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Unraveling The Connection: The Impact Of Obesity On Neurological Diseases

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Abstract

Obesity is becoming a more significant global health concern due to its connection to several detrimental health effects, especially in the development of neurological diseases, which affect 15% of the world's population and are the primary cause of physical and cognitive disability worldwide. These effects are in addition to the well-known impact of obesity on metabolic disorders and cardiovascular health. As a result, we emphasize in this article the essential understanding of the composition and properties of adipose tissue. We also address the complex molecular relationships between obesity and neurological disorders, including those involving free fatty acids, insulin resistance, inflammation, and other factors, in addition to the overall impacts of obesity on the structure and function of the brain. Given that obesity is a significant risk factor for most non-communicable diseases, it is anticipated that a thorough understanding of this issue would have a substantial impact on public health policy in the fight against disorders connected to obesity and make it easier to avoid and control the obesity epidemic. Specifically, understanding and addressing the intricate interplay between obesity and neurological diseases is crucial for developing preventive strategies and therapeutic interventions to promote brain health. Hence, prevention and education must be given top priority in public health programs aimed at reducing obesity and promoting healthy lifestyles in individuals, particularly in youngsters. Early identification of neurological disorders associated with obesity also paves the way for targeted therapeutics and a more comprehensive approach to patient treatment.

Introduction

Increased awareness of obesity's negative impacts on health is contributing to its growing global concern. More than 340 million children and adolescents between the ages of 5 and 19 and 1.9 billion adults worldwide were overweight or obese in 2016, according to estimates from the World Health Organization (WHO). **[1,2]** The World Obesity Federation has predicted that one billion people worldwide, including one in five women and one in seven men, will be obese by 2030 due to the incidence of obesity continuing to rise, especially in developing countries. Conversely, neurological diseases—which presently impact 15% of the global population—are the primary cause of both physical and cognitive disability worldwide. **[3]** Furthermore, during the course of the next 20 years, it is anticipated that the burden of chronic neurological diseases will at least double. A recent study, in addition to its well- known impact on metabolic diseases and cardiovascular health, highlights the concerning link between obesity and neurological diseases, adding to the complexity of the interaction between body weight and brain health. **[4,5]** Research on the connection between obesity and neurological diseases has grown significantly in recent years. **[6,7]** Researchers are delving into the complex relationships between excess body weight and neurodegenerative diseases (NDs) like Alzheimer's and Parkinson's as obesity becomes more commonplace worldwide. **[8-10]** This intricate association encompasses elements such as insulin resistance, inflammation, and the effects of obesity on the structure and function of the brain. **[11-15]**

Obesity: definition and types

The term "obesity" is defined by the Obesity Medicine Association as "a chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences." According to WHO (World Health Organization) recommendations, BMI (Body Mass Index) is commonly used to define and identify obesity. Adults are considered overweight or obese by the WHO if their BMI is between 25.0 and 29.9 and more excellent than 30.0. Class I (BMI 30.0 kg/m2-34.9 kg/m2), class II (BMI 35.0 kg/m2- 39.9 kg/m2), and class III (BMI 40.0 kg/m2) are additional severity categories for obesity. Significant individual variations in body fat percentage for a particular BMI score exist and can be linked to factors including sex, race, and age. On the other hand, underweight (18.5 kg/m2), average weight (18.5 kg/m2–23.0 kg/m2), overweight (23.0 kg/m2–27.5 kg/m2), and obese (27.5 kg/m2) are the four categories of BMI that are most commonly used in Asia. **[16]** Furthermore, compelling

evidence links the etiology of numerous diseases, including non-communicable diseases (NDs), to abdominal obesity, specifically the increase of visceral adipose tissue (VAT), or fat that sits within the peritoneum and surrounds the viscera. **[17,18]** The two types of adipose tissues (VAT & SAT) have pretty different anatomical positions inside the body. Subcutaneous adipose tissue (SAT) is the type of adipose tissue found beneath the skin. It's noteworthy to note that visceral obesity is more closely linked to increased morbidity associated with obesity than extra-abdominal (subcutaneous) obesity. **[19]**

