Life Sciences 233 (2019) 116707

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

# The role of inflammation and endoplasmic reticulum stress in obesity-related cognitive impairment

Yilan Liu[a], Jing Yu[a], Yan-Chuan Shi[b], Yi Zhang[a,*], Shu Lin[b,c,**]

[a] Quanzhou First Hospital, Fujian Medical University, China
[b] Department of Cardiology, Southwest Hospital, Third Military Medical University (Army Medical University), China
[c] Illawarra Health and Medical Research Institute, Wollongong 2522, Australia

ARTICLE INFO

*Keywords:*
Obesity
Cognition impairment
Endoplasmic reticulum stress
Inflammation

ABSTRACT

The epidemiological investigations and animal model experiments have confirmed the impact of obesity on the brain, behavior, and cognition. However, the mechanism by which obesity affects cognitive function is not fully understood. With the development of an aging society, there is an increase in the economic and social burden caused by the decline in cognitive function. This manuscript reviews the effects of inflammation and endoplasmic reticulum stress (ERS) on the hypothalamus, hippocampus, and the possible impact on cognitive impairment. These findings provide new insights into the pathophysiological mechanisms that lead to the development of cognitive impairment in the context of obesity.

## 1. Introduction

Obesity adversely affects almost all physiological functions of the body and hence, is a threat to public health. It increases the risk of diabetes, cardiovascular disease, certain cancers and a range of musculoskeletal diseases, obesity has also been associated with cognitive dysfunction [1].

Cognition is an intelligent processing process in which the body recognizes and acquires knowledge. It involves a series of psychological and social behaviors such as learning, memory, language, thinking, spirit, and emotion. Cognitive impairment refers to the abnormality of the brain's advanced intelligent processing process related to the above-mentioned learning memory and thinking judgment, which causes serious learning and memory disorders, accompanied with pathological processes such as aphasia or apraxia [2]. The different levels of cognitive impairment range from mild cognitive impairment to dementia [3,4].

The increase in the quantity of adipose tissue along with the increase in the release of various adipokines in obese individuals has led to widespread peripheral low-grade inflammation [5]. The inflammatory process can be involved in the development of peripheral and central nervous disorders associated with obesity symptoms, including mood and cognitive changes [6]. Endoplasmic stress (ERS) is an adaptive response to the accumulation of misfolded proteins in the lumen of the endoplasmic reticulum. Moderate ERS plays an adaptive cytoprotective role by activating unfolded protein responses, while excessive and long-lasting ERS leads to apoptosis [7]. ERS and inflammatory signaling synergistically aggravate neuronal and synaptic dysfunction and form a vicious circle when causing neuronal apoptosis [8,9].

We, in the current article, have reviewed the existing literature that associates obesity-related cognitive impairment with increased inflammation and neuronal ERS, which can lead to the dysfunction of brain regions associated with mood regulation, learning, and memory, especially in the hypothalamus and hippocampus.

## 2. The association of obesity and cognitive impairment

### 2.1. Effect of obesity on cognitive deficiency in human studies

There are a growing number of prospective cohort studies on the association between obesity and cognitive function in humans that have been conducted across various countries. The body mass index (BMI) and waist circumference are the most widely used measurements for obesity in the human surveys [10]. Some studies have observed the impact of obesity on the central nervous system through the changes in the brain imaging because of the lack of standard way to assess the human cognition [11].

Statistical analysis has shown that there is a significant U-type correlation between BMI and dementia [10]. A systematic review and

* Correspondence to: Y. Zhang, Quanzhou First Hospital, Quanzhou, China.
** Correspondence to: S. Lin, Southwest Hospital, Chongqing 400038, China.
*E-mail addresses:* zhayisn@163.com (Y. Zhang), shulin1956@126.com (S. Lin).

https://doi.org/10.1016/j.lfs.2019.116707
Received 4 May 2019; Received in revised form 16 July 2019; Accepted 28 July 2019
Available online 31 July 2019

**Table 1**
Human studies showing an association between obesity and cognitive impairment.

| Participants | Age | Study duration | Study design | Cognitive tests | Cognitive results | Conference |
|---|---|---|---|---|---|---|
| 568 men and 532 women | 60–98 years (median age 79 years) | 4-year | Observational study. | Mini-mental state examination | Abdominal obesity is associated with an increased risk of cognitive impairment | [20] |
| 3859 subjects with normal cognition at baseline. | Aged ≥ 65 years | 3-year | Prospective study | Mini-mental state examination | Overweight or obese older women at baseline had cognitive benefits. However, additional gain or loss of adiposity in late life did not affect the risk of cognitive impairment | [21] |
| 280 men and 377 women of Swedish adoption and twin study of aging | Mean age 40 and 61 years | 21-years | Prospective cohort | Verbal, spatial and fluid, memory, and perceptual speed were tested | Overweight or obesity in early midlife predicted lower cognitive function and cognitive decline in late life | [22] |
| African-American sibships with hypertension in Jackson, Mississippi ($N$ = 1108). | Aged ≥ 35 years | 14-year | Cohort study using linear mixed models. | The Mini-Mental State Examination<br>The Wechsler Adult Intelligence Scale Revised Digit Symbol Substitution Task<br>The Trail-Making Test Part (TMT) | A differential pattern of the relationship between adiposity and cognition according to age (mid- or late life) and regional distribution of adiposity | [23] |
| 80 adolescent and young adult bipolar disorder patients and 46 healthy comparison subjects. | 16–35 years | 12 months | Prospective cohort | North American Adult Reading Test full-scale IQ (FSIQ)<br>The Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery | Lower cognitive functioning in specific domains predicts increasing BMI in patients with BD and healthy young adults | [24] |

meta-analysis of a large population has highlighted a positive correlation between obesity and dementia during middle age, however, a negative correlation was observed in the later years of life [12]. Interestingly, a study has found that the negative effects on cognition are more remarkable in obese males [11].

