerous regions worldwide that have adopted the lifestyle of a Westernized society continue to show an increase in obesity, which is reflected by a worldwide increase.[1] Currently, it is projected that over 18% of adults will be obese by 2025.[4]

Defined as an increase of fat mass that adversely affects health, obesity is a known risk factor for cardiovascular disease and certain cancers. Central obesity, which is accompanied by a low-grade metabolic inflammation in visceral adipose tissue, is also recognized as both a component and a driver of the metabolic syndrome (MetS).[5] MetS is defined by the presence of multiple comorbidities, including dyslipidemia, decreased insulin sensitivity, hyperinsulinemia, hyperglycemia, and hypertension; thus, obesity is an underlying promoter of systemic metabolic dysfunction. Multiple tissues, including the liver, pancreas, kidney, and vasculature, exhibit dysfunction as a consequence of obesity via direct and/or indirect mechanisms. Accumulating evidence also links obesity with a wide array of neurological disorders in a manner that is complex and multifactorial (Box 1). Though the central (CNS) and peripheral (PNS) nervous systems are quite distinct in form and function, both are susceptible to obesity-driven dysfunction, suggesting that common mechanisms contributing to disease progression may be perpetuated by visceral adiposity. It is also important to recognize that obesity drives other components of the MetS which are strongly linked to neurological deficits (for example, strong associations exist between insulin resistance and cognitive decline). As a result, it is likely that multiple mechanisms may be interacting to culminate in neurological dysfunction, and ascertaining direct causality of visceral adiposity on neurological complications thus remains challenging.

Mechanistic insight provided by animal models of obesity suggests that excess dietary fat compromises hypothalamic control of energy homeostasis. This contributes to adipose tissue dysfunction, leading to elevated free fatty acids (FFA) and systemic dyslipidemia (Figure 1). Chronic caloric excess also impacts multiple organs, including the liver, and drives an increase in circulating triglycerides. This dyslipidemia can result in FFA-induced lipotoxicity – changes in lipid-induced intracellular signaling or changes in lipid utilization that result in tissue pathophysiology – that drives neurological dysfunction and neurodegeneration. While these events likely impact the CNS and PNS in a multifactorial

fashion, however, recent clinical and preclinical advances have fueled improved insight into the potential neurological complications that occur with obesity. This review will outline the pathophysiological development of obesity and dyslipidemia, discuss the CNS and PNS diseases that arise as a consequence, present evidence for lipotoxicity and metabolic inflammation as the principal mechanisms underlying these neurological consequences of obesity, and address potential treatment methods.

Physiological to Pathophysiological Obesity

Adipose Tissue Biology

Adipose tissue is localized into distinct anatomical regions and performs functions that include the storage and release of energy, thermal insulation, and protection of internal organs from trauma. In addition, it also possesses endocrine activity that is mediated by adipokines, a diverse set of signaling molecules which includes hormones, cytokines, acute phase reactants, and growth factors. These species are critical in regulating complex metabolic processes in metabolically active tissues involved in maintaining energy homeostasis, such as adipose tissue and the liver, pancreas, and brain. Adipose tissue is composed of adipocytes and a stromovascular compartment containing pre-adipocytes, fibroblasts, endothelial cells, resident immune cells, blood vessels, and nerve terminals. The adipocytes themselves are highly efficient fat-storing cells that stockpile energy in the form of triglyceride-rich lipid droplets. Regulation of adipocyte energy uptake and storage is primarily maintained by insulin that mediates FFA uptake and lipogenesis but inhibits lipolysis. During periods of negative energy balance, when non-adipose tissues require energy, stimulation of adipose tissue by sympathetic nerves promotes lipolysis of the stored triglycerides within adipocytes to FFA, which are released into the circulation to serve as fuel for these tissues.[6] However, during prolonged periods of positive energy balance (i.e. caloric excess), adipocytes undergo hypertrophy (adipocyte enlargement), hyperplasia (adipose progenitor cells proliferate and differentiate into new adipocytes), or both, resulting in adipose tissue expansion in order to accommodate the storage of surplus calories.

Significant increases in adipose mass, particularly in the visceral depots, contribute to adipose tissue dysfunction and promote metabolic disease via a low-grade metabolic inflammation that underlies systemic metabolic dysfunction.[5] Consequences of adipose tissue inflammation include altered adipokine secretion profile, impaired insulin signaling, compromised triglyceride storage, and increased basal lipolysis. These events culminate in increased circulating adipokines and FFA and are central to obesity-induced peripheral- and nervous-tissue dysfunction (Figure 1). Metabolic inflammation occurs primarily in hypertrophied adipose tissue as a consequence of sustained caloric excess that initiates stress-signaling pathways and consists of activated resident macrophages. Local adipose tissue inflammation is characterized by increased expression of pro-inflammatory adipokines, including C-reactive protein, interleukin (IL)-1, IL-6, IL-1β, tumor necrosis factor (TNF)-α, and leptin. Furthermore, chemotactic adipokines such as monocyte chemoattractant protein (MCP)-1 can further amplify local inflammation by promoting the infiltration and accumulation of circulating leukocytes to the adipose tissue. Specifically, activation of resident macrophages can trigger the recruitment of circulating monocytes/

macrophages, T cells, natural killer T cells, B lymphocytes, and mast cells.[7] Moreover, chronic adipose tissue inflammation can lead to 'spillover' of pro-inflammatory mediators into the circulation; hence, obese patients typically display an increase in circulating pro-inflammatory adipokines that correlates with adipose mass. Metabolic inflammation also promotes adipose tissue insulin resistance, a state of decreased responsiveness to insulin that is mediated by TNF-α signaling.[8] As adipose uptake and storage of circulating FFA is insulin-dependent, compromised insulin signaling within adipose tissue impairs clearance of circulating FFA,[9] thus contributing to increased circulating FFA (palmitic, oleic, linoleic acid) in obesity.

Obesity and Dyslipidemia

In addition to the increase in adipose-derived FFA, both liver- and diet-derived very low density lipoprotein (vLDL)-triglycerides significantly contribute to dyslipidemia in obesity.[9] FFA-induced liver dysfunction leads to an increase in production of liver-derived vLDL-triglycerides, while caloric excess increases circulating chylomicron-derived vLDL-triglycerides. These vLDL-triglycerides are hydrolyzed to their constituent long chain fatty acids (LCFA) by lipoprotein lipases present in vascular endothelium, neurons, and glia, therefore adding to the FFA load on all organ systems, including the CNS and PNS. These bioactive lipids can also become deposited along blood vessels, compromising blood flow and tissue perfusion via atherogenesis, can accumulate ectopically in tissue to compromise structure and cellular signaling, and can dysregulate local metabolism to compromise energy production. Obesity-induced dyslipidemia can therefore result in dysfunction in numerous types of tissues, including the CNS and PNS.

Effects of Obesity on the Central Nervous System

Clinical Evidence

Accumulating evidence demonstrates that the CNS and cognitive function are adversely affected by obesity. For example, a meta-analysis has shown a strong association between obesity and neurological disorders such as dementia and Alzheimer's disease (AD).[10,11] Studies indicate that obesity doubles the risk of AD when compared to individuals of normal weight[10] and that a higher BMI in midlife predicts greater risk of dementia in later life.[12] Furthermore, a post-mortem study showed that elderly, morbidly obese patients display higher levels of hippocampal markers associated with AD (β-amyloid, β-amyloid precursor protein, tau) than non-obese individuals.[13]

It is well established that mild cognitive impairment (MCI) occurs well before frank dementia, and several prospective studies (Table 1;[14–18]) have demonstrated that obesity confers increased risk of MCI, independent of age. Though there is some controversy (one study reported that lower weight in later life predicts MCI[19] and another demonstrated no increase of MCI risk with high BMI[20]) the majority of studies indicate that a high BMI is associated with attention deficits, poor executive function, impaired decision-making, and decreased verbal learning and memory. Individuals with severe obesity have MCI,[21] and obese children and adolescents, as well as those with MetS,[22] display lower cognitive function,[23] further distinguishing obesity-associated MCI from age-related dementia.

