Chapter

Diet-Induced Overweight Conditions: Effect on Brain Structure, Cognitive Function, and Neurogenesis

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Abstract

Obesity, a chronic condition that is currently prevalent in both developed and developing nations, is associated with pathological features that ultimately put individuals at risk for a number of negative health issues. Cognitive decline and insulin resistance are two aspects of metabolic syndrome that are closely linked to neurological dysfunction during obesity. Several studies suggest that obesity is associated with regional structural changes, especially signs of cortical thinning in specific brain regions like the hippocampus, and reduced microstructural integrity of the white matter tract is associated with an overall lower academic performance. Obesity causes a loss of brain size and volume indicating a loss of neurons which leads to poor cognitive performance and reduced neurogenesis. An increase in the production of free fatty acids seen with HFD eating might result in increased oxidative stress and increased production of reactive oxygen species. The main cause of systemic inflammation in obesity is the build-up of adipose as it releases TNFα, PAI-1, CRP, IL-1β, and IL-6 which contribute to a pro-inflammatory state in the central nervous system. These elements can all lead to the central IKK/NF-B inflammatory signalling cascade being activated, which can cause a vicious inflammatory cycle that quickens and causes neurodegeneration and cognitive decline.

Keywords: obesity, oxidative stress, inflammation, neurodegeneration, cognitive loss

1. Introduction

Overweight/obesity, a disease condition currently reaching epidemic proportions, particularly in industrialised countries, and linked to pathological changes that ultimately put people at risk for a variety of adverse health effects [1]. Obesity results from the accumulation of excessive body fat due to the consumption of excessive calories and is typically fuelled by western food habits and a sedentary lifestyle [2]. Food that has been processed and refined typically contains saturated fats, added

sugar, and salts, which over long-term contribute to increased calorie intake. There is much speculation and considerable debate about whether obesity-associated cognitive function is a result of weight gain, or whether it is a result of behaviours that lead to weight gain (such as hedonic overeating) [3, 4]. Body mass index (BMI) 25 and 30 are the World Health Organisation's (WHO) definitions of overweight and obesity, respectively [5]. Body mass index (BMI, kg/m^2), which divides weight (kg) by height squared (m^2), is widely used to determine obesity. Based on BMI, there are three categories: normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI 30.0 kg/m^2).

However, metabolic syndromes arise when caloric intake significantly outweighs expenditure while there is a sustained lack of physical activity. The presence of low-grade metabolic inflammation in visceral adipose tissue is also considered to be a primary component of metabolic syndrome, which is characterised by central obesity [6]. The metabolic syndrome consists of a number of risk factors that contribute to chronic non-communicable disorders such as cardiovascular diseases (CVD), type 2 diabetes, dyslipidaemia and hypertension as well as other diseases. In addition to CVD, obesity has also been linked to pathological changes in brain morphology and function and cognitive impairments [7]. Even though the central nervous system (CNS) and the peripheral nervous system (PNS) have very different structures and functions, both are vulnerable to the deleterious effects of obesity, indicating that visceral adiposity may facilitate a common pathophysiologic mechanism. The metabolic syndrome includes components that are strongly associated with neurological dysfunction, such as insulin resistance and hypertension leading to cognitive decline. Such factors are generated by obesity. As a result, several processes may be working together to cause neurological dysfunction, while it can be difficult to determine the precise impact of visceral adiposity on neurological dysfunction. Animal obesity models' mechanistic insights reveal that excessive dietary fat impairs the hypothalamic coordination of energy homeostasis [8]. This pathway may be associated with the disintegration of adipose tissue, resulting in increased levels of free fatty acids, systemic inflammation and dyslipidaemia. As a consequence of chronic calorie overconsumption, circulating triglycerides increase and are adversely affected by numerous organs, including the liver. Dyslipidaemia caused by free fatty acids can result in neurological dysfunction because of lipotoxicity and altered intracellular signalling. Despite these mechanisms affecting the CNS and PNS in multiple ways, obesity is known to have neurological complications [9].

While wide range of functions in human brain requires significant energy, there are limited energy stores in the brain, and those stores can meet only a portion of its energy requirements. The blood-brain barrier (BBB) allows nutrients to continuously enter the brain from the blood, which is how the brain obtains the necessary energy for optimal functioning. Under physiological circumstances, the brain's primary fuel source is glucose [10]. During development, and at times when glucose supply is insufficient, the brain can use alternative energy substrates such as ketone bodies, triglycerides, as well as lactate [11]. Several recent studies have demonstrated that nutrition and dietary intake have a profound effect on cognition, neuronal function, neuronal signalling, and synaptic plasticity [12, 13]. The consumption of diets rich in saturated fats has consistently been linked to impaired cognitive function, both in clinical and preclinical studies [14, 15]. It is of interest to note that adult studies suggest that consuming high-fat diets (HFD) on a short-term basis may impair attention and memory capabilities [16, 17]. Remarkably, consumption of a diet high in saturated fats is frequently cited as a cause of the cognitive decline and

the development of Alzheimer's Disease [18]. Conversely, it has been suggested that diets high in polyunsaturated fatty acids enhance cognitive health Disease [18–20]. Depending on the composition, abundance, or lack of particular nutrients, the brain can be affected in different ways by different nutrient requirements. There is a known association between consuming saturated fat-rich diets and metabolic and cardiovascular diseases [21–23]. According to a growing body of research, obese individuals, and those with diabetes and with hypertension are at high risk of developing cognitive impairments and Alzheimer's disease [18, 24–27]. Since the global burden of both neurological diseases and metabolic disorders is increasing, it is necessary to investigate common underlying mechanisms associated with these rapidly increasing disease entities. In this article, we discuss how diet-induced overweight/obesity affect the function, neurogenesis and brain composure.