A short overview of adipose tissue

Adipocytes, or fat cells, are the primary building blocks of adipose tissue. Most of the body's fatty tissue (AT) comprises white and brown adipose tissue (WAT and BAT), visibly distinguishable based on tissue color. **[20]** Other types of these cells include pink and beige adipocytes. **[21]** In most mammals, including humans, WAT is the most significant proportion of AT. WAT is essential for energy storage, endocrine communication, and insulin sensitivity. BAT, on the other hand, predominates in mammals postnatally and during hibernation. Interestingly, BAT and WAT differ in terms of shape, size, and intracellular organelle organization. The thermogenic activity of brown adipocytes is conferred by the presence of uncoupling protein 1 (UCP-1), a proton transporter that uncouples the ATP (energy)-generating proton gradient from producing ATP and instead allows for concurrent heat production as protons flow back into the mitochondrial matrix. **[22]** Interestingly, adipocytes, which are white fat cells, can increase to around 100 m in diameter and store more lipids than brown fat cells, which typically only reach a diameter of 15 to 50 m. Importantly, data generally corroborate the theory that sustained positive energy balance causes brown adipocytes to transdifferentiate into white adipocytes, augmenting energy reserves. This could potentially diminish the detrimental effects of excessive fat deposition by reducing the burden of fat droplets on overworked pre-existing white adipocytes. **[23-25]**

The term "beige adipocytes" refers to neither brown nor white adipocytes that are cheerful (UCP-1), located in WAT, and able to generate heat through thermogenesis. One of the distinguishing features of beige adipocytes is their capacity for a flexible phenotypic. Although specific stimuli from environmental changes like cold temperatures can cause mature white adipocytes to transform into beige adipocytes, beige adipocytes can also arise from precursor cells. **[26,27]** On the other hand, a 2014 study found that pink adipocytes were initially identified in the subcutaneous WAT of pregnant female mice on days 17–18 and remained there until lactation. **[28]** There is no conclusive proof that pink adipocytes exist in humans. Furthermore, in addition to adipocytes, AT also includes endothelial cells, blood cells, fibroblasts, pericytes, preadipocytes, macrophages, different immune cell types, and stem cells. The group of non-adipocyte cell types known as the AT stromal vascular fraction (SVF) work together to regulate the immunological response, exhibit remarkable flexibility in adapting to the host environment, and facilitate the formation of a strong, self-assembled, intricately networked adult vasculature. **[29,30]**

The physiological roles of adipose tissue

Interest in the biology of AT has significantly increased from what was once just thought of as an organ for storing triglycerides. Instead, AT is becoming better understood as a metabolically active organ that serves as the body's central repository for extra energy and as a crucial endocrine organ, producing a variety of biologically active substances that control metabolic homeostasis. **[31]** These calls for a deeper comprehension of the physiological functions of adipose tissue.

Adipose tissue in the regulation of lipid storage and metabolism

Adipose tissue, specifically white adipocytes, which store body fat as neutral TAGs (triacylglycerol), is mammals' primary energy reserve. When there's a surplus of energy, adipocytes store TAG; when there's a deficiency, like during fasting, they release fatty acids to supply energy to other tissues. **[32]** Adipocytes must achieve a balance between lipogenesis and lipolysis to maintain energy homeostasis. Lipolysis, a tightly controlled biochemical process that generates glycerol and FFAs, results from the enzymatic cleavage of TAGs by lipases, which is most frequent in AT, where most TAG is stored. **[33]** Moreover, these breakdown products can either be re- esterified inside the adipocyte or released into the bloodstream to be utilized by peripheral tissues like the liver for gluconeogenesis **[34]** and oxidative phosphorylation **[35]** by muscle or other oxidative tissues.