Reports also suggest that obese males are more susceptible than females to MCI,[14] with males also displaying greater brain atrophy,[24] which may be due to estrogen-dependent protection from MetS components.[25]

In both AD and MCI, impaired neurological function in the CNS may be a consequence of structural changes in the brain and decreased cerebral integrity, particularly in the hippocampus, a structure essential for learning and memory that is susceptible to aging-related atrophy.[26] AD patients display brain atrophy in the medial temporal lobe, which contains the hippocampus, while patients with MCI display a similar pattern of hippocampal loss, but to a lesser degree than AD patients.[27] In patients with obesity or MetS, there is also evidence for a decrease in hippocampal volume.[28] Using computed tomography, a cross-sectional analysis demonstrated that women with temporal lobe atrophy had higher BMI,[26] while longitudinal analysis of the same cohort revealed that BMI was a predictor for temporal lobe atrophy.[26] Magnetic resonance imaging (MRI) analysis has also shown an inverse relationship between BMI and brain volume[29] and neuronal viability,[30] as well as gliosis in the hypothalamus that is coincident with obesity.[31] Likewise, voxel-based morphometry has similarly revealed a relationship between BMI and gray matter ratio, with gray matter volume of the bilateral medial temporal lobes, anterior lobe of the cerebellum, occipital lobe, frontal lobe, precuneus, and midbrain displaying negative correlations with BMI.[24,32] More recently, use of tensor-based morphometry to examine gray matter and white matter volume in a bivariate analysis of elderly patients with normal cognitive function linked increased BMI, hyperinsulinemia, and type 2 diabetes to atrophy in frontal, temporal, and subcortical brain regions.[33] In the same study, an Analysis of Covariance model showed atrophy in the frontal lobes, anterior cingulate gyrus, hippocampus, and thalamus of obese patients.[33] Even individuals with a high BMI and no apparent cognitive defects displayed brain atrophy in the frontal lobe, hippocampus and thalamus when compared to non-obese individuals.[33] Children and adolescents with high BMI also exhibit decreased volume of frontal and limbic cerebral gray matter regions[34] and decreased hippocampal volume compared to children with healthy BMI.[22] The hippocampus and prefrontal cortex, which are particularly vulnerable to obesity-related changes,[35] are essential for learning and memory, and changes in hippocampal volume correlate with declines in memory performance.[36] In fact, increased hippocampal atrophy in MCI patients predicts the development of AD.[37]

Mechanisms Underlying Obesity-Mediated Cognitive Impairment: Role of the Hypothalamus

Consistent with clinical data, numerous experimental studies using animal models of high fat diet (HFD)-induced obesity reveal altered hippocampal structure and function, with animals displaying learning and memory deficits and impaired executive function.[38–44] These animal models provide insight into the mechanisms underlying obesity-induced cerebral changes. For example, long term potentiation, considered to be a major mechanism that contributes to learning and memory, in the hippocampus is impaired in HFD-fed mouse models.[45,46] HFD feeding also leads to a reduction in markers of neurogenesis, synaptic plasticity, and neuronal growth, including brain-derived neurotrophic factor.[47,48] Interestingly, many studies that involve the use of these animal models provide strong

evidence that hypothalamic inflammation is an early step in a vicious feed-forward cycle of CNS dysfunction leading ultimately to cognitive decline.[31]

The hypothalamus is pivotal in maintaining global energy homeostasis by regulating food intake and energy expenditure.[49] To rapidly monitor and regulate metabolic homeostasis, the hypothalamus senses circulating nutrients and hormones via the median eminence, which contains a unique capillary system, and, importantly, integrates these signals of satiety and nutritional status to maintain metabolic homeostasis via neuroendocrine and autonomic signaling.[50] Notably, the median eminence is not protected by the blood-brain barrier, which likely contributes to its vulnerability to circulating factors such as FFA and inflammatory adipokines.

Early markers of inflammation, including TNF-α and microglial activation, are present in the arcuate nucleus (ARC) of the hypothalamus.[51] Hypothalamic inflammation is an early acute response to elevated FFA: after one day of HFD feeding, inflammatory markers, including TNF-α, are present in the mediobasal hypothalamus,[31] and HFD-induced inflammation occurs in the hypothalamus before the adipose tissue or peripheral blood.[52] Glial cell activation is an early critical step in diet-induced hypothalamic inflammation, with microglial and astrocyte reactivity occurring after HFD feeding.[31] In particular, microglia have been proposed as the sensors of diet-induced hypothalamic inflammation since they express toll-like receptor (TLR)-4, which recognizes LCFA.[53] In animal models of obesity, activation of TLR4 signaling promotes cytokine production (TNF-α, IL-1β, and IL-6)[54], activation of endoplasmic reticulum (ER) stress,[55] and subsequent activation of the c-Jun N-terminal kinase (Jnk)[51]/inhibitor of κB kinase-β/nuclear factor-κB (IKKβ/NF-κB)[53,55,56] pathways, resulting in the propagation of pro-inflammatory signaling and promotion of gliosis in the hypothalamus.[31]

Inflammation can drive further downstream dyslipidemia by compromising the neural circuitry governing satiety control (Figure 2a).[54] In obese animals, leptin-induced satiety is blunted;[57] although leptin positively correlates with adipose tissue mass, increased hypothalamic inflammatory signaling leads to leptin-resistance. This can impair appetite control mediated by hypothalamic proopiomelanocortin (POMC) neurons, which function to reduce appetite and increase energy expenditure. Moreover, HFD feeding leads to a reduction in POMC neurons, resulting in decreased inhibition of feeding.[58] Dysregulation of satiety signaling promotes hyperphagia, increasing susceptibility to obesity development,[57] while loss of POMC neurons contributes to weight gain.[59]

In addition to inflammation, altered FFA metabolism may contribute to changes in CNS function. Cerebral uptake of FFA is higher in obese subjects,[60] and evidence from animal studies suggest that FFA are not completely catabolized in the hypothalamus but instead accumulate as long chain (LC)-acyl CoA esters and other bioactive lipids.[56] Indeed, diacylglycerols and ceramides are present in the hypothalamus of HFD-fed mice[61] and Zucker *fa/fa* rats,[62] with direct palmitate-induced ceramide production demonstrated in hypothalamic neurons *in vitro*.[63] These bioactive lipid species can promote ER stress and subsequent activation of IKKβ.[56,61,62] Moreover, improving β-oxidation in hypothalamic

neurons *in vitro* decreases neuronal inflammation by decreasing production of bioactive lipids[63] strengthening the association between lipotoxicity and hypothalamic dysfunction.

Hippocampal Injury in Obesity

While hypothalamic injury occurs early in obesity[31] as discussed above, unresolved inflammation, metabolic dysfunction, and a lack of satiety, in combination with alterations in FFAs, triglycerides, and insulin resistance, could all contribute in a multifactorial manner to establish a feed-forward cycle of injury that eventually affects other brain regions, most importantly the hippocampus. Hippocampal injury in response to increased blood-brain barrier permeability occurs in HFD-fed animals[64] as a consequence of reactive glial cytokine production and circulating pro-inflammatory adipokines.[65] FFA and triglycerides have also been demonstrated to directly alter hippocampal function and activity,[48] and insulin resistance has been linked to neurocognitive dysfunction[66] and been demonstrated to decrease hippocampal function.[67] Unchecked entry of pro-inflammatory proteins into the hippocampus can initiate or amplify neuroinflammation and promote neurodegeneration.[68,69] Indeed, loss of the blood-brain barrier and markers of hippocampal inflammation, including microglial activation, are present by 20 weeks of age in HFD-fed animals.[70] Over time, continued increased blood-brain barrier permeability and unchecked entry of neurotoxic cytokines and chemokines, as well as immune cells,[71] FFA, and triglycerides[48] during obesity further potentiates HFD-induced hippocampal injury and subsequent atrophy. These findings provide a mechanistic link between the observed blood-brain barrier breakdown and impaired cognition in obesity.

Effects of Obesity on the Peripheral Nervous System

The PNS is divided into the autonomic nervous system (ANS), containing the sympathetic and parasympathetic divisions, and the somatic nervous system, composed of the sensory and motor peripheral nerves. Autonomic and sensory ganglia along with unmyelinated fibers and synaptic terminals of the PNS are not protected by the blood-brain (nerve) barrier and are therefore susceptible to the pathophysiological consequences of obesity.

The ANS plays a critical role in regulating energy balance through its control of anabolic and catabolic processes and its close relationship with the hypothalamus. The ANS is particularly sensitive to obesity-induced perturbations, and ANS dysfunction is often present in young overweight individuals.[72] Obesity is associated with an imbalance between the sympathetic and parasympathetic divisions of the ANS. Increased sympathetic outflow to neuro-adipose junctions stimulates lipolysis via stimulatory G-protein coupled β-adrenoceptors. This triggers a downstream signaling pathway that ends with activation of adipose triglyceride lipase, resulting in triglyceride hydrolysis. Thus, sympathetic hyperactivation, as seen in obesity, can promote a feed-forward mechanism leading to an increased pool of circulating LCFA.[73] Increased sympathetic outflow to the cardiovascular system also results in increases in heart rate, blood pressure, and microvasculature tone. It is speculated that a sustained sympathetic outflow decreases perfusion, and in turn these physiological changes also promote further neurological dysfunction in both the CNS and PNS.

Obesity and Polyneuropathy

Polyneuropathy is clinically defined as the distal-to-proximal loss of sensory perception, affecting initially the feet, but over time also the hands. Frequently referred to as a "stocking-glove" loss of sensation, polyneuropathy occurs when there is a corresponding distal-to-proximal loss of sensory axons, with motor axons only involved in very severe or end stage disease. The most common causes of polyneuropathy in Western societies are prediabetes and type 2 diabetes. However, a Cochrane systematic review of all clinical trials of patients with diabetes where polyneuropathy was measured, including several large multicenter trials, revealed that glucose lowering therapies have little effect on the prevention of polyneuropathy in patients with type 2 diabetes[74]. These unanticipated results suggest that other MetS components, which are present in over 75% of patients with type 2 diabetes, play a role in the pathogenesis of polyneuropathy.