The association between obesity and cognitive impairment is not only supported by epidemiological cross-sectional and prospective studies [10], but also has been verified by the investigations that show that dietary intervention can improve cognitive performance [13]. Studies suggest that the cognitive changes induced by high energy diet (HED) have a chain of adverse effects on appetite control in the future, which lead to the concept of vicious cycle model [14]. In a meta-analysis of 41 studies, there was a significant association between attention-deficit/hyperactivity disorder and obesity, regardless of possible confounding factors such as psychiatric comorbidities [15]. Researchers have also found that in some cases obesity is accompanied with mild cognitive impairment [16,17]. There are also mood disorders in obese individuals, including anxiety, depression and fear [18,19] (Table 1).

### *2.2. Effect of obesity on cognitive impairment in rodent models*

To study obesity and related health complications, particularly cardiovascular disease or type 2 diabetes mellitus, various obese models have been developed, and these models have established the neurobiological basis of obesity-related emotional and cognitive changes [13]. The more commonly used obese animal models are diet-induced obesity (DIO) models, among which the high fat diet (HFD) induced obesity model is the most widely used [25]. In addition to the diet-induced obesity model, Bloch K and co-workers also established a model of obesity by administering streptozotocin in the intracerebroventricular. Using this obesity model, they found that mice exhibited severely impaired spatial learning during the acquisition and reversal phases [26].

Short-term HFD (one week) impaired spontaneous alternation in mice [27], and a chronic HFD led to cognitive impairment by causing pathological injury in brain [13,28]. Consistent with clinical findings, DIO in mice was found to be associated with multiple cognitive abnormalities, including learning and memory impairment, along with anxiety, depression, and other cognitive disorders [27,29,30]. The cognitive impairment induced by HFD was more prevalent during childhood and adolescence of the mice [31].

Some studies suggest that the cognitive impairment caused by DIO could be reversed and rehabilitated by dietary interventions [13,32,33], while other experiments have shown that the cognitive impairment in the mice offspring induced by DIO in perinatal periods could not be reversed, even if the mice were weaned and switched to a healthy diet [34]. However, the research on the contribution of critical periods, exposure doses, and diets from mothers and fathers to cognitive function in offspring is still insufficient and requires further investigations (Table 2).

## 3. Mechanisms underlying obesity-associated cognitive impairment

### *3.1. Systemic inflammation in obesity disrupts the permeability of the blood brain barrier*

Obesity is characterized by a chronic low grade inflammation, and it is accompanied by progressive infiltration of immune cells into adipose tissues [40]. In adipose tissue, macrophages play a key role in chronic inflammation and metabolic dysfunction, and many studies have shown that macrophages play a critical role in systemic insulin resistance [41]. After being exposed to a long-term high-fat diet, hyperlipidemia, and hyperglycemia, an increased level of pro-inflammatory cytokines and inflammatory cytokines was detected in the blood circulation [42]. These abnormal conditions disrupt the blood brain barrier (BBB) and

**Table 2**
The effect of diet on cognition in rodent studies.

| Subjects | Diet composition | Study duration | Task | Cognitive results | Conference |
|---|---|---|---|---|---|
| Male Wistar rats | 60% fat/ 55% fructose diet | 9 weeks | Morris Water Maze | Western-style diet influence different facets of cognitive dysfunction, high-fructose induces working memory impairment | [35] |
| Female adult Wistar rats | 68,9% carbohydrate, 18,4% protein, 5,1% lipid-hypercaloric pelletized diet | 22 weeks | The open field test<br>Object recognition test | Memory consolidation impairment | [36] |
| Wistar rats | 60%/45% high-fat diet | 4 months | T-maze | Cognitive decline, worse performance in the T-maze in HF60 animals | [37] |
| Male and female wild-type C57/BL6J, NPY-GFP, POMC-GFP mice | 60% high-fat diet | 15 weeks | The open field test<br>The elevated plus maze | HFD bi-directionally effects anxiety-related behaviors | [38] |
| Adolescent male mice | 45% high-fat diet with continuous access or sporadic limited access (2 h, three days a week). | 15 weeks | Elevated Plus Maze,<br>Spontaneous Locomotor Activity<br>Passive Avoidance Test<br>Hebb Williams Maze | Only the animals with a continuous access to the HFD marked memory and spatial learning deficits, discontinuation of fat, either in a binge or a continuous pattern, led to an increase in anxiety-like behavior | [39] |

change the permeability of the BBB [43].

In a study by Hargrave and co-workers, an increase in permeability of the BBB was observed after 90 days of Western diet feeding [44].The brain endothelial cells that form the BBB can be regulated by a series of inflammatory mediators [45]. There are many inflammatory factors that can increase the permeability of endothelial cells and enlarge the diameter of blood vessels, leading to increased BBB penetrability and transport dysfunction (Fig. 1) [46].

#### *3.1.1. Specific anatomical features of the hypothalamus*

The hypothalamus is the nerve center that regulates visceral activity and endocrine activity, which located in the ventral surface of the brain and below the thalamus [47]. It is worth noting that the arcuate nucleus lacks a typical blood-brain barrier [48]. The BBB of the hypothalamus can sense the dynamic changes in the neuroendocrine events and regulate the permeability through tight junction complexes [49]. Therefore, the BBB lesions can directly affect the normal function of the hypothalamus [50]. The hypothalamus can link visceral activities with other physiological activities, and has important physiological functions such as regulation of body temperature, nutrient uptake, water balance, endocrine, and emotional response [51]. On the one hand, the hypothalamic senses satiety and controls the intake of food to affect the energy balance, it indirectly affects cognitive function [52]. On the other hand, the hypothalamic ventrolateral nucleus and preoptic area can produce behavioral and mental abnormalities (action reduction, orientation) (Obstacles, moodiness, hallucinations, etc.), which directly affect cognition function [28].

