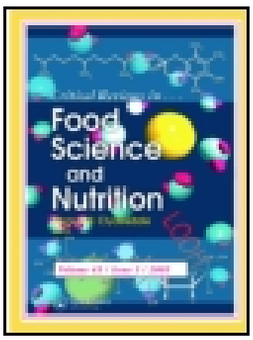

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REVIEW

High-fat or high-sugar diets as trigger inflammation in the microbiota-gut-brain axis

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ABSTRACT

Microbiota, intestine, and brain interact one with another through the afferent fibers of the vagus nerve, which is the major linkage of this one. It has been established that long-term dietary habits influence gut bacterial diversity and are capable of inducing changes in hypothalamic energy homeostasis. The biological effects are mediated by microglial activation, systemic inflammation, and vagal afferent nerve signaling, culminating in neuroinflammation. It has been emphasized the need for a further approach regarding the influence of the dietary factors as well as their direct impacts or outcomes on the gut dysbiosis. This review aimed to understand the role of some dietary triggers of neuroinflammation on changes in the gut microbiota. Each of the diets significantly altered the microbial composition in distinct ways, leading to neuroadaptations. Hyperlipidic diets (SFA and MUFA) can stimulate TLR4 inflammatory pathway by increased LPS translocation and LBP activation and modulate brain functions, mainly in the center of feeding. Overconsumption of sucrose seems to be more detrimental for metabolic alterations, whereas fructose has a more pronounced effect on gut barrier dysfunction and subclinical inflammation; nevertheless, sucrose absorption favors fructose bioavailability, contributing to adiposity and sugar addiction.

KEYWORDS

overconsumption; fatty acids; simple sugar; gut bacteria; neuroinflammation

Introduction

The mammalians' intestine harbors around 100 trillion bacteria of at least 1000 distinct species forming a symbiotic relationship with the host. This ecosystem comprises several physiologic functions in the human host, such as protecting against pathogens, improving immunity function, inflammatory response, and assisting in nutrient processing and digestion, especially complex carbohydrates, in which the human organism cannot be fully digested. For this reason, the gut function is mediated by endocrine, paracrine, neural and immune control mechanisms (Hamilton and Raybould, 2016; Bonaz, Bazin, and Pellissier, 2018).

Microbiota composition is influenced by long-term dietary habits, explaining 57% out of structural variations in total bacteria; however, it is very sensitive to daily variations in feeding (Zhang et al., 2010). This interaction can attenuate or even contribute to the metabolic profile in the plasma as well as the inflammatory status (Blander et al., 2017).

The Western dietary pattern – rich in refined carbohydrates and saturated fatty acids, high-n-6 and low-n-3 polyunsaturated fatty acids, and low in fiber derived from plants, phytochemicals, and fermented foods – reduces total bacterial load and alters microbial diversity in the gut (dysbiosis), besides disrupting gut barrier function (Torres-Fuentes et al., 2017). The scenario allows the passage of lipopolysaccharide (LPS) into the bloodstream (Caesar et al., 2015). These factors may interact with extracellular pattern-recognition receptors – Toll-like receptors (TLRs) – which promote downstream from nuclear transcription factor kappa B (NF-κB) signaling pathway, inducing systemic inflammation; characterizing a pathological process so-called metabolic endotoxemia (Hamilton and Raybould, 2016; Marques et al., 2016).

The microbiota, the gut, and the brain interact in a bidirectional way through large participation of the vagus nerve. Afferent fibers from the vagus nerve comprise the major linkage of the gut-brain axis, once their axonal terminals are positioned within the gut mucosa to respond to some mediators released from gut epithelial cells, such as gut hormones and LPS (de La Serre, de Lartigue, and Raybould, 2015; Forsythe, Kunze, and Bienenstock, 2016; Bonaz, Bazin, and Pellissier, 2018).

Therefore, LPS can bind to the TLRs present on the microglia (the resident innate immune cells in the brain) surface and activate several signal transductions, which culminate in the NF-κB activation. This process induces the expression of proinflammatory molecules, implicating in inflammation in the hypothalamic arcuate nucleus – a center of feeding regulation – and consequently, neuronal death (Thaler et al., 2012; Shabab et al., 2016). It has well established that inflammation plays a critical role in the development of obesity, insulin resistance, and glucose intolerance

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in the early-term, key diseases for other comorbidities (Carabotti et al., 2015). In longer-term, low-grade inflammation may result in changes in brain structure and synaptic plasticity, leading to the development of neurologic dysfunction as far as several psychopathologies (Marques et al., 2016).