2. Overweight/obesity: the pathophysiology

In addition to storing energy and releasing it, adipose tissue serves as an insulation system for internal organs and a protection against trauma. Adipokines mediate the endocrine function of adipose tissue through hormones, cytokines, acute phase reactants, and growth factors [28]. These molecules play an important role in maintaining energy homeostasis along with the liver, pancreas, and brain. The major mechanism for achieving energy balance is via controlling energy intake and energy expenditure. Calories are truly calories, and they are all equal according to this fundamental energetic equation [29]. However, when we consider the pathophysiology of obesity-related comorbidities in addition to this merely energy balance aspect, we see that not all calories are created equal [29]. In order to properly explain the pathophysiology of obesity, two simultaneous discussions—one from an energy perspective and the other from a nutritional perspective—must be included. Here, we primarily concentrate on the second because there is controversy regarding the optimal nutritional composition, whereas there is significant agreement on the principles of energy balance management [6, 30]. Managing obesity-related diseases, such as CVD, requires a clear understanding of obesity-independent and obesity-dependent pathophysiologic effects.

Based on genome-wide association studies (GWAS), more than 140 chromosomal regions are associated with obesity [31]. The central nervous system has a significantly enriched gene expression profile associated with BMI and overall obesity [32]. Nevertheless, only a small number of genes, have been found to have a significant impact on BMI thus far. These are the paternally expressed genes along a specific region of chromosome 15 that cause Prader-Willi syndrome, as well as the genes that encode elements of leptin and melanocortin signalling [33]. Most researchers concur that environment, lifestyle, and genetic predisposition contribute to obesity predisposition [34]. Scientists generally agree that increased body weight or adiposity is actively regulated and mitigated by the body under constant environmental conditions, regardless of short-term perturbations in weight or adiposity [35]. Researchers have found that obesity is often defended as a disease, diverting blame from the person to the body's physiology, just as it is for normal-weight subjects [36]. In addition to adipocytes, adipose tissue contains stromovascular compartments, which are made up of nerve endings, blood vessels, preadipocytes, fibroblasts, endothelial cells, and resident immune cells [37]. As fat-storing cells, adipocytes store triglyceride-rich lipid droplets as a source of energy. Insulin is primarily responsible for regulating adipocyte energy uptake and storage, as it mediates fatty acid influx and lipogenesis while

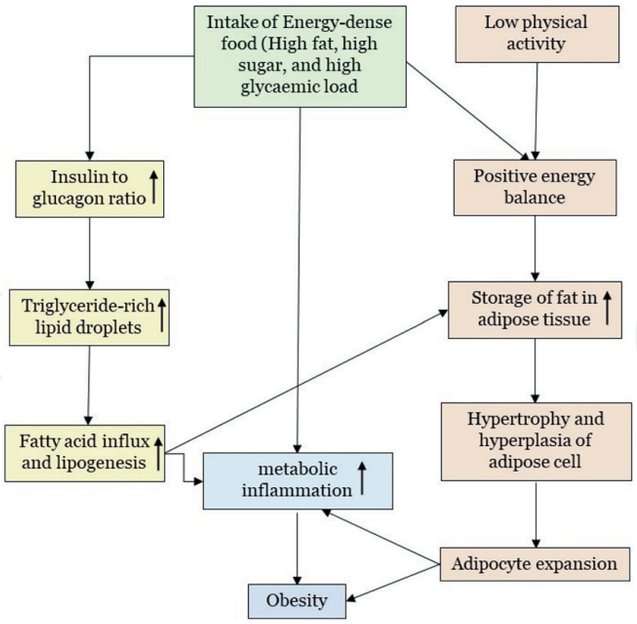

Figure 1.
Pathophysiology of obesity.

inhibiting lipolysis [38]. When adipocytes are in a negative energy balance, sympathetic neural stimulation promotes lipolysis of stored triglycerides where fatty acids are delivered into the bloodstream to feed non-adipose tissues [39]. The adipocyte undergoes hypertrophy (enlargement of adipocytes) or hyperplasia (proliferation and differentiation) when there is a positive energy balance (i.e., excess caloric intake), it causes the adipocytes to expand in order to store excess calories.

Low-grade metabolic inflammation is associated with increased adipose mass, especially visceral depots, which promote metabolic disease as a consequence of malfunctioning adipose tissue. By increasing adipose mass, especially in visceral depots, metabolic inflammation is linked to metabolic disease, which occurs when adipose tissues malfunction [6]. Adipose tissue inflammation has negative effects on adipokine release, insulin signalling, triglyceride accumulation, and basal lipolysis, among other things. These alterations produce peripheral-tissue and nervous system dysfunction because they result in elevated levels of circulating adipokines and free fatty acids Smith [40]. A chronic caloric surplus that triggers stress signalling pathways and activates local macrophages causes metabolic inflammation, which mostly affects hypertrophied adipose tissue resulting overweight and obesity (**Figure 1**).

3. The relationship between obesity and structural and functional changes in the brain

Various structural changes in the brain can be measured by changes in brain volume or density. Several studies suggest that obesity is associated with regional structural changes, especially in elderly populations [41]. Researchers have reported reduced frontal lobe, anterior cingulate gyrus, hippocampus, and thalamus volume in cognitively healthy obese older individuals. Middle-aged adults and the elderly with high BMI have also been found to have impaired frontal lobe integrity [42–44]. The volume and density of the brain are often used as indicators of structural changes.