In support of this idea, we recently reported that the likelihood of polyneuropathy increases as the number of MetS components increases in the 2,382 participants of the Health, Aging, and Body Composition (Health ABC) study, independent of glycemic control.[75] Our study supports several reports that obesity alone is an independent risk factor for polyneuropathy,[76] including multiple clinical studies linking obesity with polyneuropathy (Table 2).[75–80] Indeed, lipid profiles are often abnormal early in type 2 diabetes and correlate with early polyneuropathy onset,[81] and triglycerides are associated with polyneuropathy progression in diabetes.[82] Moreover, elevated triglycerides are significantly higher in patients with idiopathic polyneuropathy,[83] and prediabetes, which is highly prevalent in obese individuals, is also associated with polyneuropathy.[77,84–86] Taken together these data suggest a role for obesity, prediabetes, and dyslipidemia in the pathophysiology of polyneuropathy.

Mechanisms Underlying Obesity-mediated Peripheral Nervous System Injury

Sensory nerves are comprised of neurons within the dorsal root ganglia (DRG), axons, and supporting Schwann cells, with each nerve covered by a connective tissue layer known as the epineurium. A second connective tissue layer known as the perineurium surrounds groups of nerves to form nerve fibers, and bundles of nerve fibers along with blood vessels are encapsulated by the final layer of connective tissue, the endoneurium, to form a pure sensory, pure motor, or mixed sensorimotor nerves. Like the blood-brain barrier, the PNS has a blood-nerve barrier consisting of the endoneurial microvessels and the perineurium. The blood-nerve barrier protects the peripheral nerve in the same fashion as the blood-brain barrier protects the CNS, except for two important exceptions: DRG and all sensory nerve endings in the skin lack the blood-nerve barrier. These two unprotected components of the PNS along with the endoneurial microvessels and the perineurium of the blood-nerve barrier are susceptible to initial obesity-mediated inflammatory injury with corresponding loss of function (Figure 2b).

To reveal the mechanisms underlying obesity-mediated PNS injury, we and others have employed HFD-fed mice that develop obesity, dyslipidemia, prediabetes, and polyneuropathy without developing frank type 2 diabetes.[87] LCFA and inflammatory mediators, that are found in HFD-fed animals[88], can injure and penetrate the blood-nerve

barrier and activate neurogenic inflammation[89]. In response, DRG neurons release vasoactive and chemoattractant signals to increase vasculature permeability and attract innate and adaptive immune cells to sites of damage. While this response is initially protective, chronic dysfunction secondary to obesity-mediated inflammation can lead to changes in nerve structure and subsequent pain.[89] Moreover, HFD-fed mice exhibit increased accumulation of macrophages in peripheral nerves, increased TNF-α and IL-1β mRNA, and polyneuropathy,[88] all without developing type 2 diabetes.[87]

Studies using animal models of obesity and type 2 diabetes with microvascular complications also support a role for lipotoxicity in polyneuropathy. Gene expression analyses of peripheral nerves of *ob/ob* and *db/db* mice identified common dysregulation of inflammation and immune-related functions as early as 5 weeks.[90] In *db/db* mice, pioglitazone treatment improved small fiber function and cutaneous innervation,[91] and in Zucker *fa/fa* rats, acipimox treatment normalized sensory nerve conduction velocities and alleviated thermal and mechanical hypoalgesia, independently of prediabetes.[92] These drugs are known to lower triglycerides and reduce FFAs, respectively; however, they also exert effects on other metabolic and endocrine measures which may contribute to their effectiveness for polyneuropathy. Together, these data suggest a role for obesity and lipid-induced inflammation in polyneuropathy.

As with the CNS, there is evidence that obesity- mediated increases in FFA and LCFA alter normal lipid metabolism in the PNS. Excess LCFA promote increased Schwann cell mitochondrial β-oxidation[93,94] that is coincident with polyneuropathy.[95,96] Products of LCFA metabolism, LC-acylcarnitines, accumulate in peripheral nerves of mice[94] and these bioactive lipids are associated with Schwann cell dysfunction,[93] axonal degeneration,[94] and polyneuropathy. Accumulation of LCFA or LC-acylcarnitines in non-obesity-mediated diseases affecting mitochondrial β-oxidation also results in polyneuropathy, strengthening the association between aberrant lipid metabolism and PNS dysfunction.[97]

Injury to the PNS by LCFA is not limited to metabolism but also occurs when excess LCFAs in Schwann cells induce a cascade of ER dysfunction that includes a decrease in ER Ca^{2+} content followed by ER stress, mitochondrial depolarization, and generation of toxic reactive oxygen species.[98] As anticipated, these LCFA-mediated markers of ER dysfunction are present in the PNS of *fa/fa* rats and HFD-fed mice with polyneuropathy, supporting their role in disease pathogenesis.[99] In parallel, LCFA induced ER dysfunction also negatively impacts mitochondrial ATP production in nerves, a function required for normal nerve physiology. It is well established that tightly regulated ER Ca^{2+} release is critical for proper mitochondrial Ca^{2+} uptake and ATP production. This delicate balance is disrupted in the nerves of HFD-fed mice with polyneuropathy where disruption of ER-mitochondrial tethering results in mitochondrial Ca^{2+} overload and impaired ATP production[100]. In aggregate, these results suggest that disruption of interorganellar Ca^{2+} transport between the ER and mitochondria in the PNS contributes to obesity-mediated polyneuropathy and supports the idea that LCFA-induced ER stress in Schwann cells acts in a feed-forward manner to disrupt ATP mitochondrial energy production and to promote further nerve injury. Finally, mitochondrial trafficking from neuronal cell bodies along the length of the axons is required to deliver ATP for normal nerve function, and in man, this distance can be greater

than one meter. Because mitochondrial trafficking is an ATP-dependent process,[101] compromised ATP generation during obesity can disrupt mitochondrial trafficking in a feed-forward loop, resulting in even greater peripheral nerve damage.

Neurological Benefits of Targeting Obesity

As the neurological consequences of obesity and dyslipidemia are highly morbid, the optimal disease-modifying therapy is to target obesity itself. Lifestyle interventions, consisting of dietary modification combined with exercise, provide an accessible and inexpensive strategy that is effective in combating obesity and restoring neurological function (Table 3). The physiological benefits of lifestyle interventions, greatest when dietary and exercise regimens are used in concert, improve the systemic metabolic profile and strongly correlate with improved cognitive function and improved nerve function. Global physiological benefits include improved cellular metabolism, restoration of glucose and insulin homeostasis, decreased metabolic inflammation, and improved lipid profiles.

For example, weight loss via a 12-month regimen of decreased caloric intake in obese elderly patients with MCI resulted in improved verbal memory, verbal fluency, executive function, and global cognition.[102] Moreover, a randomized control trial consisting of dietary intervention, coupled with increased exercise and cognitive training over a two year period, prevented cognitive decline.[103] Combined effects of omega-3 fatty acid supplementation, aerobic exercise, and cognitive stimulation also positively benefited brain structure and function in patients with MCI.[104] In terms of polyneuropathy, obese patients placed on a diet and exercise regimen exhibited increased cutaneous nerve fibers as a marker of polyneuropathy improvement along with decreased neuropathic pain.[105] Indeed, increased exercise alone can increase cutaneous nerve density in type 2 diabetic patients without neuropathy[106] and in patients with the MetS.[107] The sympathetic and parasympathetic nervous system imbalance that is observed in obesity is also modifiable by dietary intervention.[108] Finally, animal studies support the findings in man and also demonstrate that resolving obesity improves cognitive performance.[109–111] Switching mice from a HFD to a regular diet to reduce caloric intake results in improved metabolic health, with increased insulin sensitivity and improvement in cognitive function. These improvements are associated with reduced blood brain barrier-leakage, decreased glial activation, and increased vascular perfusion.[109–111]

While diet and exercise interventions provide the ideal therapeutic regimen, compliance is an issue supporting a role for both pharmacotherapy and bariatric surgery in the treatment of obesity-mediated neurological disorders. An observational study of 342 AD patients reported that treatment with lipid lowering agents (statins and/or fibrates) is associated with a slower cognitive decline in AD.[112] In parallel, the Fremantle Diabetes Study demonstrated that statin or fibrate treatment may protect against the development of polyneuropathy,[113] and the FIELD study showed that fenofibrate treatment resulted in fewer non-traumatic distal amputations, a consequence attributed to improved polyneuropathy.[114] Despite these studies, more definitive clinical trials are needed, and there are no clinical guidelines on the use of statins or fibrate in the treatment of CNS or PNS disorders.

Bariatric surgical procedures, such as Roux-en-Y Gastric Bypass are a highly effective and accepted treatment for patients who are morbidly obese.[115] Although many patients regain weight and medical complications are frequent, post-operative patients display profound improvements in metabolic homeostasis and exhibit improved neurocognitive function[116] (Table 3) due to improvement in adipokine,[117] insulin,[118] and inflammation signaling.[119] One study demonstrated decreased inflammation and reduced β-amyloid precursor protein expression in peripheral blood of patients following bariatric surgery, leading the authors to speculate that a similar benefit could be occurring in the hippocampus.[120] Roux-en-Y Gastric Bypass surgery also improves polyneuropathy one year post-procedure.[121] These surgical intervention studies support the pathogenic role of obesity in both the CNS and PNS, but are not the treatment of choice due to the high prevalence of obesity worldwide. Performing invasive surgical procedures in a large population is also not practical, so feasible alternatives focused on lifestyle intervention are urgently needed.