#### *3.1.2. The hippocampus is primarily for the memory and learning*

The hippocampus is an important part of the limbic system, and the dorsal hippocampus is associated with learning and memory and ventral hippocampus is involved in the regulation of emotions and stress response [53]. Therefore, the hippocampus is considered to have the closest relationship with cognitive dysfunction. Many studies have also found that the BBB of the hippocampus is susceptible to damage and a high-energy diet (HED) can lead to hippocampal dysfunction [43,44,54].

According to one study, continuous feeding of HED in mice increases the permeability of fluorescein sodium across the BBB of hippocampus [55]. HED can deplete tight junction proteins between the brain endothelial cells, and in particular can reduce the expression of claudin-5 and claudin-12 mRNA in choroid plexus and BBB [56]. It is one of the important mechanisms leading to cognitive impairment.

### *3.2. Inflammation in hypothalamus and hippocampus*

Over a decade ago, researchers have suggested an inflammatory response in the hypothalamus of obese animals [57]. In recent studies, the correlation between hypothalamic inflammation and HFD induced obesity can be observed through the Magnetic Resonance Imaging (MRI) of the brain in obese animal models as well as human subjects [40]. Histologically, glial cell proliferation is a characteristic of hypothalamic inflammation [58], including the infiltration of microglia cells and the proliferation of astrocytes, which is evident by the increased density of the glial cells (Fig. 1) [52].

#### *3.2.1. Inflammation of the hypothalamus*

The inflammation of the hypothalamus and the proliferation of glial cells are related to the systemic low-grade inflammation caused by obesity [59]; and the latest research shows that the hypothalamus inflammation is mediated by the interaction between neurons and non-neuronal cells (microglia and astrocytes) [33]. The signaling pathway involved in hypothalamic inflammation, includes toll-like receptor 4 [60], IκB kinase-β/nuclear factor-κB [40], c-Jun N-terminal kinase (JNK), suppressor of cytokine signaling 3 and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-10) [52,61].

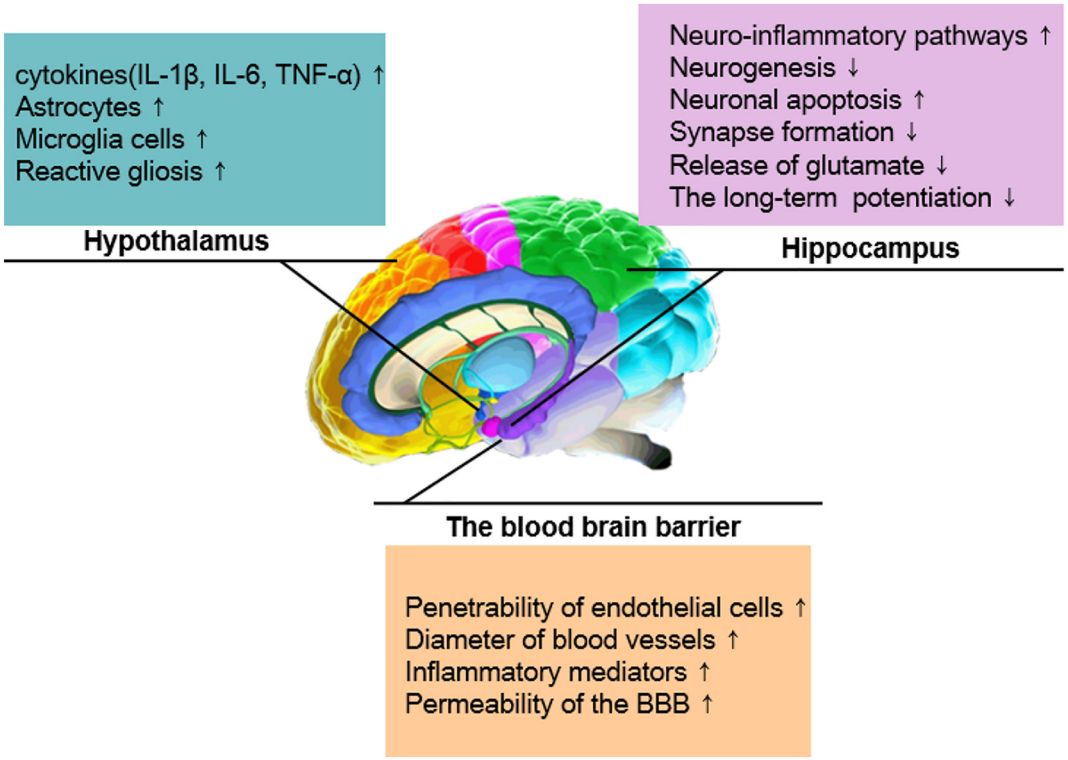


**Fig. 1.** Effect of diet-induced obesity on the central nervous system.
As a result of diet-induced obesity the expression of cytokines, microglia, and astrocytes in the hypothalamus were found to be increased. The inflammatory pathway in the hippocampus is activated and apoptosis is increased, and the glutamate release, long-term potentiation, synapse formation, and neurogenesis were all reduced in the hippocampus; the degree of permeability of the BBB, endothelial cell penetration, blood vessel diameter, and inflammatory mediators were all increased. All these factors combined can lead to cognitive dysfunction.

Free fatty acids have shown to activate the innate immune system through toll-like receptors, which further activate downstream transcription factors (such as nuclear factor κB, NF-κB) [62]. IKB kinase-B/nuclear factor-Kb (IKKB/NF-kB) pathway plays a vital role in promoting inflammatory response within the cells [63], therefore, it is often referred to as the "start switch" of the innate immune system [61]. Studies have shown that as a regulator of microglial activation in high-fat diets, NF-κB, can cause hypothalamus dysfunction [64]. Microglial cells recruit unique bone marrow cells through NF-κB pathway [64], which then migrate to the hypothalamus from the bone marrow and induce hypothalamus metabolic inflammation [60,61,65]. JNK, on the other hand, can be stimulated by various environmental conditions and inflammatory cytokines, and it promotes inflammation via stabilization of the mRNA of inflammatory cytokines and other inflammatory mediators [59].