A growing body of evidence indicates obesity is associated with regional structural changes in obese populations, especially in elderly people [41]. The hippocampus, cingulate gyrus, and frontal lobes of obese older individuals were found to have reduced volume according to a tensor-based morphometry study [44]. Middle-aged adults and the elderly with high BMI have also been shown to have damage to their frontal lobes [42, 43]. The presence of obesity has been also linked to global structural changes in the brain, including an overall reduction in grey matter and white matter volumes [44].

Grey matter volume structural anomalies in obese patients were discovered by a recent systematic review [45]. The left middle frontal gyrus left middle temporal gyrus, left amygdala, and left cerebellar hemisphere all showed a consistent decline in grey matter in obese people when compared to the control regions, according to an analysis of 10 research published up to December 2017 [41, 43, 46–53]. A study by Kurth et al. found that the superior frontal gyrus on the left, middle and inferior frontal gyri, the right frontal pole, the left insula, as well as the bilateral superior and middle temporal gyri were negatively affected by body mass index [54]. According to García García et al., obesity and body mass are associated with significantly less grey matter volume in the areas of the brain that play a crucial role in executive control [55]. Obesity-related factors are consistently linked to decreased grey matter volume in a number of regions, including the left temporal pole, bilateral cerebellum, and medial prefrontal cortex. Similar to lean and overweight persons with increasing BMI, obese people have less total grey matter volume. Yokum et al., found that future weight increase is associated with a reduced amount of grey matter in the areas involved in inhibitory regulation [56]. Weight gain is primarily the result of abnormalities in the white matter volumes of the regional spine, not in the grey matter volumes, whereas abnormalities in grey matter volumes increase the likelihood of weight gain in the future.

Similarly, here is compelling evidence that people with increased BMI experience a brain-wide white matter decrease [57, 58]. The result is in line with a major investigation that found links between increased BMI and decreased white matter integrity in two separate, sizable populations [59]. Uncinate fascicle, internal capsule, corticospinal tract, inferior fronto-occipital fascicle, inferior and superior longitudinal fascicles, corpus callosum (cingulate gyrus and hippocampus), and cingulum are just a few of the white matter regions that are known to decrease with a higher BMI [45, 48, 50]. The critical limbic structures are connected to the prefrontal regions by local changes in the white matter fibre tracts linked to greater BMI, which may help to explain why obesity in older age is associated with an increased risk for cognitive impairments and dementia [60]. Obese people could age more quickly than average people, which is thought to raise the risk of cognitive impairment [61]. The fibre tracts that link limbic systems to prefrontal regions are the most commonly affected. These abnormalities are indicative of a loss of white matter integrity brought on by demyelination or inflammatory effects, and can be described by axonal injury or cellular death [61]. The bilateral thalamus, putamen, and globus pallidus in obese individuals are larger than those of normal weight, although the bilateral caudate is smaller [62]. Even obese people (with a BMI of 25 to 30 kg/m^2) have symptoms of basal ganglia atrophy and radiating crown [44].

Yau et al. [63] found evidence of cortical thinning in some areas of the brain and decreased microstructural quality of the white matter circuit in obese adolescents. In this study, obese youths performed no worse in cognitive tests than non-obese youths, but structural impairments were associated with a lower academic performance overall [63]. While these findings, do not prove causality,

it is biologically conceivable to connect brain anatomical alterations to impaired cognitive function. Poor cognitive performance can be linked causally to smaller brain sizes and volumes since these changes are suggestive of a loss of neurons. Adolescents who are obese may show signs of brain abnormalities, but it may take them until later in life for these changes to cause cognitive impairment. In the early phases of cognitive decline, advanced brain imaging techniques that are more likely to detect anatomical micro alterations do not immediately translate into cognitive dysfunction [64]. As a result, it is particularly important to examine how obesity affects brain function by integrating physiological assessment with cognitive tests. [65] investigated the impact of weight loss (sustained fasting) on brain function in obese persons [65]. Fourteen subjects in this study met the BMI criteria for being classified as obese. During an overnight fast, a 48-hour fast, and an 8-week weight loss programme, brain imaging data were collected using whole-brain resting-state functional magnetic resonance imaging (MRI). The weight loss intervention, according to the researchers, decreased activation in the brain regions in charge of salience, sensory-motor control, and executive control, indicating a connection between weight loss and changes in neurological activity brought on by obesity [65].

A recent meta-analysis on anomalies in brain structure and obesity was undertaken by Opel et al. who also took into account the effects of ageing, hereditary risk, and psychiatric problems [66]. This study involved 6420 participants and examined the relationship between obesity (BMI > 30 kg/m^2) and brain anatomy. Results showed a strong relationship between obesity and cortical and subcortical abnormalities, particularly in the lower temporal-frontal cortex thickness. Cortical thickness was influenced by the combination of age and a higher polygenic risk score [66].

4. Cognitive effects of diet-induced obesity/overweight

Cognitive impairment can be caused by obesity when the physiology of the human energy system is impaired. In addition to affecting cognition and the Central Nervous System (CNS), obesity may also affect verbal learning, executive function, and decision-making [67]. An individual's cognitive function plays an important role in acquiring knowledge and information through the constant use of language, memory, and attention [68]. The effects of obesity on cognitive function can be attributed to structural and functional changes in the brain [69–71]. In executive functioning tests, obese females performed worse than normal-weight females. There was a reduction in grey matter volume in the left orbitofrontal region associated with a decrease in executive functioning [71]. Older people who are obese during midlife are more likely to develop dementia [72]. Several CVD risks factors, including obesity, T2D, dyslipidaemia, and hypertension, were demonstrated to negatively impact cognition in a systematic review [73]. According to studies, older women who have more body fat have poorer cognitive functioning [71].