Clinical Implications and Future Directions

While extensive data exists to support obesity as a mediator of CNS and PNS injury, we currently do not know the ideal intervention to prevent cognitive impairment, AD, autonomic neuropathy, and polyneuropathy. Future studies are needed to determine the comparative effectiveness of pharmacologic, medical weight loss, surgical weight loss, and exercise interventions using rigorous study designs and patient oriented outcomes. These studies will also have to evaluate the cost-effectiveness of these different interventions. A combination of approaches may be ideal, but also requires multiple life-altering changes in behavior, which makes implementation more difficult. Given the available data to date, clinicians should advise obese individuals, especially those that already have early evidence of CNS and PNS injury, to pursue at least one of the obesity interventions listed above.

Conclusion

In conclusion, increased visceral adiposity is a risk factor for the development of a wide range of neurological conditions, and obesity and the resulting metabolic disorders will be one of the greatest medical challenges of the 21st century. Though the precise mechanisms of obesity-induced nerve and cognitive dysfunction need to be fully elucidated, it is clear that obesity, insulin resistance, and dyslipidemia converge at the CNS and PNS as FFA-induced lipotoxicity, resulting in inflammation, neurological dysfunction, and neurodegeneration. And while inflammation may play a critical role in the development of neurological dysfunction, it is also likely that it impacts and can be influenced by the other proposed mechanistic pathways linked to obesity, such as oxidative stress, ER stress, sympathetic alterations, and metabolic dysfunction. Additional research is needed to identify the best treatment targets and most efficient and practical combination of approaches to ensure sustained positive health outcomes. While pharmacotherapy and bariatric surgery have shown promising results, more research is necessary, and in the case of bariatric surgery large-scale application is not feasible. Based on published reports, we maintain that lifestyle intervention consisting of dietary changes and increased activity should be adopted, as it is both inexpensive and highly accessible.

Panel 1: Obesity Screening

In clinical research, accurate and absolute methods for obesity quantification include dual energy x-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), and computed tomography (CT). However, as it is not feasible to perform these routinely in the clinic and for large population studies, body mass index (BMI) and, to a lesser degree, waist-hip ratio (WHR) are used to assess the degree of obesity as they are inexpensive, easy to perform, and act as adequate surrogate markers. For Caucasian males, a BMI of 25–29 kg/m^2 is defined as overweight, a BMI > 30kg/m^2 is defined as obese, and a BMI > 40 kg/m^2 is defined as morbidly obese (as adipose distribution varies depending on age, sex, and ethnicity, different criteria are used for children, women, and ethnic groups). Though routinely used to screen for obesity, BMI does not reveal differences in fat distribution, and therefore BMI can give an inaccurate assessment of disease risk. For example, a subgroup of individuals who are obese according to BMI criteria (BMI >30) still remain relatively metabolically healthy with low fasting insulin, glucose, and triglycerides and exhibit protection from diseases related to metabolic dysfunction.[122] This protection can likely be attributed to increased adiposity in lower fat depots than in abdominal regions; these depots (e.g. gluteal, femoral, subcutaneous, and intramuscular) exhibit distinct physiological features from abdominal depots and are comprised of adipocytes which have greater capacity to deal with an increased metabolic load.[123] Moreover, both obese and non-obese individuals[124] with excess fat in the intra-abdominal region (visceral fat comprised of omental and mesenteric depots) are more susceptible to obesity-related diseases. For these reasons, clinical assessment of abdominal waist circumference, a surrogate marker of abdominal adipose fat mass, is a better marker for disease risk than BMI.

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References

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384(9945):766–81. [PubMed: 24880830]
2. Grarup N, Sandholt CH, Hansen T, Pedersen O. Genetic susceptibility to type 2 diabetes and obesity: from genome-wide association studies to rare variants and beyond. Diabetologia. 2014; 57(8):1528–41. [PubMed: 24859358]
3. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet. 2011; 378(9793):804–14. [PubMed: 21872749]
4. Collaboration NCDRF. Di Cesare M, Bentham J, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016; 387(10026):1377–96. [PubMed: 27115820]

5. Kloting N, Bluher M. Adipocyte dysfunction, inflammation and metabolic syndrome. Rev Endocr Metab Disord. 2014; 15(4):277–87. [PubMed: 25344447]
6. Bartness TJ, Shrestha YB, Vaughan CH, Schwartz GJ, Song CK. Sensory and sympathetic nervous system control of white adipose tissue lipolysis. Mol Cell Endocrinol. 2010; 318(1–2):34–43. [PubMed: 19747957]
7. Anderson EK, Gutierrez DA, Hasty AH. Adipose tissue recruitment of leukocytes. Curr Opin Lipidol. 2010; 21(3):172–7. [PubMed: 20410821]
8. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993; 259(5091):87–91. [PubMed: 7678183]
9. Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: time for a reevaluation. Diabetes. 2011; 60(10):2441–9. [PubMed: 21948998]
10. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev. 2011; 12(5):e426–37. [PubMed: 21348917]
11. Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016; 45(1):14–21. [PubMed: 26764391]
12. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology. 2008; 71(14):1057–64. [PubMed: 18367704]
13. Mrak RE. Alzheimer-type neuropathological changes in morbidly obese elderly individuals. Clin Neuropathol. 2009; 28(1):40–5. [PubMed: 19216219]
14. Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol Aging. 2005; 26(Suppl 1):11–6. [PubMed: 16223549]
15. Cournot M, Marquie JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006; 67(7):1208–14. [PubMed: 17030754]
16. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. Am J Clin Nutr. 2009; 89(2):601–7. [PubMed: 19073790]
17. Hassing LB, Dahl AK, Pedersen NL, Johansson B. Overweight in midlife is related to lower cognitive function 30 years later: a prospective study with longitudinal assessments. Dement Geriatr Cogn Disord. 2010; 29(6):543–52. [PubMed: 20606436]
18. Dahl AK, Hassing LB, Fransson EI, Gatz M, Reynolds CA, Pedersen NL. Body mass index across midlife and cognitive change in late life. Int J Obes (Lond). 2013; 37(2):296–302. [PubMed: 22450854]
19. Alhurani RE, Vassilaki M, Aakre JA, et al. Decline in Weight and Incident Mild Cognitive Impairment: Mayo Clinic Study of Aging. JAMA Neurol. 2016; 73(4):439–46. [PubMed: 26831542]
20. Qizilbash N, Gregson J, Johnson ME, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 2015; 3(6):431–6. [PubMed: 25866264]
21. Rochette AD, Spitznagel MB, Sweet LH, et al. Gender Differences in Cognitive Test Performance in Adults With Heart Failure. J Cardiovasc Nurs. 2016 Epub ahead of print.
22. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. 2012; 130(4):e856–64. [PubMed: 22945407]
23. Liang J, Matheson BE, Kaye WH, Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes (Lond). 2014; 38(4):494–506. [PubMed: 23913029]
24. Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring). 2008; 16(1):119–24. [PubMed: 18223623]

25. Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ. 2015; 6:14. [PubMed: 26339468]
26. Gustafson D, Lissner L, Bengtsson C, Bjorkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004; 63(10):1876–81. [PubMed: 15557505]
27. De Santi S, de Leon MJ, Rusinek H, et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging. 2001; 22(4):529–39. [PubMed: 11445252]
28. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. Arch Neurol. 2005; 62(10):1545–8. [PubMed: 16216937]
29. Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. BMC Neurol. 2005; 5:23. [PubMed: 16321166]
30. Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Ann Neurol. 2008; 63(5):652–7. [PubMed: 18409192]
31. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest. 2012; 122(1):153–62. [PubMed: 22201683]
32. Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage. 2006; 31(4):1419–25. [PubMed: 16545583]
33. Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. Hum Brain Mapp. 2010; 31(3): 353–64. [PubMed: 19662657]
34. Alosco ML, Stanek KM, Galioto R, et al. Body mass index and brain structure in healthy children and adolescents. Int J Neurosci. 2014; 124(1):49–55. [PubMed: 23789910]
35. Gomez-Pinilla F. Brain foods: the effects of nutrients on brain function. Nature reviews Neuroscience. 2008; 9(7):568–78. [PubMed: 18568016]
36. Kramer JH, Mungas D, Reed BR, et al. Longitudinal MRI and cognitive change in healthy elderly. Neuropsychology. 2007; 21(4):412–8. [PubMed: 17605574]
37. Henneman WJ, Sluimer JD, Barnes J, et al. Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. Neurology. 2009; 72(11):999–1007. [PubMed: 19289740]
38. Molteni R, Barnard RJ, Ying Z, Roberts CK, Gomez-Pinilla F. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002; 112(4):803–14. [PubMed: 12088740]
39. Jurdak N, Lichtenstein AH, Kanarek RB. Diet-induced obesity and spatial cognition in young male rats. Nutr Neurosci. 2008; 11(2):48–54. [PubMed: 18510803]
40. Ledreux A, Wang X, Schultzberg M, Granholm AC, Freeman LR. Detrimental effects of a high fat/high cholesterol diet on memory and hippocampal markers in aged rats. Behav Brain Res. 2016; 312:294–304. [PubMed: 27343935]
41. Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiol Aging. 2005; 26(Suppl 1):46–9. [PubMed: 16219391]
42. Kanoski SE, Davidson TL. Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet. J Exp Psychol Anim Behav Process. 2010; 36(2): 313–9. [PubMed: 20384410]
43. McNeilly AD, Williamson R, Sutherland C, Balfour DJ, Stewart CA. High fat feeding promotes simultaneous decline in insulin sensitivity and cognitive performance in a delayed matching and non-matching to position task. Behav Brain Res. 2011; 217(1):134–41. [PubMed: 20974195]
44. Kosari S, Badoer E, Nguyen JC, Killcross AS, Jenkins TA. Effect of western and high fat diets on memory and cholinergic measures in the rat. Behav Brain Res. 2012; 235(1):98–103. [PubMed: 22820146]
45. Stranahan AM, Norman ED, Lee K, et al. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus. 2008; 18(11):1085–8. [PubMed: 18651634]
46. Karimi SA, Salehi I, Komaki A, Sarihi A, Zarei M, Shahidi S. Effect of high-fat diet and antioxidants on hippocampal long-term potentiation in rats: an in vivo study. Brain Res. 2013; 1539:1–6. [PubMed: 24095795]

