

# Effect of Western Diet on Cognition

Subjects: **Endocrinology & Metabolism**

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Traditional eating habits have been replaced by a more globalized diet, rich in saturated fatty acids and simple sugars. Extensive evidence shows that these dietary factors contribute to cognitive health impairment as well as increase the incidence of metabolic diseases such as obesity and diabetes.

diet

cognition

memory

learning

hippocampus

synaptic function

## 1. Introduction

The growing prevalence of cognitive impairment and dementia, with 100 million cases estimated by 2050, is becoming a serious public health concern with both individual and socioeconomic burdens <sup>[1]</sup>. Although the rise in life expectancy is one of the main causes of the increased prevalence, multiple other factors are likely to play a role. In recent years, increasing attention has been paid to the impact of diet on brain health and mental function <sup>[2]</sup> <sup>[3]</sup>, with several dietary components, such as carbohydrates, fats, and hormones, reported to influence cognition <sup>[1]</sup>. Indeed, the consumption frequency of healthy or unhealthy foods perfectly correlates with better or worse cognitive performance in older adults <sup>[4]</sup>. It would seem, therefore, that the researchers' diet directly affects brain health and the probability of developing dementia and neurodegenerative disorders in later life.

The consumption of high-fat/high-sugar diets in modern civilizations, combined with overeating behaviors and sedentary lifestyles, has led to exponential growth in obesity cases worldwide, reported to be 650 million people in 2016, according to the World Health Organization (WHO) <sup>[5]</sup>. Obesity increases the risk of developing dementia in later life <sup>[6]</sup><sup>[7]</sup>, and has been associated with immediately altered cognitive performance, including impaired verbal learning, working memory, stimulus reward learning, and executive functions (adaptation to novel situations, cognitive flexibility, attention span, planning, and judgment) <sup>[8]</sup><sup>[9]</sup><sup>[10]</sup>. Obesity is also considered a risk factor for developing multiple comorbidities, such as type 2 diabetes (T2D), hypercholesterolemia, hypertension, and metabolic syndrome (MetS), all of which may have an independent impact on cognition. In fact, T2D (with 422 million cases in 2014, according to the WHO, <sup>[11]</sup>) correlates with cognitive dysfunction, including reduced information processing speed and altered verbal, visual memory, and executive functions <sup>[12]</sup><sup>[13]</sup><sup>[14]</sup>. Even impaired glucose tolerance, which develops prior to T2D, is considered a risk factor for cognitive damage <sup>[15]</sup>. In addition, also associated with a higher risk of cognitive impairment and dementia is MetS <sup>[16]</sup><sup>[17]</sup><sup>[18]</sup>, defined as a multifactorial disorder characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia <sup>[19]</sup>. However, still poorly understood are the physiopathological mechanisms by which metabolic diseases affect learning and memory processes, and raise the risk of late-life dementia and neurodegeneration.

During learning and memory task performance, neural networks, in a process called neuroplasticity [20], make new connections and/or adjustments in synaptic strength, especially in the hippocampal glutamatergic circuits. This reorganization is carried out by tight control of the number of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate ionotropic receptors (AMPARs) in the post-synaptic zone (PSZ). Since glutamate is the major excitatory neurotransmitter in the central nervous system, AMPARs are the main mediators of fast synaptic transmission. Functional receptors are tetrameric assemblies of subunits GluA1-4. Whereas GluA4 is mostly expressed during early development stages, in mature excitatory neurons, AMPARs contain two dimers of GluA1/GluA2 (~80% of all synaptic AMPARs) or GluA2/GluA3 heteromers [21]. In resting conditions, the presence of GluA2 in surface AMPARs makes these  $\text{Ca}^{2+}$ -impermeable [20]. Following stimulation with glutamate, precise regulation leads to synaptic incorporation of GluA1-GluA1 homomers. These GluA2-lacking AMPARs are  $\text{Ca}^{2+}$ -permeable (CP-AMPARs), and, over a restricted period of time, induce  $\text{Ca}^{2+}$ -sensitive signaling events that sustain synaptic potentiation or modulate subsequent neuroplasticity. However, aberrant incorporation of CP-AMPARs can result in excessive  $\text{Ca}^{2+}$  influx, inducing excitotoxicity and cell death, as reported for brain diseases [22]. An excitotoxic influx of  $\text{Ca}^{2+}$  is also mediated by overactivation of N-methyl-D-aspartate (NMDA)-type glutamate ionotropic receptors (NMDARs) [23]. Functional NMDARs are tetramers of GluN1 (A or B) and GluN2 (A-D), and are also involved in neuroplasticity modulating synaptic incorporation of CP-AMPARs.