5. Childhood obesity and cognitive functions

With childhood obesity is currently on the rise, deficits in attention and cognitive flexibility have been linked to childhood obesity [74]. According to cross-sectional

research on overweight children, overweight status was linked to worse test scores, particularly in the areas of arithmetic, reading, and executive function, while being physically fit was linked to better cognition performance, and behaviour [75]. Children who are overweight struggle with spatial cognitive tasks, and studies have revealed variations in both motor and mental rotation efficiency [76]. When rotation activities were challenging, overweight children made more mistakes than children of average weight [76]. Obesity can affect cognitive abilities, particularly executive abilities, in children and adolescents [77, 78]. According to studies, adolescents who are obese have lower executive and attentional cognitive abilities [79, 80]. Insufficient cognitive domains, including executive function and attention deficits, were found in obese adolescents in pilot research [79].

Data analysis from the general population revealed links between gender-specific features of developmental functioning with obesity and impairment [81]. Infants with high subcutaneous fat and children who are overweight or obese had delayed motor development [82]. It has been demonstrated that overweight children have significantly worse perceived and actual physical competence [83]. Overweight children had varying levels of difficulty with basic motor skills [84]. Compared to their peers who were of a healthy weight, obese children reported reduced degrees of gross motor function. The most significant variations were found in balance and locomotor abilities [85]. In comparison to children who were of a healthy weight, children who were overweight performed less effectively in the domains of intelligence, coordination, and gross motor abilities [86]. Significant abnormalities in gross and fine motor skills related to weight were observed in obese children [87].

5.1 Possible mechanisms for cognitive impairment driven by diet-induced overweight

5.1.1 Role of oxidative stress on cognitive impairment

The brain is thought to be the organ most susceptible to harm from oxidative stress [88]. This is explained by the greater lipid content, the high oxygen demand, and the scarcity of antioxidant enzymes [11]. Consistent overnutrition brought on by HFD diet may result in an abundance of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [89]. Because of the excessive production of these species, macromolecules like DNA, membrane lipids, and protein structures are harmed [90]. Reduced glutathione, catalase, and superoxide dismutase act as endogenous antioxidant enzymes to neutralise these free radicals. A high fat diet causes excessive ROS production that exceeds the antioxidant enzymes' capacity [91].

Here, it is briefly mentioned how an HFD diet might leads to increased oxidative stress. HFD consumption results in an increase in free fatty acid production. In the normal diet-feeding process, electrons are transferred from cofactors (NADH and FADH2) to complex I of the mitochondrial respiratory chain, where they combine safely with oxygen and protons to form water [92]. Free fatty acids are then oxidised in the mitochondria through the mitochondrial respiratory chain. Superoxide radicals are created when some of these electrons interact with oxygen. Conversely, HFD feeding results in increased mitochondrial -oxidation of FFAs, resulting in increased levels of superoxide anion and an excess electron flow [92, 93]. The natural antioxidant enzymes can also be consumed by ROS, which increases the risk of oxidative injury to the brain [92, 94]. According to a growing body of research, the development of cognitive decline and increased oxidative stress may be correlated, [95–98]. These

findings suggest that increased oxidative stress is a major contributor to the cognitive abnormalities caused by HFD.

Many studies have demonstrated that HFD eating causes the levels of oxidative stress indicators in the brain to increase [99–104]. One of the most delicate areas of the brain to suffer from selective oxidative stress damage is the neocortex and hippocampal region. The impairment of cognition is also closely related to hippocampal oxidative stress [105–108]. Researchers have used antioxidant therapy to demonstrate cognitive benefits in support of the idea that oxidative stress may be a potential mechanism underlying the cognitive impairment associated with HFD eating. In HFD-fed mice, deficiencies can be restored by employing this strategy [99, 109, 110].

5.1.2 Role of neuroinflammation on cognitive impairment

Inflammation is controlled in a variety of ways by macrophages, depending on their differentiation level. Traditionally activated macrophages (M1) release pro-inflammatory cytokines and reactive oxygen species (ROS) to initiate an immune response, whereas alternatively activated macrophages (M2) reduce inflammation, promote tissue remodelling, and release growth factors in the later stages of an immune response [111]. Adipose tissue macrophages in healthy, nonobese humans appear to act similarly to M2 macrophages in that they contain arginase, which limits nitric oxide synthesis and promotes polyamine synthesis, and they release little to no proinflammatory cytokines [112]. Chemokine CCL2, formerly called monocyte chemotactic protein-1 (MCP1), is released by macrophages. TNF and IL-6 are also macrophage-released cytokines [113]. It is possible for M1 and M2 macrophages to coexist, which might result in fibrosis and prolonged inflammation [114]. Systemic inflammation in obesity is the result of build-up of adipose tissue and the increase in the levels of tumour necrosis factor-alpha (TNF-α), plasminogen activator inhibitor-1, C-reactive protein, interleukin-1-beta (IL-1β), and interleukin-6 (IL-6), Adipose tissue, particularly lymphocytes and macrophages, contains hypertrophic adipocytes and immune cells that contribute to inflammation [115, 116]. It is possible that processes of necrotic clearance are similar to inflammatory responses mediated by M1 in obese individuals [117, 118]. Macrophages release chemokines like CC-chemokine ligand 2 (CCL2; formerly known as monocyte chemotactic protein-1 (MCP1)) and cytokines like TNF and IL-6. Type 2 diabetes (T2DM) might result from interference in insulin signalling pathway in adipocytes caused by TNF and IL-6 [119]. Over time, macrophages build up in adipose tissue, and the cytokines they release can cause insulin resistance and T2DM [112, 113]. These inflammatory macrophages can increase atherogenic and CVD risks that are a feature of the metabolic syndrome associated with obesity by overexpressing procoagulant proteins [119].

