Mechanisms by which an HFD impairs memory and strategies to reverse this.

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Abstract. The World Health Organization points out that obesity is increasing. And the overconsumption of food high in saturated fat and refined carbohydrate appears to be a primary driving force behind the obesity epidemic. This highlights the importance of understanding the effects of this type of diet on metabolism. In this context, a high-fat diet (HFD), composed primarily of saturated fatty acids, is associated not only with obesity but also with other metabolic disorders. Furthermore, it has been proposed that a HFD even affects areas of the brain, for example, the hippocampus, interfering with cognitive function, such as learning and memory. However, the precise mechanisms of how it happens are not yet well understood. Therefore, here are reviewed the potential mechanisms by which a HFD affects the brain and impairs learning and memory function that relays on the hippocampus, such as inflammation, oxidative stress, lipid peroxidation, neuronal apoptosis, increased blood-brain barrier permeability, and neuroepigenetic dysregulation of memory-related genes. In addition, the review introduces some interventions, such as endurance exercise, dietary restriction (every other day fasting), and antioxidants (vitamin E and extra virgin olive oil), that have the potential to counterbalance the metabolic and cognitive effects due to the consumption of a HFD.

Keywords. High-fat-diet, hippocampus, memory, learning, cognitive impairment

1. Introduction

Obesity is increasing all over the world (1,2). And a diet rich in saturated fatty acids or refined carbohydrates has long been associated with an increased risk of obesity (3), but also type 2 diabetes and cardiovascular disease. Furthermore, a link between dietary components and the development of cognitive impairment has been proposed.

And recently, several studies have pointed out that a high-fat diet (HFD) alters memory and learning functions that depend on the integrity of the hippocampus (4–6).

But the exact mechanisms by which HFD impairs the brain are not well established, despite the fact several potential mechanisms have been proposed.

In this context, this review aimed to investigate the current mechanisms that may underlie the connection between HFD consumption and cognitive impairments.

2. Hippocampus

A great number of evidence indicate the link between the consumption of a HFD and impairments in learning and memory performance (7–9). This is consistent with studies that point out that a HFD affects the hippocampus, a brain area that is related to cognitive functions, such as learning and memory (10).

That is, a HFD activates signaling pathways associated with inflammation (11), alters the levels of oxidative stress (12), leads to lipid peroxidation (12–14) and neuronal apoptosis (11,14), and alters gene expression in rodents' hippocampus (15). The same is true for a high-energy diet (HED), rich in saturated fat and refined carbohydrates. A study found that the consumption of a HED makes the hippocampus more permeable to sodium fluorescein (NaFl), an indication of loss of integrity of the blood-brain barrier (BBB) (6).

Furthermore, animals exposed to both a HFD (12) or a HED (6) show impaired performance in learning and memory tests, like object-place recognition (12,15), radial arm water maze (13), and nonspatial Pavlovian discrimination, specifically the feature negative discrimination (6), that mostly relies on the integrity of the hippocampus.

3. Mechanisms

3.1 Inflammation

There are many inflammation signaling pathways initiated by the Toll-like receptor 4 (TLR-4), a receptor expressed on various cells involved in the first line of defence against infections (16).

For example, the activation of TLR-4 leads to the phosphorylation of lκB, which is responsible for keeping the transcription factor NF-κB inactive, and, under phosphorylation, it becomes ubiquitinated and is degraded through the ubiquitin-proteasomal pathway. This allows the NF-κB to move into the nucleus, leading to the expression of inflammatory cytokines (17–19).

And rats exposed to a HFD for 20 weeks to induce obesity exhibited increased expression of TLR-4 and of the proinflammatory cytokines related to TLR-dependent signal transduction, such as IL-1β and TNF-α (11). And consumption of a HFD for 16 weeks also increases the levels IL-1β and IL-6 mRNA levels in the hippocampus, as well as TLR-4 (20).