Changes in the expression of a particular subunit of AMPARs produce an imbalance in AMPAR tetrameric composition or dysregulate its trafficking toward the PSZ, and both have been linked to Alzheimer's disease (AD) and cognitive aging [21][24]. In AD, high levels of amyloid- $\beta$  oligomers ( $\text{A}\beta$ )—a main pathological hallmark, together with Tau phosphorylation—induce readjustments in the synaptic insertion of CP-AMPARs [25][26]. Soluble  $\text{A}\beta$  oligomers reduced surface expression of AMPARs and blocked their extrasynaptic delivery mediated by chemical synaptic potentiation in neuronal cultures [26]. However, intracellular infusion of oligomeric  $\text{A}\beta$  enhanced AMPAR-mediated synaptic transmission in hippocampal slices, but the knockdown of GluA1 prevented this effect, suggesting that intracellular  $\text{A}\beta$  induced synaptic insertion of CP-AMPARs [25]. In any case,  $\text{A}\beta$  dysregulates AMPAR trafficking [27] and AMPAR-mediated synaptic plasticity impairment is one of the early onsets of AD (reviewed by [21]). This early synaptic dysfunction largely precedes any sign of cognitive decline, in both neurodegenerated and aged brains [21][28]. The fact that impaired learning and memory processes in AD and aged people are exacerbated by unhealthy diets [29], underlines the impact of nutritional factors at the synaptic level. Additionally, dynamic regulation of AMPARs has been associated with different metabolic situations, orexigenic and anorexigenic hormones (like leptin and ghrelin), and dietary factors [30][31][32][33][34].

In summary, it is becoming evident that dietary habits and specific nutrients play an essential role in brain health. However, solid evidence of nutritional control of synaptic function focused on AMPARs and its correlation with cognitive performance is not completely understood.

## 2. Western Diet

In recent decades, most societies have gradually abandoned dietary traditions to globalize their lifestyles. In southern Europe, for instance, the Western diet (WD), featured by high animal-based food, fat, and simple sugar

intake, is gradually replacing the primarily plant-based Mediterranean diet (MedDiet), rich in vegetables, fruit, whole grains, olive oil, and fish, and low in red meats and refined sugars [35], and associated with a lower rate of cognitive function decline [36].

It has been documented that diets high in either fats or simple sugars have deleterious effects on cognition (discussed below), so the combination of both in the WD evidently contributes to memory and learning impairments. In lean young humans, a 4- or 8-day intervention with a Western style-based breakfast (high in saturated fats and added sugars) was enough to reduce hippocampal-dependent learning and memory [37][38]. In a longitudinal study of elderly people, the WD was a predictor of poorer memory and processing speed [39]. There is, however, little literature analyzing the effects of the WD and its components on brain function in humans [40], which is why the researchers revisit experimental approaches with animal models.

2.1. Cognition Studies in Animal Models

While several high-fat diet (HFD)/high-sugar diet (HSD) protocols in animal models aim to mimic the WD in humans, many factors determine cognitive outcomes, such as the nature and percentages of fats and sugars (in WD-mimetics approaches, and in healthier control diets typically composed of 45–65% carbohydrates and 5–15% fats), palatability, exposure over time, individual susceptibility or resistance to obesity, and cognition tests used to measure learning and memory. With just a few exceptions, in which no differences were reported at 5, 10, or 12 weeks of the WD [41][42][43], a wide range of experimental models have demonstrated negative WD effects on learning and on short- and long-term memory, the details of which are summarized in **Table 1**.

Table 1. WD effects on synaptic function and cognition in animals.