The upstream signaling pathways mentioned above can up-regulate the expression of cytokines (interleukins IL-1β, IL-6, tumor necrosis factor-alpha TNF-α) [63], chemokines (chemokine ligand 2 CCL2, C-X-C chemokine ligand 10 CXCL10) and other pro-inflammatory factors [66]. Comparative experiments have demonstrated the higher levels of mRNA and protein of inflammatory cytokines (TNF-α, IL-1 and IL-6) in hypothalamus after HFD feeding or intravenous free fatty acids [61].

Considering the time-line and regional distribution of central inflammation, and the special anatomical location of hypothalamus with incomplete blood brain barrier, researchers have suggested that the inflammation of the hypothalamus after an HFD stay one step ahead of other brain areas [47,58]. It can be inferred that the inflammation of hypothalamus can alter the internal hypothalamic circuitry and hypothalamic neural outputs to other brain regions. This leads to impaired cognitive function in hippocampus, amygdala, reward processing centers, and other brain areas. And these brain regions have an inflammatory response in the later stages of high-fat feeding [28,40]. Therefore, the central inflammation in obese individuals not only can result in the destruction of hypothalamic satiety signal and the constant overeating, but also can cause negative effects on cognitive function [52].

#### 3.2.2. *The influence of inflammation on hippocampus*

The influence of inflammation on hippocampus induced by obesity is one of the topics of recent research. Obesity-mediated inflammation in the hippocampus is characterized by an increase in inflammatory factors (IL-1β, IL-6, TNF-α), which triggers a series of inflammatory processes [67]. The inflammatory factor IL-1β inhibits aspartate-dependent or non-dependent synaptic enhancement, long-term potentiation, and glutamate release in the hippocampus. The researchers also found that TNF-α is overexpressed in the hippocampus of the obese individuals and it impairs neurogenesis in adults by inhibiting cell division of hippocampal progenitors, resulting in memory and learning deficits [31].

### 3.3. *The endoplasmic reticulum stress of the central neurons*

The endoplasmic reticulum is metabolic organelles within the eukaryotic cells, which can detect the nutritional changes in cells. And it plays a vital role in the protein folding, secreted proteins and transmembrane protein modification after translation, protein maturation, and other step of protein synthesis [68]. The functional homeostasis of the endoplasmic reticulum is destroyed and ERS is triggered by both over nutrition induced by a HFD and hyperglycemia and hyperlipidemia accompanied with obesity [69].

#### 3.3.1. *Three pathways for endoplasmic reticulum stress*

The known unfolded protein response (UPR) signals mainly composed of the following three pathways: PERK-eIF2α, IRE1α and ATF-6.

PERK and IRE1 are both protein kinases that can be activated by dimerization and self-phosphorylation in the case of ERS and then activate their downstream signaling pathways [70]. Glucose-regulating protein 78 (GRP78) is a molecular chaperone that promotes protein folding [71]. It can make IRE1, PERK, and AFT6 inactive by linking with the endoplasmic internal segment of the three UPR pressure-sensitive proteins (IRE1 and PERK's amino terminal and ATF6 carboxyl terminal) when the protein folding load of the endoplasmic reticulum is mild [71–73]. GRP78 belongs to the family of Heat Shock Protein 70 (HSP70), which is the key molecule of ERS reaction [62].

Normally, the content of GRP78 in cells is less, but its mRNA can promote expression under the ERS response. When the endoplasmic reticulum in the state of overload stress, unfolded or misfolded proteins are stored in the endoplasmic reticulum and combined with GRP78, so that GRP78 can be separated from the UPR signal response protein [71]. The UPR signaling pathway is active after GRP78 separated from IRE1, PERK and AFT6, followed by the inhibition of proteins synthesis, correct folding of unfolded proteins, and degradation of the misfolded proteins [8].

#### 3.3.2. Unfolded protein response of the endoplasmic reticulum

During the early stage of ERS in cells, an adaptive cellular protective mechanisms is activated by unfold or misfolded proteins, which is called the UPR. UPR can help to relieve stress, restore the homeostasis of the cells and keep the cells alive [68].

URP has a protective effect on cells in the initial stage of ERS, however, it activates the apoptosis pathway when the ERS is persistent and exceeds the regulation ability of the endoplasmic reticulum [71]. The activated apoptosis includes three apoptotic signaling pathways: the growth arrest and DNA damage-inducible gene 153 (CHOP/GADD153) pathway [73], the JNK pathway, and the caspase-12 pathway (the cysteine protease pathway of the endoplasmic reticulum) [67].

Studies have shown that both genetically and DIO can trigger ERS and activate UPR signals in key metabolic tissues (such as adipose tissue, liver, skeletal muscle, pancreas) [70]. Similar to the response of the surrounding tissues to over nutrition, the hypothalamus also shows ERS under high-fat conditions [59]. A pathological hallmark of many neurodegenerative diseases is the accumulation of misfolded proteins and protein aggregates in neurons and surrounding supporting cells affected by HFD [74]. Both neurodegenerative diseases and obesity trigger similar ERS responses. Astrocytes ERS shares the UPR activation pathways in obesity and neurodegenerative diseases (Fig. 2) [68,75].

#### 3.3.3. ERS is closely related to inflammation

ERS and UPR have recently been associated with inflammation in a variety of human diseases such as autoimmune, infection, neurodegenerative diseases and metabolic disorders [8], intracellular ERS and inflammatory signals share a wide range of regulatory factors and effectors in various biological processes. Therefore, ERS can adversely affect metabolic homeostasis by affecting the inflammatory signaling network [69]. Some studies have reported that ERS and inflammation in the hypothalamus of obese mice can activate each other and cause a disturbance of leptin signaling pathway that future inhibits the normal metabolism of the cells [76].