It has been proposed that certain nutrients can trigger or prevent microglial hyperactivation, since a Western diet reduces the levels of anti-inflammatory commensal bacteria, affecting neuroinflammation (Bruce- Keller et al., 2015).

Moreover, gut microbiota can synthesize metabolites-diet-dependently, modulating neurotransmitters and neuropeptides, which have peripheral and central effects via direct or indirect mechanisms, modifying host metabolism and mediate local and systemic inflammation (Torres-Fuentes et al., 2017; Brun et al., 2015).

Recently, Bruce Keller et al. (2016) emphasize the need for further approach regarding the influence of the nutritional factors and its direct and indirect effects in the gut dysbiosis on key biological factors. Thus, we review the current knowledge about the overconsumption of fatty acids and sugar as dietary triggers of neuroinflammation arising from changes in the gut microbiota. As this is still a relatively unexplored issue, we included in vitro and in vivo studies, as well as experimental animal research and clinical trials.

Inflammation in the microbiota-gut-brain vagal pathway

The gastrointestinal tract is a communication checkpoint between the immune cells, neurons and gut microbiota (Forsythe, Kunze, and Bienenstock, 2016). The microbiota-gut-brain bidirectional communication occurs through the autonomic nervous system, which comprises the sympathetic and parasympathetic systems, involving the enteric nervous system (ENS), the central nervous system (CNS), both the brain and spinal cord, and the hypothalamic-pituitary-adrenal axis (Carabotti et al., 2015).

Efferent signals from the CNS to the intestinal wall may modulate peripheral gastrointestinal functions, altering the contractions and release of gut hormones, neurotransmitters, and immune factors, which, in turn, alter the gut microbiota composition. Conversely, afferent signals from the lumen to the CNS, through vagal nerve and its ganglia, spinal sensory neurons and intrinsic primary afferent neurons (IPANs), control the production and/or release of neuropeptides and gut hormones by direct or indirect actions on neurons with the participation of gut microbes (Carabotti et al., 2015; Torres-Fuentes et al., 2017; Bonaz, Bazin, and Pellissier, 2018).

The vagus nerve is the main component of the parasympathetic nervous system being composed of 80% afferent and 20% efferent fibers. It is able to sense the microbiota metabolites and transmit meal-related signals to the central nervous system (CNS), specifically to the nucleus of the tractus solitaries (NTS) in the medulla oblongata. Subsequently, these meal-related signals are distributed into the neurons of the arcuate nucleus of the hypothalamus (a region responsible for regulating energy balance, appetite, and food intake) and subsequently, to induce an adaptative or an inappropriate response (Schechter and Schwartz, 2016; Bonaz, Bazin, and Pellissier, 2018).

Under ordinary conditions, the ENS does not appear to be directly exposed to the luminal content. The first possible site of interaction between enteric neurons and gut microbiota seems to be the subepithelial compartment. Gut microbes are sensed by IPANs, present in the ENS once their neurites are exposed to the intestinal lumen (Forsythe, Kunze, and Bienenstock, 2016). IPANs have been considered a cellular target for neuroactive bacteria, such as *Lactobacillus rhamnosus* (Kunze et al., 2009; Perez-Burgos et al., 2014). Some experiments using germ-free animals have demonstrated that commensal bacteria are important for the normal excitability of gut sensory neurons. Such data provide some evidence on a potential mechanism for the transfer of the information between the microbiota and nervous system (McVey et al., 2013; Perez-Burgos et al., 2014).

On the other hand, the disruption of the epithelial layer integrity may occur in pathological conditions. Microbial components can also be translocated across the gut barrier by specialized cells, which are able to transpose them to the underlying immune cells located into the intestinal mucosa (Forsythe and Kunze, 2013). However, bacterial translocation is present in healthy individuals and contributes to gut-associated lymphoid tissue (GALT) development, bacterial tolerance, and constant stimulation of immune cells (Barajon et al., 2009; Cani and Knauf, 2016).

