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Review

Learning and Memory Impairment in High Fat Diet Induced Obesity

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Abstract. Obesity is a manifestation of abnormal fat accumulation which can lead to impairment in several organs, including the brain. Neuroinflammation is considered the cause of cell death as well as reactive oxygen species in hippocampal neuron cells. It results in disturbance of memory forming process. Impaired learning and memory function affects a person's ability to carry out daily tasks and lower quality of life over time, so they should be circumvented with preventive, curative, and rehabilitative measures. The understanding of the pathological mechanisms of obesity-induced memory impairment based on the changes at molecular levels is imperative for an effective management. We collected and reviewed research articles to summarize the pathological mechanisms. Twenty studies were included in this review in terms of signaling pathway, molecular markers in brain and changes in memory and behavior pattern. It is showed that memory changes in obesity could be resulted from inflammation, impaired neurogenesis and cell senescence via various mechanisms and pathways. In conclusion, the understanding of the pathomechanisms in obesity-induced memory impairment aids to its the prevention and treatment.

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1. Introduction

1.1 Obesity

Obesity is a global health problem with increasing proportions every year. WHO records that 39% of adults worldwide are overweight, and 13% of adults are obese. In addition to adults, it is known that the proportion of children aged 5-19 years who are overweight or obese is 18% [1]. In Indonesia, The National Basic Health Research (Riskesdas) in 2018 records that the proportion of obesity in adult individuals in Indonesia is 21.8%. This number shows an increase from 2007 (10.5%) and 2013 (14.8%), respectively [2].

Obesity is defined as a Body Mass Index (BMI) greater than 30 kg/m^2. The diagnosis of obesity in Indonesia follows the criteria of obesity in Asia Pacific, which is BMI of more than 27 kg/m^2. Central obesity is defined as a waist circumference of more than 90 cm in men and more than 80 cm in women [1-2]. This BMI measurement, although not directly able to measure the fat or adipose tissue levels of an individual, can be helpful for epidemiological research [3].

The pathophysiology of obesity involves various mechanisms. Recently, energy imbalance remained as of the main causes of obesity, which is known as Energy Balance Model [4]. Excess energy is being accumulated in the form of fat in adipose cells, then these cells will grow pathologically and alter metabolism control in the brain. White adipose tissue is the primary fat storage tissue that also functions as the endocrine organ producing adipokine and cytokines. The adipokines are then involved in various signaling cascades that regulate insulin, glucose absorption, fatty acid oxidation, and other energy production and metabolic processes [5].

Subcutaneous adipose tissue is the primary storage site for excess energy in the form of fat. If the capacity is exceeded, ectopic fat deposits will form in the liver and intraabdominal areas, contributing to obesity-related insulin resistance and inflammation [6]. Pathological enlargement of adipose cells also alters nutritional signals responsible for appetite regulation and metabolism. Accumulation of lipid metabolites, inflammation, or other mechanisms of disruption of hypothalamic neurons are also developed and lead to obesity [7].

Advances and novel genetic testing lead to the discovery of more specific genes responsible for obesity. Recently, researchers classified the role of genetics in obesity into two categories: monogenic obesity and polygenic obesity. Monogenic obesity is inherited in the Mendelian pattern. This type of obesity is very rare, most of the genes are known to be related to leptin/melanocortin pathway [8].

The second form is polygenic obesity or general obesity and is the result of the accumulation of hundreds of polymorphisms, each of which has a small effect. Several obesity–related genes that have been identified are proopiomelanocortin (POMC), melanocortin 4 receptor (MC4R), leptin (LEP), leptin receptor (LEPR), brain – derived neurotrophic hormone (BDNF), neurotrophic tyrosine kinase receptor type 2 (NTRK2), prohormone convertase 1 (PCSK1), and "single minded" homolog 1 (SIM 1) [9].