In the report of Salminen A, et al., it has been shown that ER stress can also induce an inflammatory response through different UPR pathways. Efficient signaling pathways include the three pathways of endoplasmic reticulum stress described above and the inflammatory caspase-induced signaling pathway, which together act on the pathogenesis of Alzheimer's disease (AD) [77]. Santos LE and co-workers also pointed out that there is a positive feedback loop between ERS and inflammation, which has a clear meaning for neurodegeneration and AD. ERS may be inseparable from inflammatory responses, leading to neuronal and synaptic dysfunction and memory decline [9].

### 3.4. Pathological mechanism of cognitive impairment caused by inflammation and ERS

#### 3.4.1. Inflammation promotes beta-amyloid production

Some studies have found that systemic inflammatory of obesity promotes the production of beta-amyloid, which may be one of the pathogenesis of (AD). Peripheral insulin resistance and hyperinsulinemia increase peripheral free fatty acid levels, while peripheral and central TNF-α levels also increase, which reduce and clearance of Aβ by the liver, leading to an increase in peripheral Aβ levels [78,79].

The high level of Aβ in plasma interferes with its metastasis that from the brain to the periphery, which in turn increases Aβ transport to the brain. As a result, release of Aβ from the nerve cells is inhibited. Studies have also found that a specific pathway, downstream of insulin receptor can regulate the expression or activation of beta-secretase or gamma secretase and hence, Aβ production. The decreased level of insulin-degrading enzymes in obese individuals also aggravates the deposition of Aβ in the neurons. Therefore, the accumulation is a consequence of several pathological mechanisms such as increased production of Aβ, peripheral clearing dysfunction, and increased brain inflammation, which can lead to memory defects and even pathological features of Alzheimer's disease [25].

#### 3.4.2. ERS increase neuronal apoptosis and reduced neurogenesis

Neurons are the basic unit of brain structure and function [80]. Abnormalities in the number and function of neurons can affect the normal operation of the central nervous system [81].

Obesity can activate the expression or activity of inflammatory response proteins, aggravate oxidative stress and ERS [82], and disrupt leptin and insulin signaling in brain regions such as the hypothalamus and hippocampus, resulting in leptin and insulin resistance [41,61]. Inflammatory signal transduction is an induction signal of pre-apoptotic cells. Cytokines such as TNF-α and IL-1β can induce apoptosis in different cell types [83]. Oxidative stress can promote apoptosis in neurodegenerative diseases through extrinsic and intrinsic pathway [84]. Intracellular chronic ERS also activates three apoptotic signaling pathways, which is one of the major pathways leading to apoptosis [85]. It is know that normal cell autophagy inhibits apoptosis. However, the cells cannot survive when autophagy causes the excessive consumption of intracellular proteins and organelles, and leads to apoptosis [73]. The state of inflammation, oxidative stress and ERS caused by obesity impair the autophagy, hence, it does not inhibits apoptosis but promotes apoptosis (Fig. 2) [59].

Neurogenesis is the continuous replacement of central nervous cells and granulosa cells, enabling newborn neurons to replace dying cells and form functional synapses [86]. The neurogenesis of the hippocampus will continue into adulthood, so it is essential for learning and memory [87]. Hippocampal neurogenesis is a unique form of neural circuit plasticity that can generate new neurons in the dentate gyrus. New neurons appearing in adults show enhanced synaptic plasticity during maturation, which is the physiological basis of cognition and emotion (Fig. 1) [83].

Inflammation can activate microglia, which then reduces neurogenesis by inhibiting neuronal stem cell proliferation, reduces the survival of newly developed neurons, reduces their integration into existing neuronal circuits [88]. On the other hand, HFD can lead to a decrease in the availability of serotonin 5-HT [89] and a decrease in the synthesis of Brain-derived neurotrophic factor (BDNF), leading to a reduction in the positive effects of promoting nerve regeneration [90].

## 4. Conclusion and prospect

Based on existing results, this article explores the association between obesity and cognitive function from the perspective of inflammation and ERS. Obesity can trigger chronic inflammation and endoplasmic reticulum stress through multiple signaling pathways

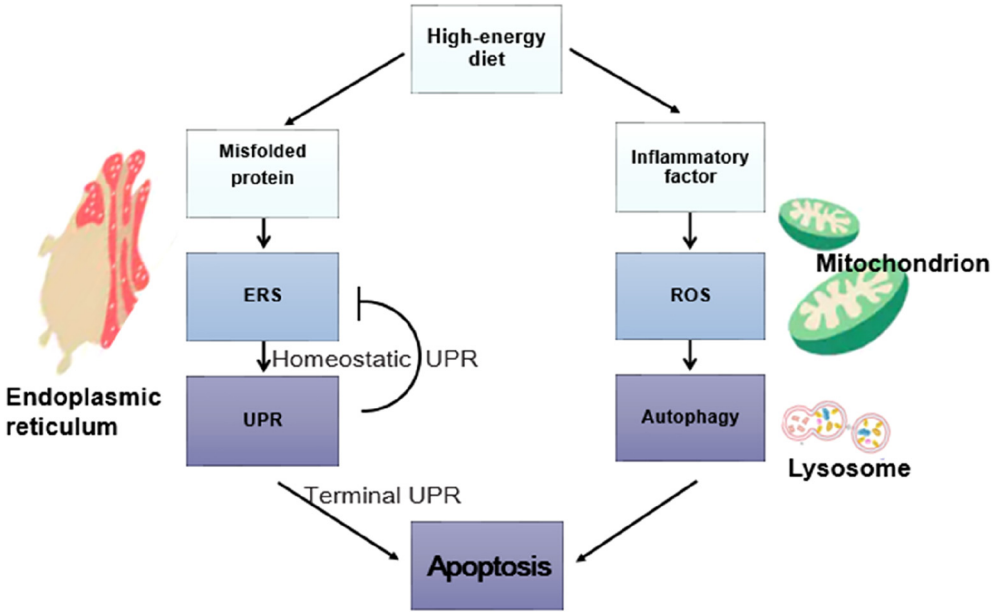


**Fig. 2.** Model of the role of endoplasmic reticulum stress and inflammation in cognitive impairment.
High-energy diets can induce endoplasmic reticulum stress, oxidative stress, and autophagy in nerve cells by inducing protein misfolding and inflammatory factors, ultimately leading to apoptosis.