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
Short periods (≤2 months)						
Young animals	Rat (♀; 3 w)	CAFD (F/sucrose: 45%) & HFru solution (11%) or HFru solution alone vs. CD (F: 13.4% & C: 56.7%) for 5 w. Reversion: 5 w with CD	Impaired memory (novel object in context) at 5 w for CAFD and HFru solution. No reversion in CAFD group	-	Gut dysbiosis (before and after reversion)	[44]
	Rat (♂; 6 w)	HFD-HDextrose (F: 41.7% & C: 36.7%) vs.	Impaired memory (NOR; no changes with MWM)	↓ dendritic arborization in HPC neurons and ↑ in	↑ TNFα levels in blood	[45]

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
		CD (F: 13.5% & C: 58%) for 11 w		entorhinal cortex neurons		
	Rat (♂; 6 w)	CAFD (cakes, biscuits & a protein source) & HSu solution (10%) vs. CD for 6 w	Impaired memory (NOR and NLR)	No changes in BDNF, TrkB and synapsin in HPC	↑ inflammation and gut dysbiosis	[46]
	Rat (♀; 2 m)	HFD (F:39%) & refined sugar (40%) vs. CD (F: 13% & complex C: 59%) for 2 m	Impaired memory (MWM)	↓ BDNF, phosphosynapsin I and phosphoCREB	-	[47]
Adult animals	Rat (♂ and ♀; 9–10 w)	HFD (F: 60% & C: 20%) HFru solution (11%) vs. CD (F: 13% & C: 62%) for 6 w	Impaired hippocampal-dependent memory (NLR) in ♂ (no changes in ♀)	-	-	[48]
	Rat (♂; adult)	CAFD (F: 45% & C: 50%) & HSu solution (10%) vs. CD (F: 15%, & C: 59%) for 5, 11 & 20 days	Impaired hippocampal-dependent memory (NLR; no changes in NOR)	No changes in BDNF	↑ inflammation in HPC at 20 d	[49]
	Rat (♂)	CAFD (CD supplemented with cakes, biscuits & protein source) & HSu solution (10%) vs. CD for 5 w	Impaired memory (NLR)	-	Gut dysbiosis	[50]
	Rat (♂; adult)	HFD-HC (F: 25%, C: 44% & P: 18%) vs.	Impaired short-term and long-	No changes in BDNF	↑ oxidative stress in HPC	[51]

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
		CD (F: 5%, C: 62% & P: 18) for 6 w	term memory (RAWM)			
	Rat (♂)	HFD (F: 40%, P: 5% & C: 15%) & HSu solution (40%) vs. CD (F: 15%, P: 25% & C: 55%) for 6 w. Reversion: 3 w with HFD-HSu and 3 w with CD and training	Impaired memory (NLR). Reversed by CD and training	-	-	[52]
	Rat (♂)	HFD (SFAs & MUFAs; 38%) & refined sugar (38%) vs. CD (F: 6% & sugar: 4.1%) for 8 w	Impaired memory (NOR) and learning (MWM)	↓ GluA3 levels in dorsal HPC and altered levels in synaptic plasticity markers	Altered levels in energy metabolism markers (by proteomic analysis)	[53]
Long periods (>2 months)						
Young animals	Rat (♂; 21 days)	HFD (F: 29%, sucrose: 34% & cholesterol 1.25%) & HGlucose-HFru solution (55%/45%) vs. CD (F: 6% & C: 44%) for 8 m	-	↓ PSD95 and BDNF, ↓ LTP in HPC	Gut dysbiosis, ↑ inflammation and microglia activation in HPC	[54]
	Rat (♀; 1 m)	HFD (30% lard & 66% sucrose) & HSu solution (30%) vs. CD (F: 3%, C: 61% & P: 19%) for 24 m	Impaired memory (NOR)	↓ TrKB, ↓ LTP in HPC	No changes in neurogenesis	[55]