In monogenic and polygenic obesity, the hypothalamus, as well as the pathways that control hedonic aspects of food intake and the eating process, have been identified as weight regulators. Food intake regulatory genes such as ADRB3, BDNF36, CNR1, MC4R38, PCSK1 and PPARG40 have been linked to obesity outcomes [10]. The Genome Wide Association Study (GWAS) method has been used to investigate single-nucleotide polymorphisms (SNP) genes that may be associated with the phenotype of obesity. SNP RALGAPA1 was also discovered to be a specific genetic predisposing factor for increased BMI [11].

Observational studies show that obesity is one of the risk factors for decreased memory function as well as worsen condition of dementia in elderly. Memory function, along with the ability to learn and make decisions, is important for an individual to be able to live his life functionally and to be able to carry out his daily activities [12]. Working memory and long-term memory can be impaired in obese people due to changes in brain structure. These structural changes are characterized by decreased volume in several areas of the brain, including the hippocampus and prefrontal cortex [13].

Another observational study of 2,000 middle-aged workers studied the relationship between elderly obesity and cognitive performance globally, including the memory domain. Although aging is a physiological process that causes minor changes in cognitive structure and function, obesity in old age is likely to worsen memory function. According to the study, the elderly with obesity remember fewer words when taking the word-list learning test than the elderly with normal BMI. The result showed that BMI had negative relationship between with learning performance and memory in the subjects [14].

1.2 Mechanism of Memory Formation

The process of memory formation involves many areas of the brain, including primary sensory cortex, which receives sensory information from the five senses as well as somatosensory input. After the primary sensory cortex receives the information, it is passed on to the association area, which continues to the parahippocampal area, rhinal cortical area, and hippocampus. Memory is then strengthened and coordinated with the neocortex (particularly the medial-temporal lobe area), which regulates motor responses in declarative memory and long-term memory storage [15].

We will explain briefly about the memory formation including maintenance, encoding, consolidation and retrieval. Maintenance can be learned during the formation of working memory. There is a population of neurons in the DLPFC that will continue to fire even after the stimulus has been removed. DLPFC contains neurons that release the neurotransmitter dopamine, which acts as a modulator in the gating process [16]. Glutamatergic afferent neurons relay sensory stimulus information to the PFC. Dopamine binds to the spina dendrite receptor, modulating glutamate transmission at the synapse via somatostatin interneurons. Layer II pyramidal cells form functional clusters with highly repeating excitatory connections [17].

Memory encoding is a molecular process that involves glutamate activity at the synapse cleft. When new information or knowledge is received, a group of neurons is activated to encode the new memory. Glutamate, an excitatory neurotransmitter, is released by presynaptic neurons and then binds to its receptors in postsynaptic neurons, namely the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPAR) and the N-methyl-D-aspartate receptor (NMDAR) [18].

This synapse then undergoes plastic changes in the form of the initial phase of long-term potentiation. Glutamate binding to AMPAR receptors causes changes in cell polarity due to the movement of K^+ and Na^+ into postsynaptic neurons, resulting in depolarization. The positive charge inside the postsynaptic neuron allows the release of a "magnesium plug" from another glutamate receptor, the NMDAR. Continuous neuronal stimulation opens the NMDAR pore channel, which is a calcium ion channel [19].

Calcium influx into postsynaptic neurons causes cytoskeletal protein modifications, actin polymerization, and actin branching. Rac1 and Cdc42 activate Arp2/3, which is an actin nucleation factor that functions to induce actin polymerization, actin filament elongation, and actin branching. Rho GTPases also help anchoring, stabilization, phosphorylation and inserting AMPAR into the postsynaptic density area membrane [19-20].

The consolidation process converts information that is temporarily stored and still labile into a stronger and more stable network. Consolidation is the final phase of LTP, which is the presence of gene expression and protein synthesis that cause structural changes in the synapse, also known as gene expression dependent, and can last for several hours to several days [21].