[91]. The accumulated adipose tissue produces and secretes inflammatory factors, which can further induce a series of inflammations and injuries after entering the brain through the BBB, resulting in increased apoptosis and decreased nerve regeneration in the hypothalamus and hippocampus. Over time, structural changes occur in the brain regions such as the hypothalamus and hippocampus, which may permanently perpetuate reversible cognitive abnormalities [18].

Researchers have explored the possible mechanisms of the obesity that impact the cognitive function. However, the specific signaling pathways and related sites are still unclear and more deep experimental studies are needed. A few new potential sites, such as the prominent GPAT4 expression in the hippocampus, haven been reveals. GPAT4, a glycerol-3-phosphatidyl transferase that limits the first step of lipid synthesis, is prominently expressed in the hippocampus and is known to play an important role in the development of obesity and insulin resistance in the periphery [92], however, whether it has an impact on cognitive function is worth exploring.

Only when we fully understand the impact of obesity on cognition and explore potential mechanisms, can we find possible treatment sites and formulate effective intervention strategies.

## Declaration of Competing Interest

The authors declare that there is no conflict of interest in this work.

## Acknowledgements

This work was supported by Quanzhou High-level Talents Innovation and Entrepreneurship Project ( 2018C059R), Medical innovation subject in fujian province ( 2018-CX-50) and Fujian Natural Science Foundation Project (2019J01600)

## References

[1] Y.C. Chooi, C. Ding, F. Magkos, The epidemiology of obesity, Metabolism 92 (2019) 6–10.
[2] R.C. Petersen, et al., Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation subcommittee of the American Academy of Neurology, Neurology 90 (3) (2018) 126–135.
[3] K.M. Langa, D.A. Levine, The diagnosis and management of mild cognitive impairment: a clinical review, JAMA 312 (23) (2014) 2551–2561.
[4] Y.T. Wu, et al., The changing prevalence and incidence of dementia over time - current evidence, Nat. Rev. Neurol. 13 (6) (2017) 327–339.
[5] V. Francisco, et al., Adipokines and inflammation: is it a question of weight? Br. J. Pharmacol. 175 (10) (2018) 1569–1579.
[6] N. Castanon, G. Luheshi, S. Laye, Role of neuroinflammation in the emotional and cognitive alterations displayed by animal models of obesity, Front. Neurosci. 9 (2015) 229.
[7] S.A. Oakes, F.R. Papa, The role of endoplasmic reticulum stress in human pathology, Annu. Rev. Pathol. 10 (2015) 173–194.
[8] S.S. Cao, K.L. Luo, L. Shi, Endoplasmic reticulum stress interacts with inflammation in human diseases, J. Cell. Physiol. 231 (2) (2016) 288–294.
[9] L.E. Santos, S.T. Ferreira, Crosstalk between endoplasmic reticulum stress and brain inflammation in Alzheimer's disease, Neuropharmacology 136 (Pt B) (2018) 350–360.
[10] M.A. Beydoun, H.A. Beydoun, Y. Wang, Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis, Obes. Rev. 9 (3) (2008) 204–218.
[11] Y. Taki, et al., Relationship between body mass index and gray matter volume in 1,428 healthy individuals, Obesity (Silver Spring) 16 (1) (2008) 119–124.
[12] E. Pedditizi, R. Peters, N. Beckett, 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 45 (1) (2016) 14–21.
[13] Z.F. Bhat, et al., Obesity and neurological disorders: dietary perspective of a global menace, Crit. Rev. Food Sci. Nutr. (2017) 1–17.
[14] M.R. Yeomans, Adverse effects of consuming high fat-sugar diets on cognition: implications for understanding obesity, Proc. Nutr. Soc. 76 (4) (2017) 455–465.
[15] S. Cortese, L. Tessari, Attention-deficit/hyperactivity disorder (ADHD) and obesity: update 2016, Curr. Psychiatry Rep. 19 (1) (2017) 4.
[16] M.H. Eskelinen, et al., Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study, Int. J. Geriatr. Psychiatry 23 (7) (2008) 741–747.
[17] N. Pannacciulli, et al., Brain abnormalities in human obesity: a voxel-based morphometric study, Neuroimage 31 (4) (2006) 1419–1425.
[18] G. Shefer, Y. Marcus, N. Stern, Is obesity a brain disease? Neurosci. Biobehav. Rev. 37 (10 Pt 2) (2013) 2489–2503.
[19] P.D. O'Brien, et al., Neurological consequences of obesity, Lancet Neurol. 16 (6) (2017) 465–477.
[20] Q. Hou, et al., Associations between obesity and cognitive impairment in the Chinese elderly: an observational study, Clin. Interv. Aging 14 (2019) 367–373.
[21] H.M. Noh, et al., Sex differences in the relationship between cognitive impairment and overweight or obesity in late life: a 3-year prospective study, Medicine (Baltimore) 98 (9) (2019) e14736.
[22] A.K. Dahl, et al., Body mass index across midlife and cognitive change in late life, Int. J. Obes. 37 (2) (2013) 296–302.
[23] N.A. West, et al., Adiposity, change in adiposity, and cognitive decline in mid- and late life, J. Am. Geriatr. Soc. 65 (6) (2017) 1282–1288.
[24] D.J. Bond, et al., Lower cognitive functioning as a predictor of weight gain in bipolar disorder: a 12-month study, Acta Psychiatr. Scand. 135 (3) (2017) 239–249.
[25] N. Hariri, L. Thibault, High-fat diet-induced obesity in animal models, Nutr. Res. Rev. 23 (2) (2010) 270–299.