47. Lindqvist A, Mohapel P, Bouter B, et al. High-fat diet impairs hippocampal neurogenesis in male rats. Eur J Neurol. 2006; 13(12):1385–8. [PubMed: 17116226]
48. Farr SA, Yamada KA, Butterfield DA, et al. Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 2008; 149(5):2628–36. [PubMed: 18276751]
49. Richard D. Cognitive and autonomic determinants of energy homeostasis in obesity. Nat Rev Endocrinol. 2015; 11(8):489–501. [PubMed: 26122319]
50. Fekete C, Lechan RM. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev. 2014; 35(2):159–94. [PubMed: 24423980]
51. De Souza CT, Araujo EP, Bordin S, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology. 2005; 146(10):4192–9. [PubMed: 16002529]
52. Maric T, Woodside B, Luheshi GN. The effects of dietary saturated fat on basal hypothalamic neuroinflammation in rats. Brain Behav Immun. 2014; 36:35–45. [PubMed: 24075847]
53. Milanski M, Degasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci. 2009; 29(2):359–70. [PubMed: 19144836]
54. Thaler JP, Schwartz MW. Minireview: Inflammation and obesity pathogenesis: the hypothalamus heats up. Endocrinology. 2010; 151(9):4109–15. [PubMed: 20573720]
55. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell. 2008; 135(1):61–73. [PubMed: 18854155]
56. Posey KA, Clegg DJ, Printz RL, et al. Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. Am J Physiol Endocrinol Metab. 2009; 296(5):E1003–12. [PubMed: 19116375]
57. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metab. 2010; 21(11):643–51. [PubMed: 20846876]
58. Li J, Tang Y, Cai D. IKKbeta/NF-kappaB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. Nat Cell Biol. 2012; 14(10): 999–1012. [PubMed: 22940906]
59. Gropp E, Shanabrough M, Borok E, et al. Agouti-related peptide-expressing neurons are mandatory for feeding. Nat Neurosci. 2005; 8(10):1289–91. [PubMed: 16158063]
60. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. Diabetes. 2010; 59(9):2171–7. [PubMed: 20566663]
61. Borg ML, Omran SF, Weir J, Meikle PJ, Watt MJ. Consumption of a high-fat diet, but not regular endurance exercise training, regulates hypothalamic lipid accumulation in mice. J Physiol. 2012; 590(17):4377–89. [PubMed: 22674717]
62. Contreras C, Gonzalez-Garcia I, Martinez-Sanchez N, et al. Central ceramide-induced hypothalamic lipotoxicity and ER stress regulate energy balance. Cell Rep. 2014; 9(1):366–77. [PubMed: 25284795]
63. McFadden JW, Aja S, Li Q, et al. Increasing fatty acid oxidation remodels the hypothalamic neurometabolome to mitigate stress and inflammation. PLoS One. 2014; 9(12):e115642. [PubMed: 25541737]
64. Hargrave SL, Davidson TL, Zheng W, Kinzig KP. Western diets induce blood-brain barrier leakage and alter spatial strategies in rats. Behav Neurosci. 2016; 130(1):123–35. [PubMed: 26595878]
65. Abbott NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. Cellular and molecular neurobiology. 2000; 20(2):131–47. [PubMed: 10696506]
66. Stoeckel LE, Arvanitakis Z, Gandy S, et al. Complex mechanisms linking neurocognitive dysfunction to insulin resistance and other metabolic dysfunction [version 2]. F1000Res. 2016; 5:353. [PubMed: 27303627]
67. Grillo CA, Piroli GG, Lawrence RC, et al. Hippocampal Insulin Resistance Impairs Spatial Learning and Synaptic Plasticity. Diabetes. 2015; 64(11):3927–36. [PubMed: 26216852]

68. Sims-Robinson C, Bakeman A, Glasser R, Boggs J, Pacut C, Feldman EL. The role of endoplasmic reticulum stress in hippocampal insulin resistance. Exp Neurol. 2016; 277:261–7. [PubMed: 26775176]
69. Cai M, Wang H, Li JJ, et al. The signaling mechanisms of hippocampal endoplasmic reticulum stress affecting neuronal plasticity-related protein levels in high fat diet-induced obese rats and the regulation of aerobic exercise. Brain, behavior, and immunity. 2016; 57:347–59.
70. Jeon BT, Jeong EA, Shin HJ, et al. Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. Diabetes. 2012; 61(6): 1444–54. [PubMed: 22362175]
71. Buckman LB, Hasty AH, Flaherty DK, et al. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system. Brain, behavior, and immunity. 2014; 35:33–42.
72. Lambert E, Sari CI, Dawood T, et al. Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults. Hypertension. 2010; 56(3):351–8. [PubMed: 20625075]
73. Zeng W, Pirzgalska RM, Pereira MM, et al. Sympathetic neuro-adipose connections mediate leptin-driven lipolysis. Cell. 2015; 163(1):84–94. [PubMed: 26406372]
74. Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. The Cochrane database of systematic reviews. 2012; 6:CD007543.
75. Callaghan BC, Xia R, Banerjee M, et al. Metabolic Syndrome Components Are Associated With Symptomatic Polyneuropathy Independent of Glycemic Status. Diabetes Care. 2016; 73(12):1468–76.
76. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. The New England journal of medicine. 2005; 352(4):341–50. [PubMed: 15673800]
77. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A, Group KS. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care. 2008; 31(3): 464–9. [PubMed: 18039804]
78. Lu B, Hu J, Wen J, et al. Determination of peripheral neuropathy prevalence and associated factors in Chinese subjects with diabetes and pre-diabetes - ShangHai Diabetic neuRopathy Epidemiology and Molecular Genetics Study (SH-DREAMS). PloS one. 2013; 8(4):e61053. [PubMed: 23613782]
79. Lee CC, Perkins BA, Kayaniyil S, et al. Peripheral Neuropathy and Nerve Dysfunction in Individuals at High Risk for Type 2 Diabetes: The PROMISE Cohort. Diabetes Care. 2015; 38(5): 793–800. [PubMed: 25665810]
80. Smith AG, Rose K, Singleton JR. Idiopathic neuropathy patients are at high risk for metabolic syndrome. Journal of the neurological sciences. 2008; 273(1–2):25–8. [PubMed: 18606421]
81. Clemens A, Siegel E, Gallwitz B. Global risk management in type 2 diabetes: blood glucose, blood pressure, and lipids–update on the background of the current guidelines. ExpClinEndocrinolDiabetes. 2004; 112:493–503.
82. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes. 2009; 58(7):1634–40. [PubMed: 19411614]
83. Hughes RA, Umapathi T, Gray IA, et al. A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy. Brain: a journal of neurology. 2004; 127(Pt 8):1723–30. [PubMed: 15201191]
84. Callaghan BC, Xia R, Reynolds E, et al. Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. JAMA Neurol. 2016; 73(12):1468–76. [PubMed: 27802497]
85. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol. 2011; 7(11):682–90. [PubMed: 21750507]
86. Papanas N, Ziegler D. Polyneuropathy in impaired glucose tolerance: is postprandial hyperglycemia the main culprit? A mini-review. Gerontology. 2013; 59(3):193–8. [PubMed: 23207896]

87. O'Brien PD, Sakowski SA, Feldman EL. Mouse models of diabetic neuropathy. ILAR journal/ National Research Council, Institute of Laboratory Animal Resources. 2014; 54(3):259–72.

88. Jayaraman A, Lent-Schochet D, Pike CJ. Diet-induced obesity and low testosterone increase neuroinflammation and impair neural function. Journal of neuroinflammation. 2014; 11:162. [PubMed: 25224590]

89. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nat Neurosci. 2012; 15(8):1063–7. [PubMed: 22837035]

90. O'Brien PD, Hur J, Hayes JM, Backus C, Sakowski SA, Feldman EL. BTBR ob/ob mice as a novel diabetic neuropathy model: Neurological characterization and gene expression analyses. Neurobiology of disease. 2014; 73C:348–55.