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
	Rat (♂; 5–7 w)	HFD & HSu solution (5%) vs. CD for 4 m. Reversion: 3 m with bioactive food	Impaired spatial and working memory (T-maze and NOR). Reversed by bioactive foods	-	Gut dysbiosis. Reversed by bioactive foods	[56]
	Rat (♂; 6 w)	HFD-HFru (F: 30% & fructose: 15%) vs. CD for 6 m	Impaired learning (MWM)	-	↑ BBB permeability, neurodegeneration and microglia activation	[57]
	Rat (♂; 6 w)	HFD-HFru (saturated F: 45% & fructose: 20%) vs. CD for 11 w	Impaired memory (NOR)	-	↓ IGF1 and ↑ oxidative stress	[58]
	Mouse (♂; 6 w)	HFD-HSu (F: 60% & sucrose: 7%) vs. CD (F: 17%) for 13 w	Impaired memory (NOR)	↓ GluA1, BDNF, phosphoCREB, TrkB in HPC and PFC	↓ neurogenesis	[59]
	Mouse (♂; 7 w)	HFD (F: 40% & C: 20%) & HSu solution vs. CD (F: 12% & C: 67%) for 14 w	-	↓ PSD95 and ↑ phosphoTau in brain (no changes in synaptophysin)	↓ GLUT1/3, ↑ ER stress and inflammation responses and INS resistance in brain	[60]
	Rat (♂; 7 w)	CAFD (CD with cookies, cakes & biscuits) vs. CD once per day, 5 days per week for 5 m	-	↑ BDNF and TrkB and ↓ phosphoTrkB in PFC. No changes in HPC	Redox imbalance	[61]
	Rat (♀; 8–10 w)	HFD (F: 40%, C: 45% & P 15%) & HFru solution (15%) vs. CD (F: 6%, C: 64% &	Impaired memory (MWM) at 16 and 24 w (no changes at 12 w)	-	↑ oxidative stress and reduced antioxidant levels in HPC and CTX	[43]

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
		P: 25%) for 12, 16 & 24 w				
	Rat (♂; 2 m)	HFD-HGlucose (F: 40%) vs. CD (F: 13%) for 3 m	Impaired learning (nonspatial discrimination learning problem)	-	↑ BBB permeability in HPC	[62]
	Rat (♀; 2 m)	HFD (SFAs & MUFAs: 39%) & refined sugar (40%) vs. CD (F: 13% & C: 59%) for 1, 2 & 6 m or 2 y	Impaired learning and memory (MWM) at 1 and 2 m	↓ BDNF and synapsin I in HPC	-	[63]
	Rat (♂; 2 m)	HFD (high-lard or high-olive oil) & HSu solution vs. CD for 10 w	No changes in spatial memory (Y-maze)	↓ GluN2A in high-lard-HSu (no changes in high-olive oil-HSu) in CTX	-	[42]
	Rat (♂; 2 m)	HFD-HSu & HFru corn syrup solution (20%) vs. CD for 8 m	Impaired learning (MWM)	↓ dendritic spine density, ↓ LTP and ↓ BDNF levels in CA1-HPC	-	[64]
	Mouse (♀ and ♂; 10 w)	HFD (F: 60%) & HSu solution (20%) vs. CD (F: 10%) for 4 or 6 m. Reversion: 8 w with CD	Impaired memory (NOR and NLR. No change in working memory (Y-maze). Recovered after 8 w of CD		↑ microglia activation (no inflammation and neuronal loss). Recovered after 8 w of CD	[65]
	Guinea pigs (♀; 10 w)	HFD-HSu (F: 20% & sucrose: 15%) vs. CD (F: 4% & sucrose: 0%) for 7 m	-	↓ BDNF levels in HPC	-	[66]
	Rat (♂; adolescent)	HFD-HDextrose	Impaired memory (NOR)	-	-	[67]

Exp. Approach	Species, Sex, Age	Model	Learning/Memory	Synaptic Function, Neuroplasticity	Other Pathways	Refs.
		(SFAs: 41.7%) vs. CD (F: 13.4%) for 10 w				
Adult animals	Mouse (♂; 3 m)	HFD (F: 45%) & HFru solution (10%) vs. CD for 10 w	Impaired memory (MWM)	↓ PSD95 and SNAP25 in HPC	INS resistance, ↑ microglia activation and inflammation in brain	[68]
	Rat (♂)	HFD-HDextrose (F: 38%, P: 24%, C: 18% & dextrose: 20%) vs. CD (F: 18%, P: 24%, C: 58%) for 10, 40 & 90 days	Impaired learning at 10 and 90 d, no changes at 40 d (Y-shaped maze)	-	↑ BBB permeability in HPC (only in obese rats)	[41]
	Mouse (♂; 3 m)	HFD-HFru (F: 48%, fructose: 33% & P: 19%) or HFD (F: 48%, C: 33% & P: 19%) vs. CD for 14 w	Impaired memory (NOR and NLR). HF-HFru more affected than HFD	↓ glutamate and glutamine in HPC (no changes in GABA)	[49] [44]	[69]
[48]	Rat (♂)	HFD-HDextrose (F: 40%, P: 21% & C: 38%) or HFD-HSu (F: 40%, P: 21% & C: 38%) vs. CD (F: 12%, P: 28% & C: 59%) for 3 m	Impaired learning (nonspatial Pavlovian discrimination and reversal learning problem)	↓ BDNF in prefrontal CTX and HPC with HF-HDextrose (no changes with HF-HSu) [48][71]	-	[70]
	Rat (♂ and ♀)	HFD-HFru (CD: 60%, fructose: 30% & pork fat: 10%) vs. CD for 12 w	Impaired learning (MWM and passive avoidance test). ♂ more affected than ♀	-	↑ oxidative stress	[71]
		[73]				