5.1.3 Effects of gut dysbiosis on obesity-related disorders

Abnormalities in neurochemistry and inflammation may also be caused by the gut microbiota associated with obesity [120, 121]. The modification of the gut microbiota, or dysbiosis, can help to explain obesity since it is a factor that is central to host physiology and environmental stressors (such as diet and lifestyle) [120].

Gut dysbiosis (imbalance in gut microbiota composition caused by host genetics, lifestyle, and exposure to microorganisms) may facilitate diet-induced obesity and metabolic complications through a variety of mechanisms, including immune

dysregulation, altered energy regulation, altered gut hormone regulation, and proinflammatory mechanisms (such as lipopolysaccharide endotoxins that cross the gut barrier and enter the portal circulation) [121–123]. Recent studies have indicated that changes in the composition of the gut and inflammation brought on by a leaky gut may have an impact on the pathophysiology of many disorders, such as depression, chronic fatigue syndrome, obesity, and type 2 diabetes (T2DM) (a loss of intestinal barrier integrity that reduces the ability of the gut to protect the internal environment) [124].

Obesity-related inflammation can impact the amygdala, cerebral cortex, hippocampus, and brain stem [125]. Numerous routes, including alteration of the blood–brain barrier (BBB) and choroid plexuses, have been used to link obesity-related low-grade inflammation to neuroinflammation [126]. Insulin resistance is caused by peripheral inflammation, which is seen in obesity [112, 113]. Although it is widely acknowledged that the brain plays a special role in immunity, there have been some instances of transitions between peripheral and central inflammation. It is also possible to express adipokines in the CNS, where these factors have receptors. Adipose tissue produces adipokines, which are expressed in the CNS as well. Peripherally produced adipokines can influence the CNS by crossing the BBB or changing its physiology by interacting with the cells that make up the BBB [127]. There is a strong correlation between neuroinflammation and oxidative stress and a wide range of chronic neurodegenerative diseases [128]. These processes can be regulated by adipokines. Inflammation in the brain can also result from damage to the BBB with ageing [129]. The most significant contributor to cognitive dysfunction may be neuroinflammation, which might also act as a primary pathogenic mechanism for ageing [130].

There is a connection between the activation states of cytokines and chemokines produced by different cell types in adipose tissue outside the central nervous system (quiescent or activated). Obesity and neurodegeneration are linked via the production of inflammatory cytokines and resistance to insulin-like growth factor 1 (IGF-1) [115, 116, 128, 130, 131]. As a result of central inflammation in obesity, hypothalamic satiety signals are interrupted, which perpetuates overeating and has negative consequences for cognition [132]. Different disorders associated with ageing are also thought to be influenced by chronic inflammation. Peripheral inflammation and associated metabolic abnormalities promote T2DM, insulin resistance, and neurodegenerative diseases [133]. In the abdominal adipose tissue, macrophages promote the synthesis of cytokines and proinflammatory chemokines that can cross the BBB. Interferon-gamma can activate microglia, which then serve as relays for neuroinflammation [134].

A number of pathological mechanisms are exacerbated by hypertension, diabetes, and obesity, including cerebral hypoperfusion and glucose hypometabolism. Neuroinflammation and oxidative-nitrosative stress are triggered by these risk factors. There are several cycles of pathological feedback caused by proinflammatory cytokines, endothelin1, and oxidative-nitrosative stress [135]. These cascades cause neurodegeneration and an increase in neuronal Ca2+ [60]. Long-term damage to mitochondria, proteins, DNA, and fatty acids is promoted by oxidative-nitrosative stress. These elements magnify and sustain a variety of problematic feedback loops [136]. Chronic cerebral hypoperfusion results from dysfunctional energy metabolism (compromised mitochondrial ATP production), formation of -amyloid, endothelial dysfunction, and modification of the BBB [115, 130]. Hypoperfusion deprives the brain of oxygen and nutrition, which are its two most critical trophic factors. As a result, the brain experiences synaptic dysfunction and neuronal death,

which causes grey and white matter atrophy [136]. The decline of M2 macrophages in the CNS is associated with many neurodegenerative diseases and the subsequent increase of M1-induced inflammation [134]. Microglia and macrophages express the macrophage-stimulating protein receptor (MST1R). In the periphery, obesity-mediated inflammation is attenuated by activating MST1R with its ligand, a macrophage-stimulating protein. Cleavage to the MST1R ligand in vivo regulates the activation of macrophage-dependent repair (M2) [137]. Apoptosis can be caused by neuroinflammation [138]. Its fundamental physiological function, which helps to maintain homeostasis, is a tightly controlled process of cell death. A variety of proteins, signal transducers, and signalling pathway cascades collaborate to fully implement apoptosis [139]. Numerous disorders' origin and/or progression are strongly correlated with poor apoptotic regulation [138, 140]. TRAIL, TNF, and Fas ligand (Fas-L) bind to the extracellular domain of DR (transmembrane receptors) to initiate the TNF pathway, the main apoptosis pathway [138–140]. During an inflammatory response, TNF- and Fas-L can cause certain neurons to apoptose [138].