[26] K. Bloch, et al., Intracerebroventricular streptozotocin induces obesity and dementia in Lewis rats, J. Alzheimers Dis. 60 (1) (2017) 121–136.
[27] E.E. Noble, S.E. Kanoski, Early life exposure to obesogenic diets and learning and memory dysfunction, Curr. Opin. Behav. Sci. 9 (2016) 7–14.
[28] J.P. Thaler, et al., Obesity is associated with hypothalamic injury in rodents and humans, J. Clin. Invest. 122 (1) (2012) 153–162.
[29] S.K. Sah, et al., Effect of high-fat diet on cognitive impairment in triple-transgenic mice model of Alzheimer's disease, Biochem. Biophys. Res. Commun. 493 (1) (2017) 731–736.
[30] C.D. Morrison, et al., High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling, J. Neurochem. 114 (6) (2010) 1581–1589.
[31] C. Boitard, et al., Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats, Brain Behav. Immun. 40 (2014) 9–17.
[32] J. Wang, et al., Childhood and adolescent obesity and long-term cognitive consequences during aging, J. Comp. Neurol. 523 (5) (2015) 757–768.
[33] K.E. Berkseth, et al., Hypothalamic gliosis associated with high-fat diet feeding is reversible in mice: a combined immunohistochemical and magnetic resonance imaging study, Endocrinology 155 (8) (2014) 2858–2867.
[34] S.D. Bilbo, V. Tsang, Enduring consequences of maternal obesity for brain inflammation and behavior of offspring, FASEB J. 24 (6) (2010) 2104–2115.
[35] L. Woodie, S. Blythe, The differential effects of high-fat and high-fructose diets on physiology and behavior in male rats, Nutr. Neurosci. 21 (5) (2018) 328–336.
[36] P. Zanini, et al., Diet-induced obesity alters memory consolidation in female rats, Physiol. Behav. 180 (2017) 91–97.
[37] M. Cifre, A. Palou, P. Oliver, Cognitive impairment in metabolically-obese, normal-weight rats: identification of early biomarkers in peripheral blood mononuclear cells, Mol. Neurodegener. 13 (1) (2018) 14.
[38] P. Sweeney, et al., HFD-induced energy states-dependent bidirectional control of anxiety levels in mice, Int. J. Obes. 41 (8) (2017) 1237–1245.
[39] M.C. Blanco-Gandia, J. Minarro, M. Rodriguez-Arias, Behavioral profile of intermittent vs continuous access to a high fat diet during adolescence, Behav. Brain Res. 368 (2019) 111891.
[40] C. Kreutzer, et al., Hypothalamic inflammation in human obesity is mediated by environmental and genetic factors, Diabetes 66 (9) (2017) 2407–2415.
[41] H. Xu, et al., Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Invest. 112 (12) (2003) 1821–1830.
[42] M.L. Alosco, J. Gunstad, The negative effects of obesity and poor glycemic control on cognitive function: a proposed model for possible mechanisms, Curr. Diab. Rep. 14 (6) (2014) 495.
[43] Z. Tucsek, et al., Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease, J. Gerontol. A Biol. Sci. Med. Sci. 69 (10) (2014) 1212–1226.
[44] S.L. Hargrave, et al., Western diets induce blood-brain barrier leakage and alter spatial strategies in rats, Behav. Neurosci. 130 (1) (2016) 123–135.
[45] N.J. Abbott, Inflammatory mediators and modulation of blood-brain barrier permeability, Cell. Mol. Neurobiol. 20 (2) (2000) 131–147.
[46] B. Obermeier, R. Daneman, R.M. Ransohoff, Development, maintenance and disruption of the blood-brain barrier, Nat. Med. 19 (12) (2013) 1584–1596.
[47] K.W. Williams, J.K. Elmquist, From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior, Nat. Neurosci. 15 (10) (2012) 1350–1355.
[48] S. Morita-Takemura, A. Wanaka, Blood-to-brain communication in the hypothalamus for energy intake regulation, Neurochem. Int. 128 (2019) 135–142.
[49] C. Coisne, B. Engelhardt, Tight junctions in brain barriers during central nervous system inflammation, Antioxid. Redox Signal. 15 (5) (2011) 1285–1303.
[50] A.C. da Fonseca, et al., The impact of microglial activation on blood-brain barrier in brain diseases, Front. Cell. Neurosci. 8 (2014) 362.
[51] G. Williams, J.A. Harrold, D.J. Cutler, The hypothalamus and the regulation of energy homeostasis: lifting the lid on a black box, Proc. Nutr. Soc. 59 (3) (2000) 385–396.
[52] A.A. Miller, S.J. Spencer, Obesity and neuroinflammation: a pathway to cognitive impairment, Brain Behav. Immun. 42 (2014) 10–21.
[53] S.E. Kanoski, H.J. Grill, Hippocampus contributions to food intake control: mnemonic, neuroanatomical, and endocrine mechanisms, Biol. Psychiatry 81 (9) (2017) 748–756.
[54] T.M. Hsu, S.E. Kanoski, Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia, Front. Aging Neurosci. 6 (2014) 88.
[55] T.L. Davidson, et al., The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats, Physiol. Behav. 107 (1) (2012) 26–33.
[56] S.E. Kanoski, et al., The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat, J. Alzheimers Dis. 21 (1) (2010) 207–219.
[57] C.T. De Souza, et al., Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus, Endocrinology 146 (10) (2005) 4192–4199.
[58] S. Kalin, et al., Hypothalamic innate immune reaction in obesity, Nat. Rev. Endocrinol. 11 (6) (2015) 339–351.
[59] L.M. Williams, Hypothalamic dysfunction in obesity, Proc. Nutr. Soc. 71 (4) (2012) 521–533.