The secretory functions of adipose tissue

AT secretes many mediators that function in paracrine and endocrine processes, including exosomes, miRNA, lipids, inflammatory cytokines, and peptide hormones.**[36]** These mediators participate in various physiological and pathological processes through extensive systemic effects in a complicated web of interconnections whose specifics are now beginning to be understood. WAT is the most extensive endocrine tissue in humans due to its capacity to release a wide range of substances with endocrine functions, such as hormones, growth factors, enzymes, cytokines, complements, and matrix proteins. **[19,20,36]** Among the substances secreted by WAT that contribute to its multifunctional nature as an endocrine organ are adiponectin, leptin, angiotensin, resistin, visfatin, acylation stimulating protein (ASP), glucocorticoids, tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and free fatty acids (FFAs). **[37,38]** For example, the WAT secretes a small peptide (16 kDa) known as leptin. Leptin levels are more significant in obese individuals and rise in response to overeating. Conversely, lean individuals have lower blood levels of leptin, and fasting lowers blood levels of leptin, demonstrating the relationship between leptin and the body's energy state. **[39]** First discovered in 1995, the adipokine adiponectin is released by AT. Adipocytes are the only cells that produce the 30 kDa full-length protein (fAdp), which circulates in trimeric, hexameric, and higher-order complexes. **[40,41]** In models of genetic and diet-induced obesity, adiponectin has been shown to boost overall body

insulin sensitivity. In skeletal muscle and adipose tissue, adiponectin also promotes fatty acid oxidation and glucose uptake; this effect is primarily mediated by AMP-activated protein kinase (AMPK) signaling. **[40-43]** Visfatin, a highly conserved 52 kDa protein prevalent in VAT and produced mainly through adipocytes but also by macrophages of the VAT and, to a lesser extent, by SAT, is an additional example of an adipokine. **[44]**

The function of adipose tissue in insulin sensitivity

An increasing amount of data indicates that adipocytes react to insulin in a manner that contributes to maintaining the homeostasis of nutrients in the body and that alterations in adipocyte function significantly influence the physiological actions of insulin. **[11,12,45]** This is demonstrated by the fact that insulin can reversibly and quickly (by 2–10 fold) accelerate glucose uptake in isolated adipocytes and muscle cells, a phenomenon known as insulin-stimulated glucose uptake. **[46]** An increase in the quantity of the glucose transporter GLUT4 in the plasma membrane is caused by insulin-induced translocation of GLUT4 from intracellular storage pools to the cell surface. As a result, adipocytes are master controllers of glucose/insulin homeostasis and systemic energy balance, as is increasingly clear from several research on insulin- stimulated glucose uptake by adipose tissue. Insulin inhibits lipolysis in adipocytes, which is a crucial method via which it regulates systemic metabolism. **[47]** By controlling the movement of fatty acids and glycerol into the liver, insulin's anti-lipolytic effect links the metabolism of adipose tissue to hepatic gluconeogenesis. **[48]** Additional evidence points to the role of insulin in regulating adipose tissue remodeling in adaptive energy balance. **[49]**

Obesity accelerates the development of neurological diseases.

Numerous epidemiological studies over the years have suggested that obesity plays a significant role in the development of both communicable and non-communicable diseases, including type 2 diabetes (T2D), cardiovascular diseases (CVDs), cancer, liver diseases, mainly non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and other disorders, especially neurological diseases, placing a significant burden on the general population and the healthcare system each year. **[50,51]** Although incredible progress has been made over the years in understanding the underlying mechanisms of obesity development in numerous preclinical and clinical studies, the progression and pathogenesis of obesity, particularly obesity-induced diseases, are complex and unclear to date. This calls for a deeper understanding of their connection to better guide treating obesity and associated diseases. Nevertheless, the exact mechanism by which obesity impairs cognitive function and psychological well-being is still unknown. The current evidence linking weight gain and brain function appears less conclusive. Therefore, it is critical to examine the roles played by several elements connecting obesity to neurological diseases and underlying mechanisms, which are crucial for therapeutic interventions, to establish the direct effect of obesity on brain physiology.