According to research, memory that is fixed and insensitive to molecular disturbances can become labile when reactivated, such as by the retrieval mechanism. This post-retrieval fragility is temporarily limited, and the memory returns to a stable state via the reconsolidation process [22]. The medial temporal lobe is an important part of the brain in the process of consolidating declarative memory, especially during sleep. The temporal neocortex, which may be a repository of long-term memory, is

located in this lobe. The most important structure is the hippocampus, which is located near the cortical area and serves as the "pathway" that connects these structures to the rest of the brain [23].

System consolidation occurs over the next day to week, which is the process of replaying and synchronizing learning-related patterns of neural activity in the hippocampus and cortical areas. This consolidation process involves cortical areas such as the prefrontal cortex. This structure is thought to induce cortical engram cell maturation, which contributes to long memory (remote memory) [24]. Based on these facts, this article will discuss the molecular events that occur in memory and cognitive decline caused by obesity. Understanding this mechanism is expected to increase health promotion efforts to prevent obesity which in turn leads to learning and memory impairment.

2. Materials and Method

Electronic searches were conducted in Science Direct and PubMed databases published between January 2019 and December 2023. We used keywords related to molecular mechanisms of memory impairment caused by obesity, including "high fat diet" OR "obesity" AND "memory", OR "learning" OR "cognitive", AND "molecular" AND "mechanism". The following studies were included: 1) experimental studies in vitro or in vivo, 2) not a case report or review, 3) full text were available. After duplicates were removed by automated system, articles were screened based on titles and abstracts, and a thorough assessment of relevance was conducted by full text reading.

Data were extracted and collected in Microsoft Excel. We retrieved data from various articles including included authors, year of publication, type of experimental animal/cells, molecular pathway and major findings related to memory changes. When the relevant data were unavailable or could not be obtained from the article, they were written as "not available" (N/A).