Caspases, which are cysteine proteases, are activated during apoptosis, which controls all of the morphological changes that distinguish this type of cell death [138]. Activating effector caspases (caspases 3, 6, and 7) via a controlled, irreversible, and self-amplifying proteolytic route begins with activating initiator caspases (caspases 2, 8, or 10) [141].

6. Obesity and impaired neurogenesis

It has now been proven beyond a shadow of a doubt that neurogenesis takes place in specific parts of the adult brain, debunking the long-held belief that brain cells lack any capacity for regeneration [142]. Neuronal stem cells (NSCs) in the CNS of adult mammals may now be isolated and identified toas a result of advances in science and technology. Even though adult neurogenesis was first observed in the 1960s, multiple articles have argued that adult mammalian brains do not show any indications of neurogenesis [143–145]. Adult hippocampal neurogenesis in mammals, including rodents was not "rediscover[ed]" for another three decades [146, 147]. When these freshly produced cells' "stem-like" properties were first identified in the 1990s, it was believed that NSCs could auto replicate and give rise to a variety of neural lineages in adult mammalian brains, including neurons, astrocytes, and oligodendrocytes [148–150]. Later research showed that NSCs were mostly found in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampus dentate gyrus in the adult central CNS [151]. The functional integrity and plasticity of these brain regions are thought to be maintained by these adult NSCs by initiating neurogenesis in response to intrinsic and extrinsic changes, which is consistent with the observation that neurogenesis was also highly prevalent around these regions in adult mammalian brain [152]. Recent research indicates that multipotent NSCs, which have the capacity to differentiate into new neurons as well as astrocytes and oligodendrocytes, can be reprogrammed to grow in the adult mouse hypothalamus in the medio basal region of the hypothalamus (MBH) and the third ventricle wall [153]. These newly formed neurons in the adult mouse hypothalamus could integrate into the existing neuronal network and have recently been shown to be functionally active [154].

Several decades ago, neurogenesis in the adult brain was considered impossible and was refuted, but it has now been widely acknowledged as a very common phenomenon [146, 148]. Many brain regions are abundant in new neurons and NSCs

[146]. The hypothalamus, which houses the body's neuroendocrine system, has recently been found to be both a rich NSC niche and a hotspot of neurogenesis [153]. It is believed that these hypothalamic NSCs play a key role in the neuroendocrine modulation of whole-body physiology [155–157] as well as systemic ageing [158]. Through local or extrinsic insults to this hypothalamic region, disruption of their neurogenic function may lead to neurodegenerative manifestations across the neuronal milieu. A specific condition known as neurodegeneration, the loss of cognitive abilities, and hypothalamic stem cell damage, as well as obesity and chronic energy imbalance, have been reported to occur after chronic inflammation or inflammation induced by overnutrition or ageing. Additionally, there is data linking brain diseases to overnutrition. Neuroinflammation is clearly to blame for poor neurogenesis and NSC depletion [159]. Furthermore, chronic inflammation slows neurogenesis, NSC survival, and differentiation, and increases ageing-related decline and neurodegenerative disorders [158, 160–163] despite providing a necessary defensive mechanism for the body. IKB kinase (IKK) and its downstream nuclear transcription factor NFκB (IKK/NFκB signalling) are part of the proinflammatory axis in the hypothalamus that is exacerbated by overnutrition [60, 164]. It has been found that overeating and age-related activation of the IKK/NFκB signalling pathway all contribute to obesity, chronic energy imbalance, neurotoxicity and cognitive impairment 21, and hypothalamic stem cell degradation [164–169]. A connection between overnutrition/ageing-induced neuroinflammation and neurodegenerative diseases is further supported by evidence and implications relating to overnutrition-induced neurological diseases including Alzheimer's (AD) and Parkinson's (PD) [170–173].

While neuroinflammation is an important defence mechanism in reaction to infections, illnesses, and brain damage, persistent inflammation compromises the body's normal defences and promotes the progressive neurological and neurodegenerative illnesses [160–163]. Additionally affected by neurological conditions and disorders, adult neurogenesis is severely impacted by inflammation [174]. For instance, neuroinflammation has been shown to inhibit neurogenesis in the adult hippocampus; neurogenesis may be restored if inflammation is blocked [159, 175]. Adult mice kept on a protracted high-fat diet (HFD) exhibit markedly reduced neurogenesis in the hypothalamus which may also be due to neuroinflammatory reactions generated by the HFD [176, 177]. Contrarily, short-term HFD intake can result in an increase in hypothalamic neurogenesis, which is most likely an adaptive response of the hypothalamus to offset the detrimental effects of HFD feeding on energy balance [176]. The proliferation and differentiation of htNSCs generated from obese mice were shown to be hindered by Li et al., in their study. Such contortion resulted from the overproduction of inflammatory cytokines such TNF- and IL-1, which are known to potently activate IKK/NFκB and were created as a result of NFκB activation, leading to the activation of an inflammatory axis with a positive feed-forward loop [153]. IKK/NFκB activation significantly reduced in vitro htNSC survival, differentiation, and neurogenesis, while IKK/NFκB pathway inhibition increased htNSC survival, differentiation, and neurogenesis, providing additional and direct evidence of the harmful consequences of inflammation [153].