Consumption of a HFD also modulates glial reactivity. The intermediate filament protein glial fibrillary acid protein (GFAP) is a biomarker used to evaluate astrogliosis, characterized by astrocyte activation and molecular, cellular, and functional alterations in these cells, which is related to central nervous damage (21,22). And IBA-1, a calcium-binding protein specifically expressed in microglia and involved in phagocytosis, is used to evaluate microglial reactivity (23–25). In this context, the expression of both GFAP and IBA-1 was elevated in the hippocampus of HFD-fed rats (11).

3.2 Oxidative stress

Oxidative stress is an excess formation of free radicals due to an insufficiency of the counteracting antioxidant response system (26).

Mice exposed to an HFD for 4 or 7 weeks (12) or for 6 weeks (13) showed higher levels of reactive oxygen species (ROS) in the hippocampus. In addition, they also showed downregulation in the activity of enzymes involved in the antioxidant defence, superoxide dismutase (SOD), and catalase glutathione reductase.

The levels of glutathione (GSH) were reduced, and its oxidized form (GSSG) increased (13). That is, the animals showed a decrease in the GSH/GSSG ratio (12,13), and this ratio is important because it can be considered a biomarker of cellular health (27).

3.3 Lipid peroxidation

One of the consequences of oxidative stress is lipid peroxidation, which is a process under which oxidants such as free radicals or nonradical species attack lipids containing double carbon-carbon bonds, especially polyunsaturated fatty acids (PUFAs). This process can play a cytotoxic role in inhibiting gene expression and promoting cell death (28).

And the studies showed that an HFD also increases the markers of lipid peroxidation, malondialdehyde (MDA) (12,14), and thiobarbituric acid reactive substances (TBARS) (13), in the hippocampus.

3.4 Neuronal apoptosis

An increase in lipid peroxidation can induce neuronal apoptosis (13). And mice exposed to a HFD for 7 weeks exhibited an impairment in neural progenitor cells in the hippocampus. Furthermore, high levels of MDA lead to decreased cell proliferation (14), pointing to another association between lipid peroxidation and neuronal impairments.

In addition, apoptosis is controlled by pro- and anti-apoptotic proteins, Bax and Bcl-2, respectively. The pro-apoptosis protein Bax translocates to the mitochondrial membrane, forming pores that facilitate the release of cytochrome C from the intermembrane space, which in turn activates the caspase pathway responsible for initiating apoptosis. While Bcl-2 inhibits apoptosis by preventing the formation of pores (29). And a 20-week HFD resulted in an increase in Bax and a reduction in Bcl-2 proteins (11).

Also, hippocampal neurogenesis is regulated by growth factors, such as brain-derived neurotrophic factor (BDNF), whose expression is reduced by exposure to a HFD for 7 weeks (14). But not all studies with the same time of exposure to a HFD found alterations in BDNF levels (12).

3.5 Blood-brain barrier

The blood-brain barrier separates the blood from direct contact with the brain parenchyma (30); therefore, when intact, it has a protective function in relation to the brain.

The claudins are tight junction proteins proposed to be vital to establish the tight junction properties of the endothelial cells and are considered to be important in the maintenance of permeability restriction (31). Exposure to a HED for 90 days reduced the mRNA expression of tight junction proteins, Claundin-5 and Claudin-12, in the BBB (6).

Additionally, HED also increased the permeability of sodium fluorescein (NaFl) from the vasculature to the hippocampal parenchyma (6).

3.6 Gene expression

Long-term memory consolidation involves the activation of memory-associated gene expression (32). And the peroxisome proliferator-activated receptor gamma coactivator 1-α (*Ppargc1a*), protein phosphatase1, catalytic subunit, β isozyme (*Ppp1cb*), reelin (*Reln*), and sirtuin 1 (*Sirt1*) are considered important genes within the hippocampus.

And a study revealed that *Ppargc1a*, *Ppp1cb*, *Reln*,

and *Sirt1* exhibited reduced gene expression within the hippocampus of mice exposed to HFD for 20 or 23 weeks (15).

One way to alter gene expression is through epigenetic mechanisms, such as DNA or histone methylation or acetylation among others, that induce alterations of gene expression without altering the DNA sequence (33).