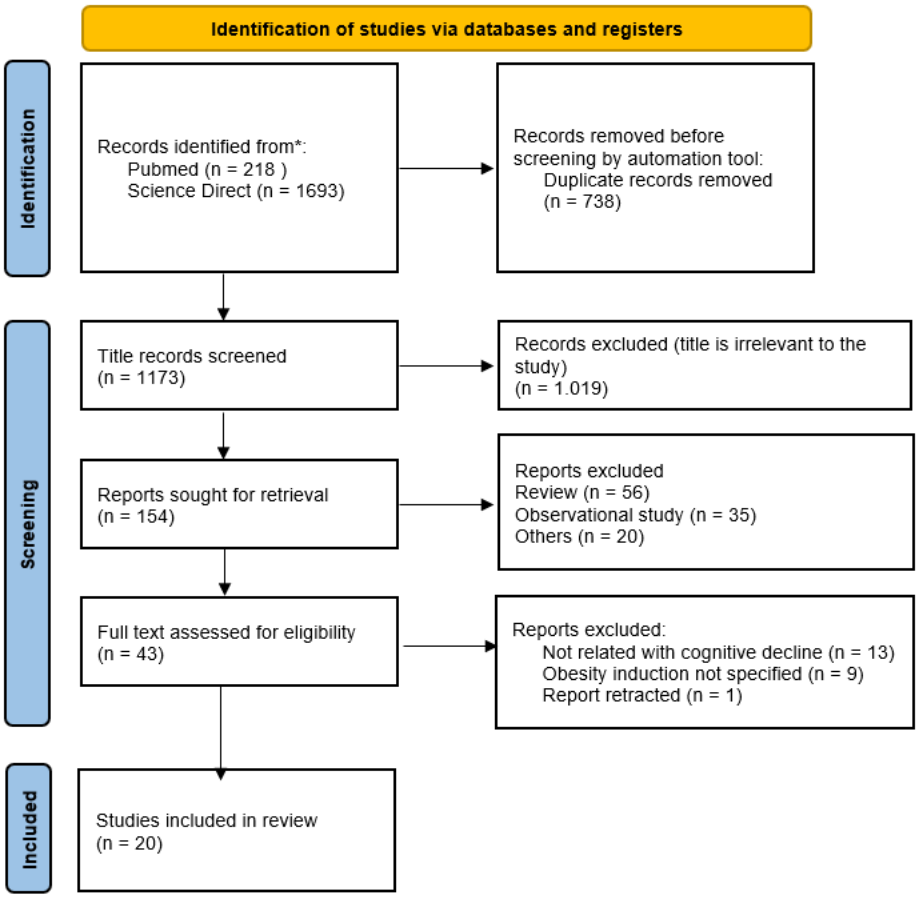

Figure 1. PRISMA flow of diagram in this review.

3. Results and Discussion

A total of 1173 studies were retrieved after screened for duplication and 154 articles were included after screened for title relevancy. We then excluded 111 articles that did not meet inclusion criteria. Among those, 35 articles were observational studies, 56 articles were review, and 20 articles were studies other than experimental studies. Forty-three articles remained for full text review. Twenty-three articles were excluded due to relevance, and 20 articles remained to be discussed in this review.

3.1 Gut Health and Neuroinflammation

Obesity which caused by excess consumption of high-fat foods could lead to the dysbiosis of the gut microbiota. Dietary fats alter intestinal permeability by changing the distribution and expression of intestinal tight junctions, causing dysbiosis [25]. The amount of beneficial microbiota that keep the intestinal integration intact decreases and the likelihood of pathogen microbiota entering the bloodstream and causing systemic inflammation is raised [26].

Research by Wang et al. showed that high fat foods induced oxidative stress and disorder of energy metabolism. Intestinal barrier integrity in obesity is disrupted, showed by the decreased levels of proteins which regulate tight junction, including SOD, GSH-Px and occludin. In the brain several changes in neurogenesis occurred, marked by decrease of some protein such as PSD95 and Nrf2 [27].

Inflammation is also associated with the disruption of blood brain barrier in the hippocampus. Immunoreactivity process and increased pro-inflammatory cytokines such as TNFα and IL1-β were found in the hypothalamus and hippocampus [28]. In another study, inflammatory agents increased oxidative stress and could lead to insulin resistance and impaired glucose tolerance, which lead to cognitive decline in mice [29].

Microglia is related to inflammatory process in brain. Activated microglia is a hallmark for neuroinflammation, showed by increase of protein marker of GFAP [30]. Furthermore, this macroglia has 2 subsets: M1 which is inflammatory phenotype and M2 which is anti-inflammatory phenotype. Wu et al. found that in obesity, microglial polarization to M2 was dominant, thus neuroinflammatory process would continue, marked by the increase of TNFα↑, IL-1β↑, IL6↑, and TLR4↑ [31].

Study from Azmi et al showed that brain lipid peroxidation and protein involved in Aβ metabolism were altered along with inflammation. This showed that high fat meal and inflammation could also lead to memory impairment related to other diseases such as Alzheimer's [32]. Furthermore, excitability of brain nuclei in hypothalamus which regulate neuroendocrine, autonomic, and behavioral responses could also be worsened. This condition can lead to cognitive impairment related to reward system, stress reactivity and anxiety-like defensive to stressful stimuli, and enhances stress reactivity and anxiety-like defensive behavioral responses [33-34].