Even while it is established that hippocampal neurogenesis plays a crucial role in appropriate hippocampus function, learning, and memory, there was some scepticism about the report [178–180]. Two recent investigations, focusing in particular on the limited population of Pro-opiomelanocortin (POMC) neurons that play essential roles in regulating energy balance, showed that chronic HFD-induced obesity and

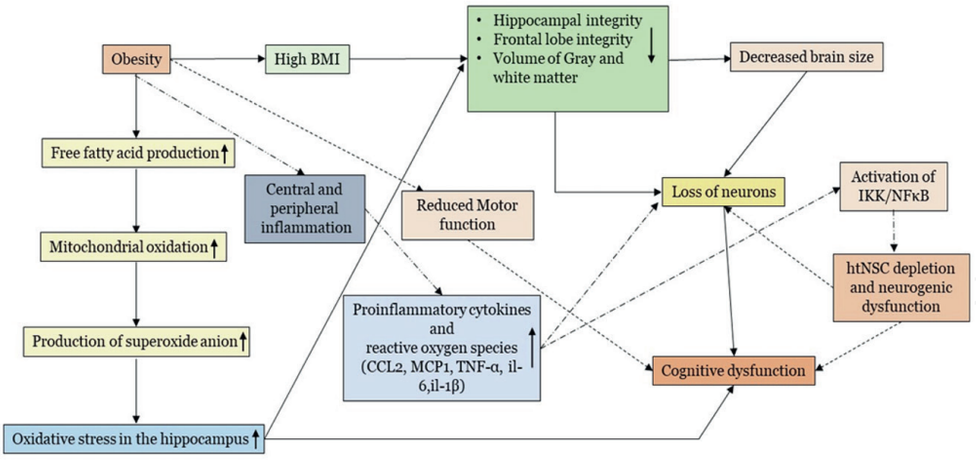

Figure 2.
Possible mechanism of obesity and cognitive dysfunction.

leptin deficit in mice resulted in a reduction in the adult NSC population and new neuron turnover [153]. Through the activation of multiple pro-inflammatory cascades, including the IKK/NFκB inflammatory axis, chronic HFD eating induces metabolic inflammation in the brain, particularly in the hypothalamus. Li et al. showed that chronic HFD eating in mice resulted in both htNSC depletion and neurogenic dysfunction linked to IKK/NFκB activation. The chronic consequences of metabolic dysfunctions, such as excessive calorie intake, glucose intolerance, insulin resistance, and obesity, were discovered in mice that had been genetically modified to have less NSCs in the MBH (**Figure 2**) [153].

7. Diet-induced obesity and synaptic plasticity dysfunction

The ability of the nervous system to dynamically modify its function in response to ongoing internal processes or outside events is referred to as the nervous system's plasticity [181]. It is a normal and important aspect of cognition as well as a key method through which the brain can heal after damage [182]. From fundamental physiological processes to integrated behavioural responses, plasticity can be understood and defined at many distinct levels of function [183, 184]. The physical morphology of synapses is related to structural plasticity [185]. Recent research has indicated that the HFD diet, which contains between 47 and 70% fat, has an impact on the brain's cognitive function [186–194]. According to this research, HFD causes negative consequences in various brain regions, including the hippocampus, via activating signalling pathways [195, 196]. HFD may have deleterious effects on memory and mood because it alters the systems that control synaptic transmission and the production of proteins associated with plasticity. HFD also causes obesity, which has an impact on the cellular and molecular mechanisms underlying synaptic plasticity in the brain, which impacts learning, memory, and mood. HFD also impaired brain-derived neurotrophic factors (BDNF), and amyloid precursor protein (APP) in the hippocampus.

7.1 Effects of obesity on BDNF

Neuroinflammation in the brain is a significant contributor to the development of neurodegenerative diseases. BDNF has the ability to regulate it [197]. This protein is

required for the proper functional development of brain structures as well as the development and retention of synaptic transmission [198]. In addition to its conventional neurotrophic roles, BDNF also seems to have neuroprotective properties against a number of brain traumas, including as ischemia, traumatic brain injuries, and Alzheimer's disease [199]. It also significantly contributes to the metabolism of energy by reducing food intake, limiting weight gain, and enhancing locomotion following intracerebroventricular injection [183, 200]. Through molecules like synapsin I and growth-associated protein 43, BDNF can control neural plasticity [201, 202]. Synapsin I promotes BDNF modulation of synaptic vesicle exocytosis of neurotransmitters in addition to stimulating axonal growth and supporting synaptic connections [203]. It has been demonstrated that BDNF activation results in synapsin I phosphorylation [204, 205]. According to studies HFD consumption impairs hippocampus synaptic plasticity and cognitive capacities by regulating BDNF expression [206–209]. Other research has shown that HFD raises brain oxidative stress, which stimulates neuroinflammation and lowers levels of BDNF [186, 210]. After 4 months of HFD ingestion in mice, decreased levels of the basic synaptic proteins SNAP-25 and post-synaptic density (PSD)-95 may increase the brain's vulnerability to the negative effects of HFD [186].

7.2 Effects of obesity on APP

The biology of APP may have a role in the association between obesity and cognitive performance [211]. APP can be converted into the two peptides Ab1-40 and Ab1-42 by the brain's neurons, where it is mostly synthesised [212]. Amyloid plaques, a component of AD, are produced when both types of peptides are together [213]. Recent research suggests that the pathophysiology of obesity may also be influenced by APP expression or function [214]. The expression of APP in adipocyte cell lines and adipose tissue has been documented [215, 216]. More significantly, obese people have elevated plasma levels of adipose APP and Ab1-40 [216, 217]. Studies have shown that greater cholesterol levels induce higher amounts of amyloid- in both AD-transgenic and low-density lipoprotein receptor-deficient animals after 8 weeks of diet-dependent obesity in mice [214, 218, 219]. The APP expression or function modifications may be coordinated between several tissue types [214]. In contrast to visceral and subcutaneous fat, one study demonstrated variations in APP expression in brain cells [193]. Inflammation, macrophage and adipocyte phenotype, and macrophage and adipocyte culture phenotype were examined for comparison with the in vivo changes [193].