[60] M. Valdearcos, et al., Microglial inflammatory signaling orchestrates the hypothalamic immune response to dietary excess and mediates obesity susceptibility, Cell Metab. 26 (1) (2017) 185–197 (e3).
[61] K.C. de Git, R.A. Adan, Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation, Obes. Rev. 16 (3) (2015) 207–224.
[62] D.Q. Tran, et al., Diet-induced cellular neuroinflammation in the hypothalamus: mechanistic insights from investigation of neurons and microglia, Mol. Cell. Endocrinol. 438 (2016) 18–26.
[63] M.D. Dorfman, J.P. Thaler, Hypothalamic inflammation and gliosis in obesity, Curr. Opin. Endocrinol. Diabetes Obes. 22 (5) (2015) 325–330.
[64] A. Lee, V.D. Dixit, Energy sparing orexigenic inflammation of obesity, Cell Metab. 26 (1) (2017) 10–12.
[65] D. Cai, Neuroinflammation and neurodegeneration in overnutrition-induced diseases, Trends Endocrinol. Metab. 24 (1) (2013) 40–47.
[66] J.L. Carlin, et al., Voluntary exercise blocks Western diet-induced gene expression of the chemokines CXCL10 and CCL2 in the prefrontal cortex, Brain Behav. Immun. 58 (2016) 82–90.
[67] F. Li, et al., Excessive endoplasmic reticulum stress and decreased neuroplasticity-associated proteins in prefrontal cortex of obese rats and the regulatory effects of aerobic exercise, Brain Res. Bull. 140 (2018) 52–59.
[68] C. Hetz, S. Saxena, ER stress and the unfolded protein response in neurodegeneration, Nat. Rev. Neurol. 13 (8) (2017) 477–491.
[69] M. Cai, 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 Behav. Immun. 57 (2016) 347–359.
[70] Z. Ye, et al., Hypothalamic endoplasmic reticulum stress as a key mediator of obesity-induced leptin resistance, Obes. Rev. 19 (6) (2018) 770–785.
[71] Y. Zhao, et al., The dynamic changes of endoplasmic reticulum stress pathway markers GRP78 and CHOP in the hippocampus of diabetic mice, Brain Res. Bull. 111 (2015) 27–35.
[72] F.J. Kong, et al., Endoplasmic reticulum stress/autophagy pathway is involved in diabetes-induced neuronal apoptosis and cognitive decline in mice, Clin. Sci. (Lond.) 132 (1) (2018) 111–125.
[73] X. Zhang, et al., Endoplasmic reticulum stress-mediated hippocampal neuron apoptosis involved in diabetic cognitive impairment, Biomed. Res. Int. 2013 (2013) 1–9.
[74] S.A. Oakes, F.R. Papa, The role of endoplasmic reticulum stress in human pathology, Annu. Rev. Pathol.: Mech. Dis. 10 (1) (2015) 173–194.
[75] C.A. Martin-Jimenez, et al., Astrocytes and endoplasmic reticulum stress: a bridge between obesity and neurodegenerative diseases, Prog. Neurobiol. 158 (2017) 45–68.
[76] X. Zhang, et al., Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity, Cell 135 (1) (2008) 61–73.
[77] A. Salminen, et al., ER stress in Alzheimer's disease: a novel neuronal trigger for inflammation and Alzheimer's pathology, J. Neuroinflammation 6 (2009) 41.
[78] O. Busquets, et al., Long-term exposition to a high fat diet favors the appearance of beta-amyloid depositions in the brain of C57BL/6J mice. A potential model of sporadic Alzheimer's disease, Mech. Ageing Dev. 162 (2017) 38–45.
[79] M.V. Lourenco, et al., TNF-alpha mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's beta-amyloid oligomers in mice and monkeys, Cell Metab. 18 (6) (2013) 831–843.
[80] A.J. Kole, R.P. Annis, M. Deshmukh, Mature neurons: equipped for survival, Cell Death Dis. 4 (2013) e689.
[81] W. Deng, J.B. Aimone, F.H. Gage, New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat. Rev. Neurosci. 11 (5) (2010) 339–350.
[82] V.P. Nakka, P. Prakash-Babu, R. Vemuganti, Crosstalk between endoplasmic reticulum stress, oxidative stress, and autophagy: potential therapeutic targets for acute CNS injuries, Mol. Neurobiol. 53 (1) (2016) 532–544.
[83] J.C. Moraes, et al., High-fat diet induces apoptosis of hypothalamic neurons, PLoS One 4 (4) (2009) e5045.
[84] Z. Cai, B. Zhao, A. Ratka, Oxidative stress and beta-amyloid protein in Alzheimer's disease, NeuroMolecular Med. 13 (4) (2011) 223–250.
[85] A. Fernandez, et al., Melatonin and endoplasmic reticulum stress: relation to autophagy and apoptosis, J. Pineal Res. 59 (3) (2015) 292–307.
[86] S.M. Ryan, Y.M. Nolan, Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: can exercise compensate? Neurosci. Biobehav. Rev. 61 (2016) 121–131.
[87] O. Lazarov, C. Hollands, Hippocampal neurogenesis: learning to remember, Prog. Neurobiol. 138-140 (2016) 1–18.
[88] V. Chesnokova, R.N. Pechnick, K. Wawrowsky, Chronic peripheral inflammation, hippocampal neurogenesis, and behavior, Brain Behav. Immun. 58 (2016) 1–8.
[89] Y. Kurhe, R. Mahesh, T. Devadoss, Novel 5-HT3 receptor antagonist QCM-4 attenuates depressive-like phenotype associated with obesity in high-fat-diet-fed mice, Psychopharmacology 234 (7) (2017) 1165–1179.
[90] G. Quesseveur, et al., BDNF overexpression in mouse hippocampal astrocytes promotes local neurogenesis and elicits anxiolytic-like activities, Transl. Psychiatry 3 (2013) e253.
[91] N. Chaudhari, et al., A molecular web: endoplasmic reticulum stress, inflammation, and oxidative stress, Front. Cell. Neurosci. 8 (2014) 213.
[92] J. Yu, et al., Update on glycerol-3-phosphate acyltransferases: the roles in the development of insulin resistance, Nutr. Diabetes 8 (1) (2018) 34.