Table 1. Studies included in review

No	Author (Year)	Animal/cell	Cognitive assessment	Molecular pathway	Major findings in Obesity	Ref.
1	Agrimi et al.(2019)	Obese mice	Elevated plus maze, Y-maze	BDNF/TrkB	Hippocampal DG volume↓, neurogenesis↓, TrkB↓, BDNF↓, GFAP↑	[35]
2	Mucellini et al.(2019)	Obese female rats	Object recognition task	MAPK	MAPK↑	[41]
3	Noronha et al.(2019)	Rats	Elevated T maze, open field test	N/A	TNF↑, IL6↑	[33]
4	Ogrodnik et al.(2019)	INK-ATTAC mouse model	Elevated T maze, open field test, Stone's T maze	N/A	SA-β-Gal+↑, p16↑, TAF↑	[46]
5	Wohua et al. (2019)	GRX-KO Mice	Y maze, Morris Water Maze	IRS1-PI3k-Akt-GSK3	GFAP↑, Iba-1↑, TNFα↑, IL6↑, IL-1β↑, pIRS1↓, p-AKT↓, p-GSK-3β↓	[29]
6	Bordeleau et al. (2021)	Mice	Elevated T maze	N/A	Mbp↓, Cspg↓, Igf-1↓, Olig2↓	[36]
7	Liskiewicz et al.(2021)	Rats	Morris Water Maze	NF-κB	DCX+↓, BrdU+/NeuN+↓	[39]
8	Makinen et al.(2021)	Rats	N/A	N/A	TLR3↑, IL1- β↑, GFAP↑, DCX+↓, SYN-1↑, SYP↓	[38]
9	Wang et al. (2021)	Mice	Y maze, Morris Water Maze	N/A	Intestine SOD↓, GSH-Px↓, occludin↓ Brain cortex NeuN↓, TUNEL↑, PSD95↓, MDA↑, SOD↓, Nrf2↓, Keap1↑	[27]
10	Lama et al. (2022)	Mice	N/A	NF-κB	Hypothalamic IL1- β↑, Crh↑, Iba-1+↑, GFAP↑ Hippocampal TNF↑, IL1- β↑, Iba-1+↑, GFAP↑, Myd88↑, Tlr2↑, Cma1↑, Tpsb2↑, Tjp1↓, Ocln↓, Cldn5↓	[28]
11	Velden et al.(2022)	Mice	N/A	N/A	BIN1↓, HDAC5↑, FNIP2↓	[44]
12	Verma et al.(2022)	Mice	Radial arm maze, OFT, NOR	N/A	Dendritic spine density ↓	[37]
13	Wu et al. (2022)	Mice	MWM, NOR, Y maze	NF-κB	Spinophilin↓, PSD95↓, synaptophysin↓, Dendritic spine density ↓, Iba-1+↑, iNOS+/ Iba-1+↑, TNFα↑, IL-1β↑, IL6↑, TLR4↑	[31]
14	Azmi et al.(2023)	Rats	N/A	N/A	MDA↑, Aβ↑, presenilin↑, ApoE↑, LRP1↓, IDE↓, BACE1↑, RAGE↑	[32]
15	Chen et al.(2023)	Mice	MWM	mTOR	IL-1β↑, IL6↑, PTEN↑	
16	Hao et al.(2023)	Mice	MWM	N/A	GLUT1↓, GLUT3↓, GLUT4↓, hippocampal GLUT1+/GFAP+↓,	[42]

					hippocampal GLUT3+/NeuN+↓, cortex GLUT1+/GFAP+↑	
17	Lin et al.(2023)	Mice	OFT	ERK-Akt	GFAP↑, Iba-1↑, SR-A4↑	[30]
18	Moreno et al.(2023)	Rats	N/A	N/A	HNE↑, MDA↑, cytosolic protein carbonylation index↑, myofibrillar protein carbonylation index↑, total protein carbonylation index↑	[45]
19	Afonso – Oramas et al. (2023)	Mice	N/A	N/A	VIP↓, NPY↓	[34]
20	Xu et al. (2023)	Rats	MWM, Passive avoidance test	N/A	insulin↑, GFAP↑, Iba-1+↑, TNFα↑, iNOS↑, Cox2↑, CAT↓, GPx↓, GSH↓, Nrf-2↓, HO-1↓, 3-NT↓, 8-isoprostate↑, p-tau↑, APP↑, BACE↑, Aβ↑, p-IRS↑, p-IKK↑, p-JNK↑, p-AKT↑, p-GSK3β↑, synaptopodin↓, synaptophysin↓, ChAT↓, p-CREB↓, BDNF↓	[43]