And these genes (*Ppargc1a*, *Ppp1cb*, *Reln*, and *Sirt1*) showed increased methylation at promoter regions, an epigenetic alteration associated with gene suppression, in general (15).

When the animals were exposed to HFD for 13 or 17 weeks, even though they showed characteristics indicative of obesity, such as weight gain and hyperinsulinemia, *Ppargc1a* was the only gene that showed a reduction in expression at an earlier time. And no difference was observed in methylation at promoter regions (15).

Therefore, these findings support the idea that neuroepigenetic dysregulation of memory-related genes within the hippocampus underlies hippocampus-dependent memory impairment in a time-dependent manner.

4. Interventions

4.1 Edurance exercise

After 20 weeks of consumption of an HFD, male rats were subjected to a protocol of treadmill running protocol 5 days a week for 8 weeks. And the study showed that treadmill exercise (TE) counterbalanced the impairments after HFD.

The practice of TE reduced abdominal visceral fat, improved insulin resistance, precluded the elevation of proinflammatory cytokines, prevented microglia activation, averted apoptosis activation, and recovered working memory function (11).

4.2 Dietary restriction

The use of every other day fasting (EODF) paradigm as a method of dietary restriction was able to normalise the alterations in the antioxidant mechanisms caused by an HFD. That is, EODF prevented the reduction of GSH and the decrease of SOD and catalase activities and also prevented the increase of GSSG and TBARS. These results demonstrated that dietary restriction has an antioxidant effect (13).

4.3 Antioxidants

The administration of vitamin E concurrently with a high-fat high-carbohydrate diet (HFCD) for 6 weeks was able to reverse the impairments caused by the diet in mice. That is, the administration of vitamin E prevented the reduction in the activities of the antioxidant enzymes, SOD and catalase, caused by the ingestion of a HFCD. Additionally, vitamin E administration reduced the increase in GSSG and TBARS generated by HFCD (34).

Furthermore, animals fed extra-virgin olive oil (EVOO) for 60 days prior to induction of Alzheimer's disease (AD) showed a reduction in the level of MDA, amyloid β protein, and hyperphosphorylated tau protein accumulation compared to those who did not receive EVOO prior to induction of AD (35).

5. Discussion

Although there are variations in the type of diet, the number of components, the time exposed to the diet, and the behavioural tests between the studies, taking all of the results, they support the hypothesis that diet has a strong effect on maintaining the integrity of brain function.

But it remains unclear if the alterations observed as a result of consumption of an HFD are due to specific dietary components, adiposity tissue, or metabolic alterations associated with diet-induced obesity.

No single mechanism may explain memory impairment induced by HFD. And some alterations might be responsible for the development of cognitive impairs while others in the progression of the impairments. Therefore, the mechanisms underlying the short- and long-term effects of HFD or HED may differ.

Regarding the interventions, the findings that antioxidants interventions, such as the EODF, vitamin E, and EVOO, prevented the behavioural, metabolic, and central alterations associated with a diet rich in saturated fatty acids or carbohydrates points to the crucial role the consumption of antioxidants, as well as nutritional strategies, can have in preventing impairments caused by diet. This also indicates that oxidative stress may play a critical role in explaining how diet affects memory.

And in terms of endurance exercise, it is revealed as a prominent noninvasive and economic strategy against alterations associated with HFD. It provides an anti-inflammatory function, counterbalances metabolic disorders, and is effective in the maintenance of the brain's cognitive functions. Regarding its anti-inflammatory effect, this supports the point that increased brain inflammation, including activated microglia, contributes to brain injury.

In addition, it encourages further investigations of the role that exercise might have as a therapeutic intervention for disorderly underlying conditions not included in the review, such as neurodegenerative diseases.

In conclusion, the most well-characterised mechanisms are inflammation, oxidative stress, lipid peroxidations, neuronal apoptosis, increased BBB permeability, and neuroepigenetic dysregulation of memory-related genes.

And understanding the mechanism by which an HFD

impairs memory provides insight into the way to approach and counterbalance the alterations caused by the sustained consumption of saturated fatty acids.

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