91. Hur J, Dauch JR, Hinder LM, et al. The Metabolic Syndrome and Microvascular Complications in a Murine Model of Type 2 Diabetes. Diabetes. 2015; 64(9):3294–304. [PubMed: 25979075]

92. Lupachyk S, Watcho P, Hasanova N, Julius U, Obrosova IG. Triglyceride, nonesterified fatty acids, and prediabetic neuropathy: role for oxidative-nitrosative stress. Free Radic Biol Med. 2012; 52(8):1255–63. [PubMed: 22366714]

93. Hinder LM, Figueroa-Romero C, Pacut C, et al. Long-chain acyl coenzyme A synthetase 1 overexpression in primary cultured Schwann cells prevents long chain fatty acid-induced oxidative stress and mitochondrial dysfunction. Antioxidants & redox signaling. 2014; 21(4):588–600. [PubMed: 23991914]

94. Viader A, Sasaki Y, Kim S, et al. Aberrant Schwann cell lipid metabolism linked to mitochondrial deficits leads to axon degeneration and neuropathy. Neuron. 2013; 77(5):886–98. [PubMed: 23473319]

95. Pande M, Hur J, Hong Y, et al. Transcriptional profiling of diabetic neuropathy in the BKS db/db mouse: a model of type 2 diabetes. Diabetes. 2011; 60(7):1981–9. [PubMed: 21617178]

96. Viader A, Golden JP, Baloh RH, Schmidt RE, Hunter DA, Milbrandt J. Schwann cell mitochondrial metabolism supports long-term axonal survival and peripheral nerve function. J Neurosci. 2011; 31(28):10128–40. [PubMed: 21752989]

97. Rector RS, Payne RM, Ibdah JA. Mitochondrial trifunctional protein defects: clinical implications and therapeutic approaches. Adv Drug Deliv Rev. 2008; 60(13–14):1488–96. [PubMed: 18652860]

98. Padilla A, Descorbeth M, Almeyda AL, Payne K, De Leon M. Hyperglycemia magnifies Schwann cell dysfunction and cell death triggered by PA-induced lipotoxicity. Brain Res. 2011; 1370:64–79. [PubMed: 21108938]

99. Lupachyk S, Watcho P, Obrosov AA, Stavniichuk R, Obrosova IG. Endoplasmic reticulum stress contributes to prediabetic peripheral neuropathy. Exp Neurol. 2012; 247:342–8. [PubMed: 23142188]

100. Arruda AP, Pers BM, Parlakgul G, Guney E, Inouye K, Hotamisligil GS. Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. Nat Med. 2014; 20(12):1427–35. [PubMed: 25419710]

101. Sajic M. Mitochondrial dynamics in peripheral neuropathies. Antioxidants & redox signaling. 2014; 21(4):601–20. [PubMed: 24386984]

102. Horie NC, Serrao VT, Simon SS, et al. Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals With Mild Cognitive Impairment. The Journal of clinical endocrinology and metabolism. 2016; 101(3):1104–12. [PubMed: 26713821]

103. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015; 385(9984):2255–63. [PubMed: 25771249]

104. Kobe T, Witte AV, Schnelle A, et al. Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. NeuroImage. 2015; 131:226–38. [PubMed: 26433119]

105. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care. 2006; 29(6):1294–9. [PubMed: 16732011]

106. Singleton JR, Marcus RL, Jackson JE, M KL, Graham TE, Smith AG. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. Annals of clinical and translational neurology. 2014; 1(10):844–9. [PubMed: 25493275]

107. Singleton JR, Marcus RL, Lessard MK, Jackson JE, Smith AG. Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. Annals of neurology. 2015; 77(1):146–53. [PubMed: 25388934]

108. de Jonge L, Moreira EA, Martin CK, Ravussin E, Pennington CT. Impact of 6-month caloric restriction on autonomic nervous system activity in healthy, overweight, individuals. Obesity. 2010; 18(2):414–6. [PubMed: 19910943]

109. Johnson LA, Zuloaga KL, Kugelman TL, et al. Amelioration of Metabolic Syndrome-Associated Cognitive Impairments in Mice via a Reduction in Dietary Fat Content or Infusion of Non-Diabetic Plasma. EBioMedicine. 2016; 3:26–42. [PubMed: 26870815]

110. Kim H, Kang H, Heo RW, et al. Caloric restriction improves diabetes-induced cognitive deficits by attenuating neurogranin-associated calcium signaling in high-fat diet-fed mice. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2016; 36(6):1098–110.

111. Sims-Robinson C, Bakeman A, Bruno E, et al. Dietary Reversal Ameliorates Short- and Long-Term Memory Deficits Induced by High-fat Diet Early in Life. PloS one. 2016; 11(9):e0163883. [PubMed: 27676071]

112. Masse I, Bordet R, Deplanque D, et al. Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. Journal of neurology, neurosurgery, and psychiatry. 2005; 76(12):1624–9.

113. Davis TM, Yeap BB, Davis WA, Bruce DG. Lipid-lowering therapy and peripheral sensory neuropathy in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia. 2008; 51(4):562–6. [PubMed: 18193189]

114. Ansquer JC, Foucher C, Aubonnet P, Le Malicot K. Fibrates and microvascular complications in diabetes–insight from the FIELD study. Current pharmaceutical design. 2009; 15(5):537–52. [PubMed: 19199980]

115. Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. Jama. 2012; 307(1):56–65. [PubMed: 22215166]

116. Miller LA, Crosby RD, Galioto R, et al. Bariatric surgery patients exhibit improved memory function 12 months postoperatively. Obesity surgery. 2013; 23(10):1527–35. [PubMed: 23636994]

117. Alosco ML, Spitznagel MB, Strain G, et al. Improved serum leptin and ghrelin following bariatric surgery predict better postoperative cognitive function. Journal of clinical neurology. 2015; 11(1): 48–56. [PubMed: 25628737]

118. Plum L, Ahmed L, Febres G, et al. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. Obesity. 2011; 19(11):2149–57. [PubMed: 21593800]

119. Vazquez LA, Pazos F, Berrazueta JR, et al. Effects of changes in body weight and insulin resistance on inflammation and endothelial function in morbid obesity after bariatric surgery. The Journal of clinical endocrinology and metabolism. 2005; 90(1):316–22. [PubMed: 15507518]

120. Ghanim H, Monte SV, Sia CL, et al. Reduction in inflammation and the expression of amyloid precursor protein and other proteins related to Alzheimer's disease following gastric bypass surgery. The Journal of clinical endocrinology and metabolism. 2012; 97(7):E1197–201. [PubMed: 22508715]

121. Zeve JL, Tomaz CA, Nassif PA, Lima JH, Sansana LR, Zeve CH. Obese patients with diabetes mellitus type 2 undergoing gastric bypass in Roux-en-Y: analysis of results and its influence in complications. Arquivos brasileiros de cirurgia digestiva: ABCD = Brazilian archives of digestive surgery. 2013; 26(Suppl 1):47–52. [PubMed: 24463899]

122. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014; 14:9. [PubMed: 24484869]

123. Tchoukalova YD, Votruba SB, Tchkonia T, Giorgadze N, Kirkland JL, Jensen MD. Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107(42):18226–31. [PubMed: 20921416]

124. Acosta JR, Douagi I, Andersson DP, et al. Increased fat cell size: a major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes. Diabetologia. 2016; 59(3):560–70. [PubMed: 26607638]

125. Witte AV, Fobker M, Gellner R, Knecht S, Floel A. Caloric restriction improves memory in elderly humans. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(4):1255–60. [PubMed: 19171901]

126. Smith PJ, Blumenthal JA, Babyak MA, et al. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension. 2010; 55(6):1331–8. [PubMed: 20305128]

127. Siervo M, Nasti G, Stephan BC, et al. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. J Am Coll Nutr. 2012; 31(2): 79–86. [PubMed: 22855912]

128. Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. The American journal of clinical nutrition. 2014; 100(1):189–98. [PubMed: 24787497]

129. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Arch Intern Med. 2009; 169(20):1873–80. [PubMed: 19901139]

130. Boraxbekk CJ, Stomby A, Ryberg M, et al. Diet-Induced Weight Loss Alters Functional Brain Responses during an Episodic Memory Task. Obes Facts. 2015; 8(4):261–72. [PubMed: 26139105]

Box 1

Neurological Consequences of Obesity

Central Nervous System

Structural

- Brain atrophy and reduced grey matter volume in frontal and temporal lobes and enlarged orbitofrontal white matter
- Decreased hippocampus and hypothalamus integrity

Psychological and Behavioral

- Altered feeding behavior and satiety control
- Mild cognitive impairment (attention, learning, and memory deficits; impairments in decision making), cognitive decline and increased risk of dementia and Alzheimer's disease
- Mood disorders including anxiety and depression

Physiological

- Cerebral ischemia and hypoperfusion
- Decreased brain metabolism and nerve function

Peripheral Nervous System

Structural

- Organ damage due to chronic activation of sympathetic nervous system
- Loss of peripheral sensory neurons and small intraepidermal nerve fibers

Psychological and Behavioral

- Symptoms of sensory polyneuropathy, including early onset pain, paresthesias, allodynia, and hyperalgesia, that over time converts to frank numbness and loss of perception of sensory modalities
- Symptoms and signs occur in a stocking-glove distribution