OFT: open field test; MWM: Morris Water Maze; NOR: Novel Object Recognition

3.2 Impaired Neurogenesis

Aside from direct brain inflammation, another molecular mechanism that could change memory function is impaired neurogenesis. This condition arises from neurosurvivability disturbance as well as insulin resistance in the brain. From recent studies, neurogenesis impairment is seen more frequently in obesity and individuals which are exposed to mental stressors. Impaired neurogenesis in those individuals was marked with the decrease of BDNF/TrkB pathway and hippocampal size particularly in DG region [35].

Besides neuron, oligodendrocytes could also undergo several changes, such as decreasing oligodendrocyte-microglia crosstalk resulting in long-term brain alterations in high fat feeding.[36] Another evidence showed that hippocampal pyramidal neuron had less dendritic spine density in obese. Interestingly, this phenomenon seemed to be reversible and could be better after some treatments [37].

Some evidence suggests that intervention such as exercise could reverse cognitive decline in obesity. Makinen et al. showed that low intrinsic aerobic fitness that was associated with reduced hippocampal structural plasticity at a young age, which indicated by the decrease of neuron structural proteins such as synaptophysin and synapsin [38]. In line with the previous study, Liskiewicz et al. found that obesity affects metabolic processes, upregulates hippocampal NF-κB, and causes proteomic differences linked to impaired cognition and neurogenesis, similar to previous studies. Weight loss was beneficial for neurogenesis and cognition [39].

As mentioned previously, neurogenesis is affected by insulin signaling in the brain. Insulin signaling has a role to mediate the process of learning and working memory in the hippocampus through the insulin/IGF-1 signaling pathway. Insulin receptors are expressed in neuron cells to maintain synapse density, dendritic plasticity, and normal cell function. Insulin receptor signaling promotes dendritic spine formation and excitatory synapse growth through activation of PI3K/Akt/mTOR and Rac1 signaling pathways [40].

Peripheral insulin enters the brain primarily via three routes: passive extravasation of fenestration capillaries and ependymal cells of the median eminence; transcytosis from the BBB to the brain; and tanycyte-mediated transport of cerebrospinal fluid. Insulin transport to the brain, on the other hand, decreases in conditions of excess nutrition. Phosphorylation of serine/threonine-protein kinases are markers of insulin resistance in neurons that correlates with lower levels of learning and memory function [40].

In previous study, admission of high-calorie meals in puberty showed insignificant increase of BNDF nor CREB signaling, but MAPK increased significantly. Increases in MAPK may indicate that BDNF intracellular signaling was being upregulated in an attempt to increase long-term potentiation mechanisms through positive feedback. Another possible explanation for the MAPK increase is central insulin resistance. It also showed that consuming a high-fat, high-sugar diet reduced peripheral insulin transport and uptake into the brain, resulting in central insulin resistance [41].

Brain glucose uptake is the process by which glucose is transported across cell membranes by integral transport proteins in the brain, such as glucose transporter type 1 (GLUT1), glucose transporter type 3 (GLUT3), and glucose transporter type 4. GLUT1 is primarily expressed in endothelial cells and astrocytes and is an important glucose transporter across the blood-brain barrier. GLUT3 is classified as a neuronal transporter, whereas GLUT4 is the primary insulin-inducible glucose transporter. Hao et al. discovered that some changes occurred in brain glucose transporter resulting from obesity, including downregulated the gene expression of glucose transporter type 4 (GLUT4), reduced the colocalization of GLUT1/glial fibrillary acidic protein (GFAP) in the hippocampus, and impaired spatial memory [42].