Epithelial cells also detect the presence of microorganisms and translate this information to the immune cells located in the lamina propria. The innate immune system performs recognition and monitoring through pattern recognition receptors (PRRs), including TLRs and NOD-like receptors (NLR). Taken together, these rapidly recognize pathogen-associated molecular patterns (PAMPs) from microorganisms – LPS, peptidoglycans (PGN), flagellin and muramyl dipeptide – or danger-associated molecular patterns (DAMPs) from damaged tissues (ÓNeil, Golenbock, and Bowie, 2013; Pisani, Estadella, and Ribeiro, 2017).

PAMPs target the enteric neurons to control gut motility and hormones secretion and inform the presence of nutrients and pathogens in the gut to the brain (Forsythe & Kunze, 2013; Brun et al., 2013). LPS, also known as endotoxins, is a breakdown product, present on the outer membrane of gram-negative bacteria being composed by an O-antigen portion in its outer part and by a lipid-A portion in the inner part. The lipid-A portion exerts most of the immunogenic effects, such as the activation of TLR4, through the formation of the complex containing LPS-binding proteins (LBP) and the CD14 co-receptor, resulting in the production of proinflammatory cytokines. In contrast, the O-antigen portion activates components of the adaptive immunity, intending to induce the production of antibodies (Greenfield and Whitfield, 2012; Bailey and Holscher, 2018). Both portions variate structurally and immunogenically, although these variations and their effects on metabolic

endotoxemia are poorly understood. LPS may achieve systemic circulation in two distinct ways: transcellular, through the absorption of dietary factors; and paracellular, through compromised enterocyte tight junctions (Seeley and Ghosh, 2017).

Enteric neurons and glial cells produce and respond to cytokines and can affect epithelial proliferation and epithelial barrier permeability, in the attempt to maintain the gut microbiota homeostasis (Cani and Knauf, 2016). TLR 2, 3, 4 and 7 are expressed in both neurons and glial cells present in the ENS and vagus nerve (Barajon et al., 2009; Brun et al., 2013). Additionally, LPS activates vagal afferent neurons, and, chronically, the activation results in nodose ganglion inflammation and impairs signaling of satiety from the gut, in the brain (de Lartigue et al., 2011; de La Serre, de Lartigue, and Raybould, 2015), implicating in neurodegeneration (Schechter and Schawartz, 2016). In this sense, a recent report showed that PGN derived from gram-positive bacteria also translocate into the brain to activate TLR2 in glial cells, occurring via physiological and pathological conditions (Arentsen et al., 2017). These studies reinforce the participation of the microbiota in the modulation of blood-brain barrier (BBB) permeability and function of the nervous systems (Michel and Prat, 2016). It is important to stress that both cytokines and PAMPs can be transported from the periphery to the CNS across the BBB and activate vagal afferent neurons to induce central inflammation (Meneses et al., 2016; Mulders et al., 2018).

Neuroinflammation is a response that involves all the cells of the CNS, including the neurons, macroglia, and microglia (Shabab et al., 2017). Low-grade inflammation in the brain is characterized by gliosis, which involves infiltration of microglia, the proliferation of astrocytes and *de novo* angiogenesis, resulting in increased cell density, and, in the long term, leads to the loss of anorexigenic neurons (Thaler et al., 2012; Valdearcos et al., 2014). Neuroinflammation has some impact on several diseases. This is associated with changes in the emotional and cognitive centers from the brain (Carabotti et al., 2015) or even with metabolic diseases, *e.g.*, obesity, evidenced to have altered vagal afferent function (de Lartigue et al., 2011). The first indication of neuroinflammation is microglia activation (Shabab et al., 2017).

Similar to peripheral macrophages, microglia express TLRs which are highly responsive to LPS stimulation (Valdearcos et al., 2014). TLR activation in the microglia induces several signal transduction, such as phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR), which ultimately culminates in the NF-κB activation. This process induces the expression of proinflammatory cytokines, activates chemokines, and enzymes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) (Shabab et al., 2016; Carraro et al., 2018).

Microglia are phagocytic innate immune cells, account for about 10% of cells in the brain (Prinz, 2014), and play a key role in brain development, plasticity, and cognition (Tay et al., 2017). Its maturation and activation are under the constant influence of the microbiota. In germ-free mice, microglia have an immature phenotype with decreased activation and inflammatory response (Bruce-Keller et al., 2015; Erny et al., 2015). Furthermore, microglia are also regulated by colonic neurotransmitters and neuropeptides (dopamine, acetylcholine, gamma-aminobutyric acid – GABA, brain-derived neurotrophic factor – BDNF, and serotonin) produced through microbiota-derived short-chain fatty acids (SCFA) (Erny et al., 2015), which modulate signaling within the ENS, and consequently affect intestinal motility, development, immune system function, and intestinal inflammation. These metabolites have been considered as mediators responsible for the complex bacterial performance on the function alterations and inflammation in distal tissues, including the brain (Yano et al., 2015; Reigstad et al., 2015).