Obesity and neurological diseases: the mechanistic connection

In recent years, increasing attention has been given to the relationship of obesity with the development of brain diseases, including depression, NDs, dementia, and vascular dementia. **[52,53]** The central nervous system (CNS) is affected by obesity in several ways, including structural changes, such as brain atrophy, decreased grey matter volume in the frontal and temporal lobes, enlarged orbitofrontal white matter, and compromised integrity of the hippocampus and hypothalamus. **[54]** Changes in eating habits and control over satiety, a higher risk of dementia, mood disorders such as anxiety and depression, and physiological changes such as cerebral ischemia and hypoperfusion, decreased brain metabolism including mitochondria dysfunctions (MD), and nerve dysfunctions are just a few of the pathological changes linked to obesity in the CNS. **[55,56]** Moreover, obesity has a significant impact on the peripheral nervous system (PNS), leading to conditions like organ damage from chronic sympathetic nervous system activation, loss of peripheral sensory neurons, sensory polyneuropathy, which includes early-onset pain, and decreased motor and sensory nerve function, etc. **[57,58]**

Obesity And Endothelial Dysfunction

In the past two decades, it has been increasingly clear that the vascular endothelium functions as an active paracrine, endocrine, and autocrine organ essential for controlling vascular tone and preserving vascular homeostasis. **[59]** For instance, endothelial dysfunction, characterized by significant changes in endothelial physiology, is a critical first step in the onset and development of cardiovascular diseases (CVDs). **[60]** Moreover, a higher risk of cerebrovascular events such as stroke, stenosis, aneurysms, and vascular malformations is linked to coronary endothelial dysfunction. **[61]** Importantly, obesity-induced inflammation is one of the primary mediators of endothelial dysfunction. **[62]** Endothelial-mesenchymal transition (EndoMT), a cellular differentiation process in which endothelial cells (ECs) gradually lose their properties and differentiate into mesenchymal cells, has been observed during development and in several adult pathological states. **[63]** For example, the downregulation of brain endothelial markers and the overexpression of mesenchymal markers linked to the EndoMT transition are usually followed by cytoskeleton reorganization-related morphological alterations, resulting in BBB malfunction. It is well accepted that inflammatory mediators like IL- 1β, TNF-α, nuclear factor kappa B (NF-κB) transcription factor, and endotoxins can activate EC and cause them to undergo the EndoMT process, which transforms them into cells that resemble mesenchymal tissue. **[64,65]** Emerging data indicates that the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome may be crucial in endothelial dysfunction in addition to its traditional role as a sensor of integrated immune response. **[66]** Furthermore, numerous investigations have revealed that the NLRP3 inflammasome triggers insulin resistance and

inflammation brought on by obesity. **[67,68]** It is noteworthy that the activation of the NLRP3 inflammasome by amyloid-β linked to AD exacerbates the severity of cerebrovascular disorders. **[69,70]**

Obesity-induced dysregulation of the blood-brain barrier

The blood-brain barrier (BBB) comprises tight junctions, specialized endothelial cells, and other elements that closely regulate the flow of molecules into and out of the brain. Its main job is to keep the CNS secure from harmful substances while enabling the movement of essential nutrients and signaling molecules. **[71]** Disruption of this delicate equilibrium can have profound effects on brain function. However, when a person is obese, this barrier becomes dysregulated, which may have adverse effects on brain function.

[72] Obesity-induced inflammation plays a pivotal role in the dysregulation of the BBB. **[73]** Adipose tissues, particularly in obese individuals, produces pro-inflammatory cytokines that can compromise the integrity of the endothelial cells forming the BBB. As inflammation escalates, the tight junctions between these cells weaken, allowing the entry of substances that would usually be restricted. **[71-73]** Obesity is often accompanied by insulin resistance, a condition where cells become less responsive to insulin. Insulin, beyond its role in glucose regulation, has neuroprotective functions. **[74]** Insulin resistance in the brain can contribute to neuroinflammation and further compromise BBB integrity. **[75]** This initiates a deleterious cycle in which neuroinflammation makes insulin resistance worse, resulting in an adverse feedback loop. Leptin and ghrelin, hormones associated with appetite regulation, also influence BBB function. **[76]** These hormones can become dysregulated in obesity, which can influence the permeability of the BBB and lead to neuroinflammation. This, in turn, is implicated in various neurological conditions, including cognitive decline, mood disorders, and other neurological disorders. **[77]** For instance, prolonged microglia activation due to neuroinflammation can lead to extensive remodeling of synapses and augment amyloid-β and tau pathology. **[78]**