HSD on synaptic and cognitive injury could lead to better diet interventions for patients with MetS, especially for women after the menopause.



agents in preclinical models of MetS [78][79]. By contrast, high adherence to the Mediterranean diet decreased the risk of developing cognitive impairment and dementia even in individuals with established MetS [77][80]. Accordingly, meals with effects on animals were classified according to experimental approach, taking into account exposure to a negative diet (≤2 months) or a positive diet (>2 months) periods, sex and age (classified as young and adult (≥2 months MetS [81][82]). Search terms used in the search followed a “vestibular diet” OR “high fat” AND “sugar” “sucrose” or “fructose” OR “dextrose” MetS “component” “loading” “synaptic plasticity” OR “AMPAR”. Only studies with rodents were included. Excluded were experimental models of maternal exposure, streptozotocin-treated animals, and pathological conditions.

## 2.2. Synaptic Function and Neuroplasticity

percentages are expressed as weight/volume unless otherwise indicated. Table symbols and abbreviations are as follows: ♀ : female; ♂ : male; ↑ : increased; ↓ : decreased; BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; C: carbohydrates; CAFD: cafeteria diet; CD: control diet; CREB: cAMP response element; LTP: long-term potentiation; LTP paradigm: LTP is an electrophysiologic high-frequency stimulation protocol that binds protein; CTX: cortex; ER: endoplasmic reticulum; F: fats; FC: fear conditioning; GABA: gamma-aminobutyric acid; GluA: AMPA receptor; GluN: NMDA receptor; GLUT: glucose transporter; h: hours; HC: high (GluA1-GluA1 tetramers) in the PSZ, inducing trafficking to the cell surface via the recycling pathway and lateral movement from perisynaptic sites, and enhancing synaptic transmission efficiency. It has been reported that long-term WD-impaired synaptic plasticity in the hippocampus (HPC) reduces dendritic spine density and LTP [54][55][64]. term depression; LTP: long-term potentiation; m: months; MUFAs: monounsaturated fatty acids; MWM: Morris water maze; NLR: novel location recognition; NOR: novel object recognition; P: protein; PFC: prefrontal cortex; cortex [45]. This last finding could be a compensatory effect due to synaptic loss in distal regions like the HPC or phospho: phosphorylated; PSD95: postsynaptic density protein 95; PUFAs, polyunsaturated fatty acids; RAWM: radial arm water maze; SFAs: saturated fatty acids; SNAP25: synaptosomal-associated protein 25; SOLF:

saturated oil-enriched food; TNF $\alpha$ : tumor necrosis factor; TrkB: tropomyosin receptor kinase B; UOLF: unsaturated WD-mediated cognitive impairment is associated with deficits in certain synaptic proteins. Levels of the main oil-enriched food; vs.: versus; and w: weeks.

neurotrophin, i.e., brain-derived neurotrophic factor (BDNF), were reduced in the HPC of adult mice after long-term exposure (2–8 months) to the WD [47][54][63][64][66][70], while no differences were observed for shorter exposure (20–42 days) [46][49][51]. A decrease in the BDNF receptor, tropomyosin receptor kinase B (TrkB), has also been reported [55][59]. Interestingly, not all nutritional sources alter BDNF levels in the same way. While a high-dextrose HFD downregulated BDNF in both the HPC and prefrontal cortex (PFC), this was not the case for a high-sucrose HFD [70]