Some reports have revealed that the microglial activation increases the levels of proinflammatory cytokines in areas such as the hippocampus (Wadhwa et al., 2017) and hypothalamus (Tran et al., 2016). This has been closely related to gut dysbiosis, once high LPS concentrations induce an inflammatory response in vagal afferent neurons with rapid activation of microglia, resulting in neuroinflammation (Cazareth et al., 2014; Jena et al., 2018). Interestingly, the pathway has also been evidenced in animal models, which indicate that dietary factors can induce an inflammatory response in the gut, in the nodose ganglion, and subsequently in the hypothalamus, leading to gliosis over 24–72 h after initiation of the Western diet (Thaler et al., 2012; Valdearcos et al., 2014). Specific microbial taxa appear be predominant in some food patterns, such as *Alloprevotella* in control-diet, *Clostridium* sensu stricto in SFA-diet, *Ruminococcaceae* unclassified in PUFA-diet, and *Porphyromonadaceae* unclassified in sugar-diet. *Lactobacillus* appeared to be driving some of the differences between the diets, mainly PUFA- and sugar-rich diets, comparing SFA diet (Beilharz et al., 2016). High-fat isocaloric diet intake was able to reduce *Parasutterella sp.* (Proteobacteria) in the gut; being significantly correlated with hypothalamic inflammation and gliosis markers. These findings suggest that the disturbance in the gut-brain axis is triggered by dietary factors independently from the caloric intake alone or combined with the obesity phenotype *per se* (Kreutzer et al., 2017) (Figure 1).

Dietary factors can modulate gut-microbes metabolism by supplying nutrients and microbial products and consequently modifying the production of metabolites (Cavallari et al., 2017), modulating the host endocrine and inflammatory responses (Stecher, Maier, and Hardt, 2013). To gain a better understanding of the differences across macronutrients types and the changes in gut microbiota and neuroadaptations, we presented some studies details in Table 1.

Fatty acids and microbiota-gut-brain inflammation

Fatty acids can be categorized into saturated (SFA: short, medium, and long-chain saturated fatty acids – *e.g.*, myristic, palmitic acids) and unsaturated (MUFA: n-9