Neurotransmitter dysregulation and obesity

Complex connections between the brain and body necessitate more than diet and exercise; they also involve a well-tuned neurotransmitter system that influences hunger, fullness, and overall metabolism. **[79]** Dopamine, a chemical messenger linked to pleasure and reward, is one of the primary neurotransmitters linked to obesity. The regulation of food intake is significantly influenced by the brain's reward pathways, namely the mesolimbic system. There is evidence that obesity-associated changes in dopamine signaling result in a reduced response to rewards related to food. **[79,80]** Because people seek more food to compensate for their diminished pleasure responses, this dampened reward sensitivity may contribute to overeating. Also, in conditions like Parkinson's disease (PD), there's a deficiency of dopamine, a neurotransmitter crucial for motor control. **[81]** The typical motor symptoms, like stiffness and tremors, are brought on by this impairment. By contrast, excessive dopamine transmission is linked to disorders such as schizophrenia, which cause disruptions in perception and thinking processes. **[82]** Often referred to as the "feel-good" neurotransmitter, serotonin also controls mood and hunger. **[83]** Disturbances in serotonin signaling may occur in obesity, leading to a dysregulated appetite control system. Similarly, in Alzheimer's disease (AD), disruptions in acetylcholine, another neurotransmitter, are observed, affecting memory and cognitive function. **[84]** Beyond classical neurotransmitters, hormones like leptin and ghrelin intricately modulate the brain's response to hunger and satiety. **[39,85]** In obesity, there is often resistance to leptin's effects, leading to an impaired ability to regulate food intake. Conversely, ghrelin increases appetite and is often seen in higher levels in obese people, which leads to a decrease in energy expenditure and an increase in food intake. **[86]** Additionally, the complicated balance of energy homeostasis is mediated by the principal excitatory and inhibitory neurotransmitters, glutamate and gamma-aminobutyric acid (GABA). **[87]** Imbalances in these neurotransmitter systems may impact the brain's ability to regulate food intake and energy expenditure, further contributing to the development and persistence of obesity. Dysregulated neurotransmitters perturb a complex balance that regulates mood, reward, and hunger, which makes it challenging to maintain healthy weight control. **[88]**

Neurological disorders and insulin resistance: Consequences for cognition

It has been demonstrated that prolonged high-fat diets (HFDs) increase insulin resistance in both the peripheral and central regions, corroborating the previous theory that suggested obesity could lead to insulin resistance and increase the risk of neurological diseases. **[89]** An increasing amount of studies indicate that insulin affects memory and cognition, has neuroprotective effects, and functions as a neuromodulator in the brain. **[90]** For instance, glutamate, a neurotransmitter crucial to sustaining synaptic transmission, may be released at the synaptic numberons in response to insulin. Therefore, brain insulin resistance may affect the neuromodulatory properties of insulin. **[91]** Furthermore, an overabundance of free fatty acids (FFAs) is present when peripheral insulin resistance occurs, and this causes the bloodstream to release cytokines that promote inflammation. **[92]** The body may become more insulin resistant due to these cytokines' ability to activate several further serine kinases, including c-Jun N-terminal kinase (JNK) and IκB kinase (IKK). **[93]** Insulin signaling in the brain may be compromised, impairing the physiological functions of multiple brain cell types. **[94]** Also, insulin resistance aggravates neuroinflammation, which results in aberrant tau phosphorylation and the deposition of amyloid β- protein linked to AD. **[95]** More evidence linking insulin resistance to cognitive impairment has been provided by intranasal insulin delivery, which has improved memory function in people with early AD or MCI (mild cognitive impairment). **[96]** Moreover, there seems to be a considerable link between peripheral and brain insulin resistance, even though the BBB protects the brain from systemic alterations. **[97]** This is corroborated by a prior study that found a reduction in

brain insulin sensitivity and a decrease in brain insulin signaling pathways were linked to the development of brain insulin resistance after 12 weeks of HFD intake. **[98]** Peripheral insulin resistance may be an early stage in the development of obesity, leading to the development of central insulin resistance. A likely explanation is that increased hepatic lipid synthesis, especially of ceramides (composed of fatty acids and sphingosines), results from peripheral insulin resistance. **[99]** Ceramide's lipid-soluble properties, such as its ability to inhibit insulin signaling, are widely known. Consequently, ceramide may be more Readily cross the weakened BBB following obesity due to oxidative stress and systemic inflammation, which may impact the brain's insulin sensitivity. **[100]**