Moreover, proteomic analysis of the dorsal HPC of rats on the WD for 8 weeks revealed alterations in synaptic plasticity markers, including a specific reduction in AMPAR subunit GluA3 [53]. In fact, selectively decreased

synaptic GluA3 has also been shown to be involved in dendritic spine loss in frontotemporal dementia [83]. Other long-term WD paradigms demonstrate reductions in other glutamate receptors, including the AMPAR subunit GluA1 (at 13 weeks) [59] and the NMDAR subunit GluN2A (at 10 weeks) [42]. The decrease in GluA1 may occur because BDNF regulates its synthesis [84]. At synaptic sites, GluN2A-lacking NMDARs may display altered synaptic plasticity, as described for its deletion in pyramidal cells from HPC slices [85]. Lower levels of glutamate and its precursor, glutamine, have also been detected in the HPC of HFD-HFru- and HFD-fed mice, while gamma-aminobutyric acid (GABA), the most common inhibitory neurotransmitter, remained unaltered [69]. Short-term studies are needed, nonetheless, to understand whether the deleterious effects of the WD on memory loss are a cause or consequence of changes in the glutamate neurotransmitter and its receptors.

## 2.3. Other Mechanisms

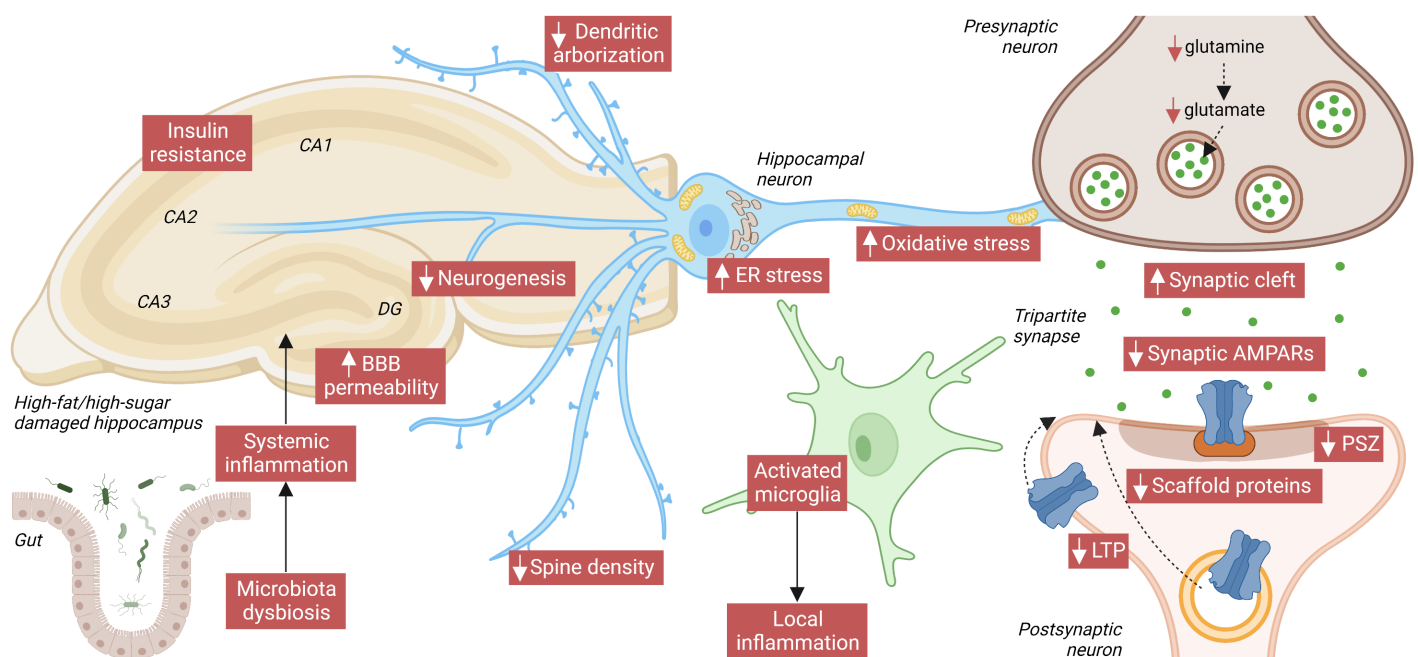
Other mechanisms are also compromised in WD-induced cognitive damage: insulin (INS) signaling in the brain [60][68], blood-brain barrier (BBB) permeability [41][57][62], HPC inflammation [45][46][49][54][60][68], microglia activation [54][57][65][68][72], endoplasmic reticulum (ER) and oxidative stress [43][51][58][60][61][71], gut microbiome composition [44][46][54][56][58], and neurogenesis [59]. Therapeutic strategies based on modulating these mechanisms have demonstrated unequal effects on memory loss.