Physiological

- Blunted but chronic activation of sympathetic nervous tone resulting in:
  - Increased efferent muscle activity, cardiac output, adrenaline release from adrenal medulla, adipose tissue lipolysis, liver gluconeogenesis, and decreased release of pancreatic insulin
- Gastroparesis and intestinal dysmotility
- Decreased motor and sensory nerve function

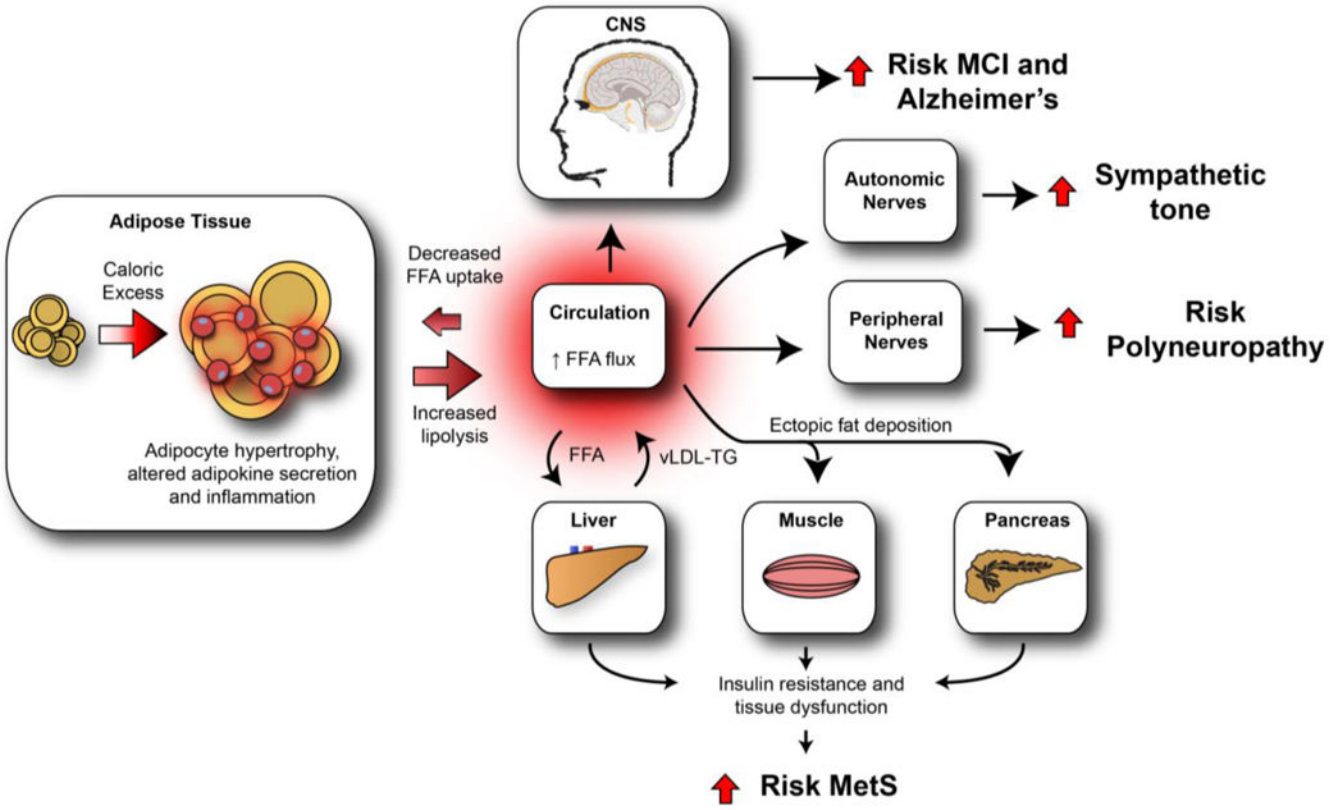

Figure 1. Neurological consequences of obesity: an overview

Increased caloric intake and decreased energy expenditure result in a net energy overload, leading to adipose tissue expansion (hyperplasia and hypertrophy). Sustained caloric excess in visceral adipose tissue activates resident adipose tissue macrophages, contributing to the development of adipose tissue dysfunction and metabolic inflammation. As a consequence, circulating FFAs rise, are lipotoxic to peripheral tissues, and contribute to the development of metabolic dyshomeostasis. High FFA flux into the liver increases vLDL-triglyceride production, further promoting dyslipidemia, while ectopic fat deposition in the muscle and pancreas promotes insulin resistance and pancreatic β-cell dysfunction, respectively. Collectively, these impairments lead to the MetS. Similarly, the CNS, ANS, and PNS are also detrimentally affected by obesity and obesity-induced metabolic dysfunction, which we hypothesize is driven by the lipotoxic effects of dyslipidemia and increased circulating FFA. In the CNS, dysfunction leads to MCI and Alzheimer's disease while in the ANS and PNS, the end result is autonomic and peripheral neuropathy, respectively. FFA = free fatty acid. vLDL = very-low-density lipoprotein. TG = triglyceride. MCI = mild cognitive impairment. MetS = metabolic syndrome.

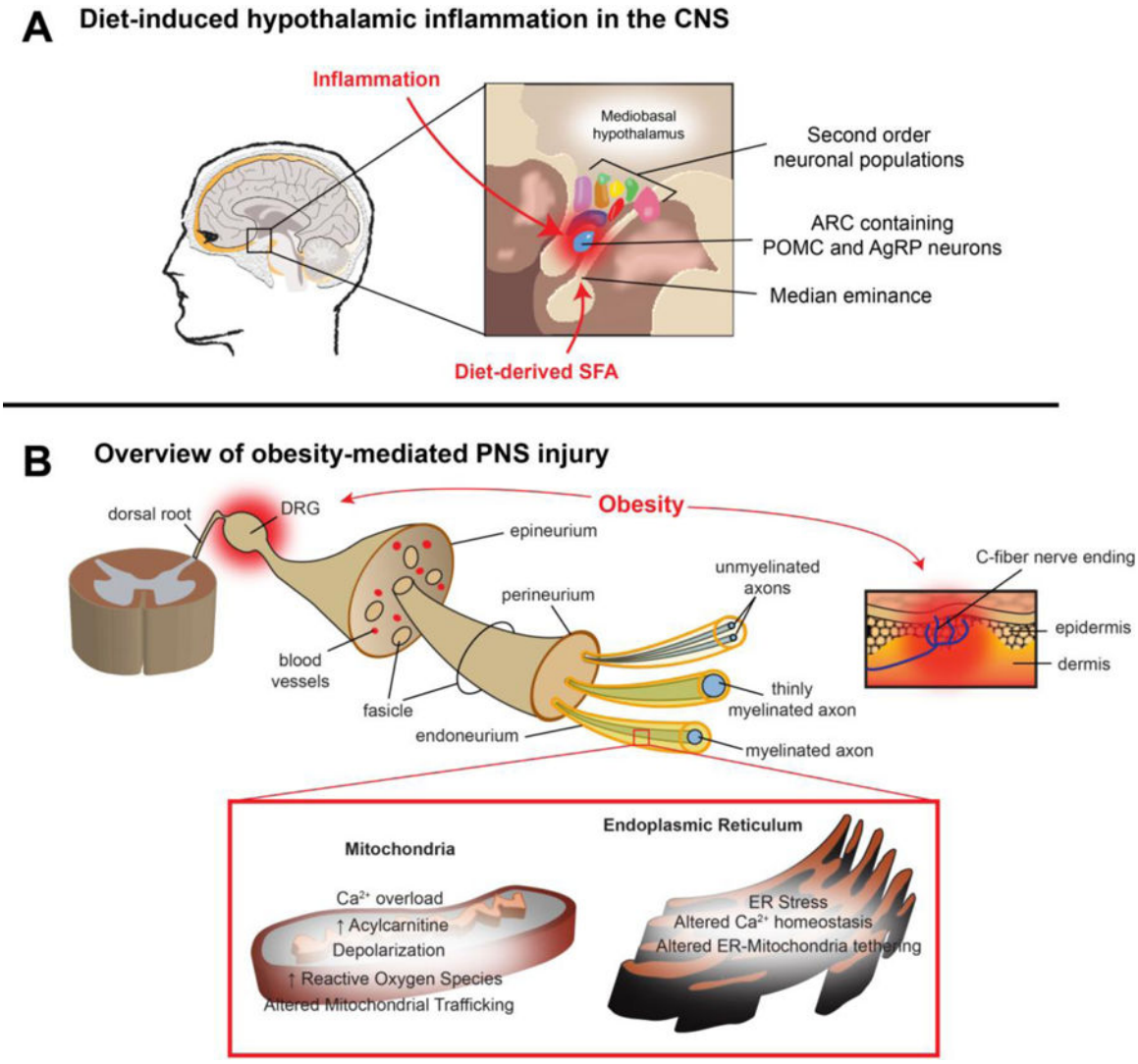

Figure 2. Neurological complications associated with obesity and dyslipidemia

A. Diet-induced hypothalamic function in the CNS. Located in the CNS, the hypothalamus is responsible for controlling global energy balance by monitoring metabolic homeostasis. Diet-derived saturated fatty acids (SFA) can enter the CNS via the median eminence and accumulate in the mediobasal hypothalamus. In response to SFA, resident hypothalamic microglia that protect against pathogenic species become activated, resulting in inflammation, gliosis and neuronal stress. Pro-inflammatory signaling in the arcuate nucleus is associated with the development of impaired leptin signaling in pro-opiomelanocortin (POMC) and Agouti-related peptide (AgRP) neurons that in turn can affect second order neurons that govern energy balance. Hypothalamic inflammation alters satiety control, thus increasing the risk of developing obesity.