Another study discovered that feeding mice a very high-fat diet (HFD) for 5 weeks lowered the amounts of the cytoskeleton-associated protein (Arc), which controls baseline activity, in the cerebral cortex and hippocampus. The latter mice developed brain insulin resistance, and acute insulin stimulation reduced phosphatidylinositol 3-kinase (PI3K)/protein kinase B/p70 ribosomal S6 kinase pathway activity, which in turn reduced activation of Arc protein expression [193].

7.3 Effects of obesity on microglia

In addition to driving the inflammatory response in response to various stimuli, microglial cells also regularly maintain neurotrophic connections by remodelling and optimising synapses [220]. Microglia are said to react to neuroinflammation by releasing several kinds of macrovesicles [221]. For instance, when lipopolysaccharide activates BV2 microglial cells, the pro-inflammatory cytokines tumour necrosis factor and interleukin-6 are released [222]. Immature dendritic spine pattern in CA1

diIlabeled neurons, which showed decreased neurogenic ability and lower levels of the scaffold protein Shank 2, suggest impaired connection following an HFD (60% fat) [223]. The medial prefrontal cortex, a part of the brain crucial for cognitive flexibility, exhibits abnormalities in microglial morphology, synapse loss, and cognitive deficits in early-stage obese rats [189]. Additionally, it enhances synaptosome internalisation and microglial activation [191]. Mice given a 60% HFD were found to have fewer dendritic spines, higher levels of microglial activation, and higher levels of synaptic profiles within the microglia. Additionally, transgenic and pharmaceutical techniques that block microglial activation shield obese animals from cognitive deterioration and dendritic spine loss. Additionally, pharmaceutical reduction of microglia's phagocytic activity has been found to be adequate to stop cognitive decline [224].

7.4 The role of insulin receptors in memory

A crucial part of controlling body metabolism is insulin. However, insulin modifies neural activity, strengthening synaptic connections and increasing memory function [225–227]. Insulin is known to have profound effects on neurotransmission [228]. PSD fractions contain insulin receptors, which are heavily concentrated in synaptosomes [229]. The scaffolding proteins shank and PSD-95 may also interact with them through insulin receptor tyrosine kinase substrate IRSp53, which is colocalized with synaptophysin and synapsin 1 [230, 231]. Neurites are promoted by insulin, catecholamine release and uptake is regulated, ligand-gated ion channel trafficking is controlled, gamma-aminobutyric acid, N-methyl-d-aspartic acid (NMDA) and AMPA receptors are expressed and localised, and NMDA and PI3K-Akt are involved in modulating synaptic plasticity [232]. There has been significant evidence that insulin resistance and the metabolic syndrome may cause cognitive impairments through mechanisms such as IPMK-mTOR/Akt, synapto-dendritic molecular neuroanatomy, and spatial working memory [233]. In mice, diets high in fat lead to insulin resistance in the cerebral cortex and hypothalamus. Several animal models have shown that insulin resistance affects cognition-related circuitry and neurotransmission [187, 226].

Studies in animals have found reduced dendritic spines in CA1 as well as impairments in long-term memory associated with HFD feeding [191, 234, 235]. Many different parts of the brain can be negatively impacted by alterations in glucose homeostasis, but the hippocampus is particularly susceptible to them [236–238]. According to research by Strahan et al., rats fed a high-fat, high-glucose diet for 8 months showed significant impairments in their hippocampal dendritic spine density, spatial learning ability, and LTP at Schaffer collateral-CA1 synapses [239]. In addition, high-fat, high-glucose-fed animals showed a reduction in BDNF levels in the hippocampus compared with controls. They suggested that the changes could be due to peripheral insulin resistance, or that some components of the diet may directly affect brain health and hippocampal plasticity. Further evidence suggests that the DG of rats fed HFD exhibit impaired stimulus-evoked LTP [240]. HFD feeding leads to a change in the expression of protein-coding genes in the cortex, but studies have not explored alterations in non-coding RNAs. The HFD feeding of mice led to changes in both coding and non-coding RNA expression in the brain cortex, according to a study by Yoon and colleagues. According to these researchers, consuming HFD for 8 weeks causes a decrease in the expression of genes linked to synaptogenesis and neurotransmitter release [241]. In the hippocampus of animals receiving HFD, Arnold,

and colleagues likewise found that PSD-95 expression was downregulated [187]. Interesting investigations have found that animals given the HFD have less neurogenesis in their dentate gyrus [242]. Thus, it is clear that HFD may significantly modify the expression of many genes linked to these processes, which may have a negative impact on brain morphology and synaptic plasticity.

8. Conclusion

Obesity is a serious public health problem that is increasing an proportions with serious health and societal problems. It mostly affects cognition through changing the structures and operations of the brain. Brain structure, leptin/insulin dysregulation, oxidative stress, cerebrovascular function, blood-brain barrier, and inflammation are all impacted by obesity and contribute to the decline in cognitive performance. Inhibition of neurogenesis is thought to be caused by neuroinflammation, which can be brought on by a variety of internal or external factors, including ER and oxidative stress, as well as, overnutrition-induced metabolic inflammation, and autophagic defects. These factors are all connected to the activation of the central IKK/NF-B inflammatory signalling cascade, which can result in a vicious inflammatory cycle that accelerates ageing, neurodegeneration, and cognitive decline.

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