Obesity-induced inflammation and oxidative stress, and neurological diseases

Over time, the association between obesity and localized and systemic inflammation has been attributed to the overexpression of pro-inflammatory cytokines in obese individuals. **[66,67,101]** AT reacts to the stimulation of additional nutrients by causing adipocytes to hyperplasia and hypertrophy. **[102]** Hypoxia can occur when there is a decrease in the blood flow to adipocytes due to obesity and progressive adipocyte growth. **[103]** The induction of necrosis and macrophage infiltration into AT, which results in the overproduction of pro-inflammatory mediators, is thought to be triggered by hypoxia. **[104]** This leads to localized AT inflammation and spreads throughout the body, contributing to the emergence of obesity-related comorbidities. Systemic pro-inflammatory cytokines derived from AT can cross BBB and enter the brain. This can lead to excessive neuroinflammation, which is a major pathological factor in several neurological conditions, including multiple sclerosis (MS), epilepsy, traumatic brain and spinal cord injuries, NDs, and chronic pain. **[105]** Numerous detrimental effects have been associated with this activation, such as increased levels of pro- inflammatory cytokines, neurotransmitter dysregulation, probable induction of neuronal degeneration, increased oxidative stress, MD, disruption of the BBB, and cognitive dysfunction, among others. To be more precise, obesity-induced neuroinflammation causes increased formation of reactive oxygen species (ROS) through MD. **[106]** This, in turn, may impede synaptic function and axonal transport in the central nervous system (CNS), particularly in the hippocampal neurons. **[107]** Notably, amyloid-β plaques produce more ROS, exacerbating ROS activity's dysregulation, which is crucial for memory consolidation and long-term potentiation. **[108]** Furthermore, there is proof that AD pathology and bone marrow- derived macrophage recruitment into the brain are both facilitated by neuroinflammation. **[109]** This highlights the common signaling pathway between obesity and AD. Also, the MI subtype of microglial cells is activated in chronic pro-inflammatory settings, characterized by a decrease in phagocytic activity and an ensuing impairment in amyloid-β clearance. **[110]** Numerous genetic investigations have connected many AD risk alleles to genes expressed predominantly or exclusively in microglia. **[111]**

Neurological diseases are linked to inflammation through dysfunctional mitochondria.

The synthesis of ATP, energy expenditure, and ROS disposal are all largely dependent on mitochondria. When their mitochondria function properly, adipocytes can only help sustain the right balance between energy storage and consumption. **[112]** Importantly, due to the high energy requirements of neural cells, the mitochondrial apparatus is crucial in maintaining a steady supply of energy to support neuronal cell function. Thus, neurological diseases like NDs may be caused by MD. **[113]** Obese persons are thought to be more susceptible to AD, which is associated with aging. A longitudinal study with an 18-year follow-up showed that older women with AD had higher levels of overweight. Additionally, studies have indicated that an elevated body mass index (BMI) is associated with significantly lower performance on cognitive evaluations and a progressive decline in cognitive abilities over time for both men and women. **[114]** It is interesting to note that obesity-induced cognitive impairment, which may also result in NDs, is significantly influenced by neuroinflammation, particularly in the hippocampus and hypothalamus. **[115]** MD can often lead to anomalies in the mitochondrial membrane and endoplasmic reticulum (ER) stress. **[116]** There have been reports linking increased ER stress in the hypothalamus to diet-induced obesity and genetic factors in mice. **[117,118]**