Reduced brain insulin sensitivity is linked to decreased cognitive function through systemic glucose homeostasis dysregulation, neuroinflammation, and oxidative stress. Docosahexaenoic acid (DHA) administration may improve cognitive function in aged rats fed by high-fat diet, by facilitating hippocampal insulin signaling. Furthermore, DHA disrupted the reciprocal cycle involving hippocampal insulin resistance [43].

Obesity worsens cognitive function via oxidative damage and cell senescence which is regulated by the process of DNA methylation. Methylation is one mechanism by which these factors may affect the hippocampus which is particularly susceptible to the negative effects of aging, environmental insults, and metabolic shifts. Obesity could interact with aging and significantly affect the hippocampal methylome. This process will change the expression of genes regulating neurodegeneration and metabolism [44].

Study conducted by Moreno et al. found that cortical MDA, cytosolic protein carbonylation index, myofibrillar protein carbonylation index increased in obesity. These results concluded that the high – calorie diet increased oxidative damage of specific proteins that regulated specific pathways for brain function, including energy production, glucose metabolism and neurotransmission [45].

Senescent cells seemed to have a role in the impaired neurogenesis induced by obesity. Senescent glial cells were found accumulated in the lateral ventricle, a region in which adult neurogenesis occurs. Furthermore, senescent glial cells exhibit excessive fat deposit. Ogrodnik et al. study suggested that the absent or clearing of senescent cells from obese mice could improve neurogenesis and alleviated anxiety-related behavior [46].

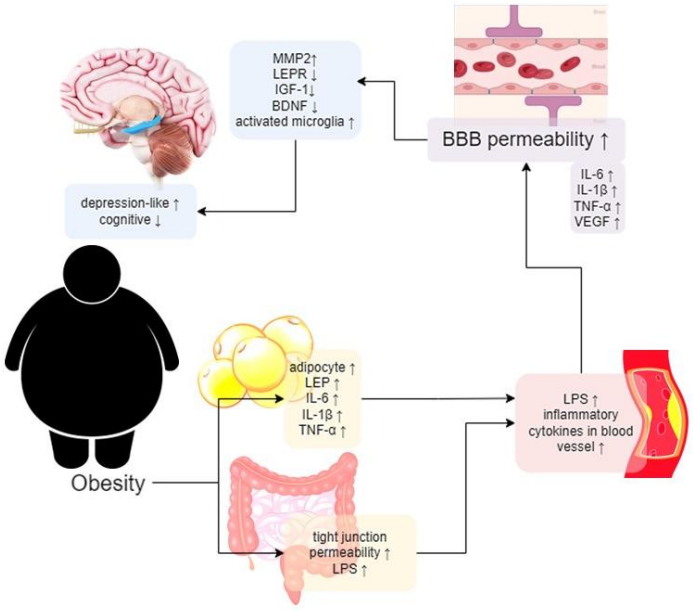

Figure 2. Pathophysiology of Obesity-Induced Neuroinflammation

4. Conclusion

Obesity is a global health issue that requires greater attention. This is demonstrated by the rising proportion of obese people both globally and in Indonesia. Obesity is caused by an imbalance of incoming and used energy, resulting in adipocyte cell hoarding. Energy imbalance also disrupts metabolic processes, resulting in leptin and insulin resistance and decreased control over food intake.

Obesity-related systemic disorders can affect a variety of organs, including the brain. The brain is an important organ that regulates all body systems and also plays a role in the process of learning and memory formation. Impaired learning and memory functions in obese people can be caused by dysbiosis in the gut microbiota, which causes neuroinflammation. This condition can lead to impaired neurogenesis particularly in hippocampus, where memory consolidation takes place. Insulin resistance and cell senescence disrupt neuron survival via impairment of gene expression and signaling in the brain, causing neural death. In conclusion, the understanding of how obesity induces memory and learning impairment should aid in its prevention, so that it can be carried out in effective manner to mitigate the impact of decreased learning and memory abilities.

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