Insulin supplementation has been shown to prevent WD-reduced neuroplasticity [54], and treatment with metformin, the first line drug for T2D, improved cognitive function in HFD-HFru-fed mice, but failed to restore BBB permeability [57]. It remains unclear whether the loss of BBB permeability mediated by the WD is a cause of memory loss. It has been reported that an HFD-HFru produced BBB dysfunction after 4 weeks, but no significant decline in learning and memory [72]. In contrast, other studies, using different HFD/HSD paradigms, showed cognitive impairment after shorter exposure to the WD [41][49][63], in one case, reporting increased BBB permeability in WD-induced obese subjects at 12 weeks, but not in WD-resistant obese subjects at 5 weeks [41]; this would suggest that BBB leakage could, depending on exposure time, diet composition, and obesity phenotype, be a consequence of the WD.

Furthermore, pre-exposure to a probiotic called VSL#3 prevented WD-induced memory deficits for an HPC-dependent task, but caused deficits for a perirhinal-dependent task, irrespective of diet and dose [50], suggesting that this probiotic may be detrimental for healthy subjects. In one study, treatment with the antibiotic minocycline, which alters microbiome composition, prevented or reverted CAFD-induced spatial memory impairment [46]; however, another study showed that dietary intervention restored CAFD-dependent memory loss, but not gut microbiota alterations [44]. Finally, vitamin E administration normalized the effect of the CAFD on HPC oxidative stress markers and prevented diet-mediated memory decline [51]. The above are just some examples of efforts focused on discovering new drugs and/or bioactive foods with neuroprotective properties that could counteract HFD/HSD-induced brain damage.

In conclusion, an association between WD and alterations in memory and learning processes has been demonstrated both in human studies and experimental approaches on animal models. Such effects correlated with synaptic and neuroplasticity dysfunctions in the hippocampus, corresponding with reduced dendritic spine density

and arborization, decreased LTP, and deficits in synaptic proteins, like AMPARs (as summarized in the following **Figure 1**). Furthermore, other mechanisms regarding INS signaling and BBB permeability, among others, appeared to be affected too. Fortunately, WD-induced cognitive decline seems to be reversible, as shown in animal studies that switched from an HFD/HSD to a more balanced control diet. However, more in-depth investigations are required to fully understand the effect of WD and its components on brain function to create better diet interventions to ameliorate cognitive alterations.



**Figure 1.** Main hallmarks of HFD/high-sugar-(HSD)-mediated HPC damage. At the systemic level, both fat and sugar produce gut microbiota dysbiosis, which can exacerbate inflammation in the brain by enhancing blood-brain barrier (BBB) permeability. BBB damage, in turn, contributes to deregulating transport of circulating orexigenic and anorexigenic hormones. In the HPC, local release of neuroinflammatory factors by activated microglia exacerbates neuronal damage. INS resistance, increased endoplasmic reticulum (ER), and oxidative stress also compromise neuronal function. In HPC neurons, HFD/HSD intake reduces dendritic arborization, spine density, and the PSZ, and widens the synaptic cleft. The glutamate neurotransmitter and its precursor, glutamine, are reduced, and also reduced over the short/medium-term are levels of AMPARs and of its scaffold protein PSD95. Finally, impaired activity-dependent synaptic plasticity (especially LTP) proves that AMPAR trafficking to the PM is also compromised by an HFD/HSD. Image created with Biorender.com

Interestingly, more knowledge about the effects of nutrients at cognitive, synaptic and neuroplasticity level can be achieved reviewing current evidence with HFD alone (especially considering the fat type) and HSD alone (comparing fructose and sucrose intake), as documented in the following chapters.

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