B. Overview of obesity-mediated PNS injury. As a consequence of obesity, increased levels of FFA lead to decreased neurotrophic support and increased neurodegeneration in peripheral nerves. Long-chain fatty acids and inflammatory mediators directly injure DRG neurons, C-fiber cutaneous nerve endings, and the blood-nerve-barrier. As the blood-nerve-

barrier is increasingly compromised, axons and their associated Schwann cells become vulnerable to injury, leading to neurogenic inflammation, mitochondrial dysfunction and ER stress. In aggregate, these changes alter nerve function and structure, contributing to the development and progression of polyneuropathy. FFA = free fatty acids. SFA = saturated fatty acids. CNS = central nervous system. ARC = arcuate nucleus. POMC = pro-opiomelanocortin. AgRP = Agouti-related peptide. DRG = dorsal root ganglia. FFA = free fatty acid.

Table 1

Prospective clinical studies demonstrating associations between obesity and cognitive deficits, independent of dementia

Study/Age/Sample Size	Design/duration	Cognitive tests/diagnosis	Observation	Ref.
Framingham Heart Study; 55–88yrs; 551 males and 872 females divided into normal, overweight or obese groups; 18 year duration; USA	Prospective 22 yr	8 subtests: logical memory-immediate recall, visual reproductions, paired associates learning, digit span forward/ backward, word fluency (Controlled Oral Word Associations), similarities, and logical memory-delayed recall	Adverse cognitive effects seen in obese men, not women	14
32–62yr baseline; 1660 male, 1576 female; France	Prospective 5 yr	Word-list learning and recall; DSST test, attention test; delayed free recall test	Cross-section: higher BMI = lower cognitive scores; Prospective: higher BMI predicted cognitive decline	15
White men/women; Whitehall II Study; aged 35–55 at baseline; n = 5131; UK	Prospective ~36 yr	Mini-Mental State Examination and tests of memory and executive function	Cumulative effect of obesity on cognition	16
Men/women; Swedish twin registry; aged 50–60 yr at baseline;; n=417; Sweden	Prospective 30 yr	Testing of long-term memory, short-term memory, speed, verbal and spatial ability	Midlife overweight is related to lower overall cognitive function in old age	17
Men/women; Swedish Adoption/Twin Study of Aging; aged 25–50 at baseline; n=657; Sweden	Prospective ~20 yr	Verbal, spatial/fluid, memory and perceptual speed were tested	Early midlife overweight/obesity = lower cognitive function and predicts cognitive decline in late life	18

DSST – Digit-Symbol Substitution Test

Table 2

Clinical studies suggesting an association between obesity and polyneuropathy

Study/Population	Size	Aim	Method	Observations	Ref.
Utah Study; Utah, USA	219	Identify whether MetS features other than hyperglycemia increase polyneuropathy risk	Clinical diagnosis and nerve conduction studies/skin biopsy for measurement of epidermal nerve fiber density to confirm when necessary	Lipid abnormalities observed in patients with polyneuropathy	80
PROMISE Study; Toronto, Ontario, Canada	467	Determine the association of MetS components with polyneuropathy risk	Vibration perception thresholds to measure nerve dysfunction; MNSI to establish polyneuropathy	Increased waist circumference confers greater neuropathy risk	79
MONICA/KORA Study; Augsburg, Germany	393	Identify risk factors for polyneuropathy in patients with IGT	MNSI to establish polyneuropathy	Waist circumference associated with polyneuropathy	77
SH-DREAMS Study; Shanghai, China	2,035	Identify risk factors for polyneuropathy in patients with IGT	Foot examination/neuropathy symptom and neuropathy disability scores	Waist circumference associated with polyneuropathy in non-diabetic patients	78
Health ABC; Pittsburgh and Memphis, USA	2,382	Determine the association of MetS components with polyneuropathy	Questionnaire plus at least one of three confirmatory tests (heavy monofilament, peroneal conduction velocity and vibration threshold)	Waist circumference associated with polyneuropathy	75
EURODIAB; Europe	1,172	Identify risk factors for polyneuropathy in patients with type 1 diabetes	Clinical evaluation, quantitative sensory testing, and autonomic-function testing	Higher BMI, total cholesterol and vLDL cholesterol significantly associated with polyneuropathy	76

PROMISE - Prospective Metabolism and Islet Cell Evaluation; MONICA/KORA - Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Research in the Region of Augsburg; SH-DREAMS - ShangHai Diabetic neuRopathy Epidemiology and Molecular Genetics Study; EURODIAB - European Diabetes Prospective Complications Study; Health ABC - Health, Aging, and Body Composition Study; MNSI - Michigan neuropathy screening instrument; MetS – Metabolic syndrome; vLDL - very low density lipoprotein; T1D - type 1 diabetes; IGT - impaired glucose tolerance

Table 3

Benefits of lifestyle intervention and surgery on neurological complications

Method	Age (years); Sample Size	Metabolic Selection Criteria	Study Duration	Metabolic Observations	Neurological Observations	Ref.
Cognitive impairment, dementia risk and cerebral volume/integrity						
Caloric restriction	60.5±7.6; n=50	Normal to overweight subjects (mean BMI of 28±3.7)	3 months	Decreased BMI (0.8), CRP (0.22pg/mL) and insulin (3.5 μIU/mL)	Improved memory performance (increase in verbal memory score)	125
Caloric restriction, dietary changes and exercise	52.3±9.6; n=124	BMI=25–40 (mean BMI of 32.8±3.8)	4 months	Decreased BMI (3.3), improved cardiovascular fitness and reduced blood pressure	Improved executive function-memory-learning and psychomotor speed	126
Intentional weight loss	56.9±9.7; n=21	BMI=30–50 (mean BMI of 36.7)	~4 months	Decreased BMI (3.5) and fat mass (7.5kg)	Improvements in hand-grip strength and cognitive function (Mini-Mental State Examination, Short Portable Mental Status Questionnaire, and Trail-Making Test)	127
Caloric restriction and exercise	70±4; n=28	BMI=37.2±5.4	12 months	Decreased body weight (8.6±3.8kg), visceral fat (787±896cm3) and CRP (1.8±3.4mg/dL) and increased insulin sensitivity	Improvement in cognitive function (Mini-Mental State Examination, Word Fluency Test and Trail-Making Test)	128
Caloric restriction	50±0.8; n=106	BMI=33.7±0.4	12 months	Decreased body weight (13.7±1.8kg), plasma glucose (5.4mg/dL) and insulin (3.6 μIU/mL)	Improved working memory (Digit span backward test)	129
Dietary intervention	61.1±1.6; n=20 (females only)	BMI=27–40	6 months	Decreased BMI (3.6), waist circumference (0.04m),plasma insulin (1.3μIU/mL) and FFA(0.13mmol/l)	Improved memory performance, increased hippocampal brain activity using MRI	130
Caloric-restriction	60+; n=80	BMI≥30	12 months	Decreased BMI (1.7 ±1.8); Improved HOMA; CRP	Improved memory, cognition and executive function	102
Diet, exercise, cognitive training	FINGER trial 69.3±4.7; n=1,260	Baseline BMI=28.3 (no exclusions)	24 months	Decreased BMI 0.49 (±0.05)	Improved processing speed and executive function	103
Omega-3 supplementation, exercise, cognitive stimulation	60–80; n=22	n/a	6 months	No significant metabolic improvements	Preserved and increased gray matter volume in intervention group compared to controls, no improvements in cognitive function	104
Bariatric Surgery	21–41; n=137	Patients with morbid obesity	12 months	Lower BMI	Improved cognitive performance	116
Polyneuropathy						
Diet; exercise	60±8.4; n=32	Baseline BMI = 32.1 ±4.4 (pre-diabetics selected)	12 months	Decreased BMI and total cholesterol	Increased intra epidermal nerve innervation; decreased neuropathic pain	105
Exercise	30–70; n=174	Patients with type 2 diabetes	12 months	Increased HDL	Increased intra epidermal nerve innervation	106

Method	Age (years); Sample Size	Metabolic Selection Criteria	Study Duration	Metabolic Observations	Neurological Observations	Ref.
Exercise	n=36	MetS	6 months	Increased intra epidermal nerve innervation	Increased intra epidermal nerve innervation	107
Bariatric Surgery	n=17	Patients with morbid obesity (BMI≥40)	12 months	Improved BMI, fasting glucose, HbA1C, C-peptide, insulin and HOMA-IR	Neuropathy incidence lower (measures not reported)	121

AD - Alzheimer's disease; BMI - body mass index; CRP - C-reactive protein; HbA1C - hemoglobin A1C; HDL - high density lipoprotein; HOMA - Homeostatic Model Assessment; FFA - free fatty acids; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; IR - insulin resistance; MetS - Metabolic Syndrome; MRI – magnetic resonance imaging