The link between free fatty acids and neurological diseases

Epidemiological research has shown that diets high in saturated fats are linked to deficits in memory and learning and that metabolic illnesses, such as obesity and T2D, are related to an increased risk of AD. **[119,120]** For example, low HDL cholesterol, high blood cholesterol, and familial hypercholesterolemia are known risk factors for AD, even though the CNS's cholesterol pool differs from the systemic pool. **[119]** Moreover, increased levels of FFAs, along with the metabolic intermediates acyl-carnitines and acyl-CoA, can cause neurotoxicity and disrupt mitochondrial function. **[121]** Changes in FFA levels in AD indicate disruptions to brain fatty acid metabolism. Additionally, emerging evidence suggests that elevated levels of FFAs may contribute to neuroinflammation, a common feature in many neurological diseases. **[122]** Increased FFAs have been linked to pro-inflammatory cytokine release and microglial activation in diseases including Parkinson's and Alzheimer's, which contribute to a chronic inflammatory milieu in the brain. **[123]** Excessive FFAs can also induce oxidative stress, which has been implicated in the pathogenesis of several neurological disorders, including multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), potentially linking FFAs to the underlying mechanisms of these diseases. **[124]** Last but not least, increased FFAs might cause insulin signaling disruptions, leading to cognitive impairment and a higher chance of developing NDs. **[125]**

The role of glucolipotoxicity in the emergence of neurological diseases

An increasing amount of evidence indicates that obesity is the primary source of lipotoxicity and a significant risk factor for neurological conditions like AD as well as T2D. **[126]** Some common molecular mechanisms in the pathophysiology of AD and T2D that are linked to lipotoxicity include inflammation, insulin resistance, oxidative stress, ceramide and amyloid accumulation, ER stress, and autophagy. **[126]**, while extensively studied in the context of diabetes and metabolic disorders, the direct role of glucolipotoxicity and neurological diseases is not fully established. It is, therefore, tempting to believe that neurological conditions will likely worsen as a result of glucolipotoxicity linked to metabolic disorders, specifically T2D associated with obesity. **[127]** Ongoing studies aim to unravel the specific connections between elevated glucose and lipid levels and the development of neurological diseases.

Obesity is closely associated with NDs such as AD and PD, and it may have unknown effects on the emergence of other neurological diseases. However, much has to be discovered on the processes linking obesity to these chronic diseases. Therefore, more research on experiments and intervention is required to understand better the pathways that are particularly important for the pathophysiology or treatment of various neural disorders in humans.

Conclusion & Future Directions

The prevalence of overweight and obesity is currently surpassing undernutrition and the concomitant underweight population in many developing countries. There are significant socioeconomic ramifications for obesity research because even malnutrition and undernutrition can lead to abdominal adiposity and the metabolic syndrome that goes along with it, which can accelerate the onset of neurological diseases. More importantly, the link between obesity and neurological disorders has significant clinical implications. For instance, stroke risk is elevated in individuals with obesity due to factors such as hypertension, diabetes, and atherosclerosis. **[128]** These conditions, often associated with obesity, contribute to the development of CVDs, leading to an increased likelihood of strokes. Hence, the prevention and control of the obesity epidemic is a crucial aspect of public health policy, as it is a significant risk factor for the majority of non-communicable diseases. Prospective avenues for study concentrate on crafting customized interventions, capitalizing on breakthroughs in genetic and metabolic studies to customize therapies for specific individuals. Public health programs should also prioritize prevention and education to encourage better lifestyles in children. Ultimately, a multimodal approach will be needed to mitigate the long-term impacts of obesity on NDs. Government and non-government organizations should advocate for the benefits of a healthy lifestyle, good eating habits, and regular exercise. In addition to being essential for controlling obesity, lifestyle modifications also assist in lowering the neurological risks that are linked with it. Furthermore, early identification of obesity-related neurological issues allows for targeted interventions and a more comprehensive approach to patient care. **[129]** Healthcare providers might potentially lessen the adverse effects of obesity on brain health and enhance patient outcomes by including weight management techniques, physical activity regimens, and dietary counseling in their neurological care plans. **[130]** In the end, a comprehensive understanding of the fundamental mechanisms linking obesity to the neurological disorders covered in this article may offer new perspectives on developing more potent therapeutic strategies to lower the incidence of obesity-related neurological diseases.

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