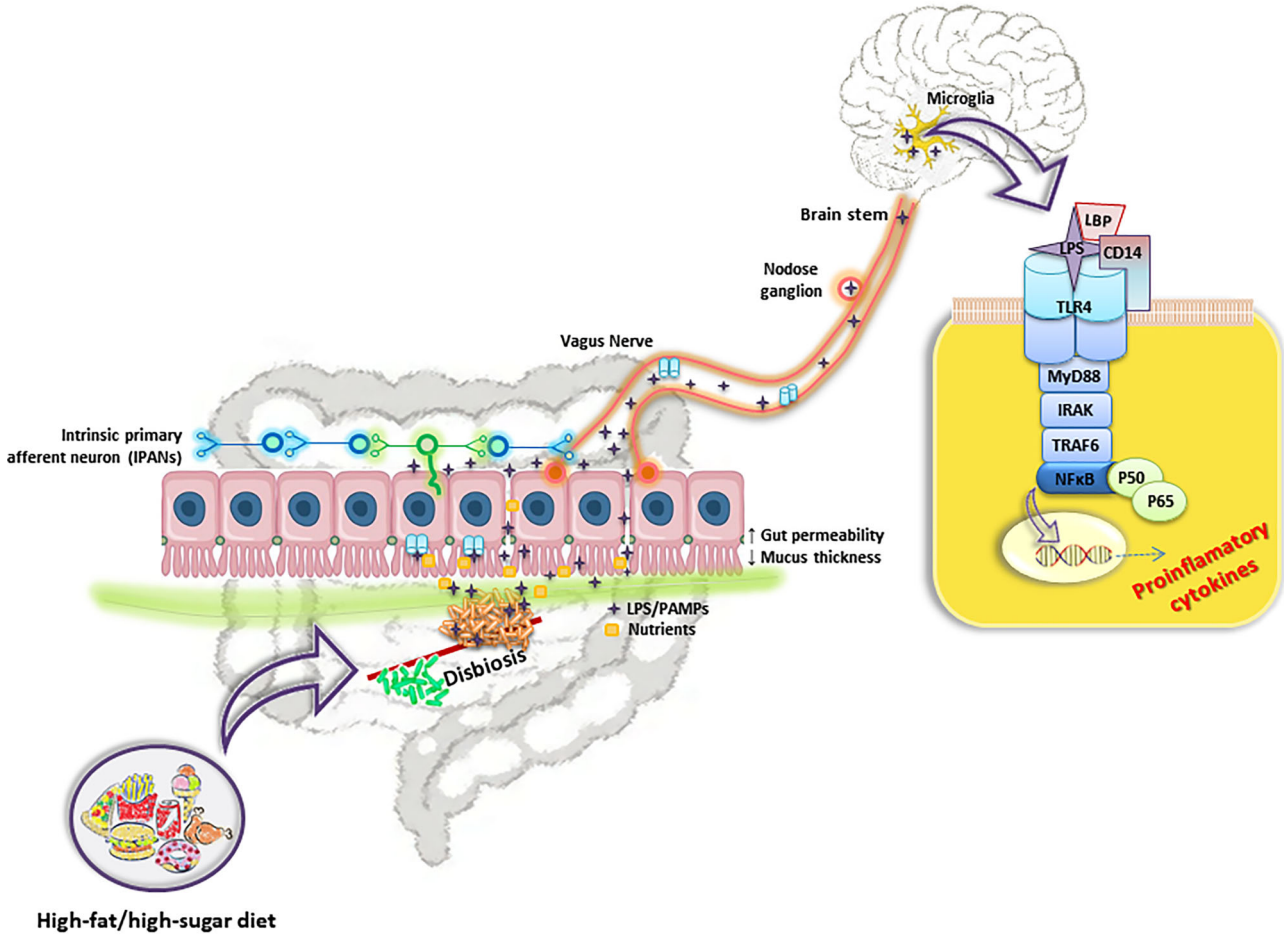

Figure 1. Disturbance in the microbiota-gut-brain axis triggered by dietary factors. Overconsumption of fatty acids and simple sugars (Western diets) alter the gut microbiota diversity (dysbiosis); increase gut permeability, gram-negative bacterium growth, and LPS translocation across the intestinal epithelium; reduce mucus layer thickness and favor microbiota encroachment. It promotes local/systemic inflammation, and consequently, microglial activation and central inflammation via interaction with the enteric nervous system and vagal afferent nerve signaling. LPS forms a complex containing LBP and CD14 to active TLRs to promote downstream NF-κB signalization (MyD88 dependent), which induces the gene expression of proinflammatory cytokines. CD14: CD14 co-receptor; IPAN: intrinsic primary afferent neuron; IRAK: interleukin-1 receptor-associated kinase; LBP: LPS-binding proteins; LPS: lipopolysaccharide; MyD88: myeloid differentiation protein; NF-κB: nuclear transcription factor-kappa B; PAMPS: pathogen-associated molecular patterns; TLRs: Toll-like receptors; TRAF-6: TNF receptor-associated factor 6.

monounsaturated fatty acids – *e.g.*, oleic acids; PUFA: n-6 polyunsaturated fatty acids – *e.g.*, linoleic acid; and n-3 polyunsaturated fatty acids – *e.g.*, α-linolenic acid) (Laugeretti et al., 2012).

Following the ingestion of fats, digestive enzymes, including lipases, are released to aid in breaking molecules of triglycerides into free fatty acids and glycerol. Moreover, bile acids are released into the duodenum being associated with these molecules, forming micelles to facilitate transport into the plasma membrane of enterocytes and the subsequent absorption of fatty acids by specific receptors in the digestion still in process (Portune et al., 2017).

Dietary fatty acids are mostly degraded and absorbed in the small intestine, although a small amount can reach the colon being regularly excreted in feces (Scott et al., 2013). Furthermore, it has been demonstrated that microbes play an important role in regulating the digestion and absorption of fatty acids (Portune et al., 2017).

A high-fat diet (HFD) leads to changes in jejunal microbiota composition, which induces an elevation in fat absorption capacity and stimulate triacylglycerol formation in enterocytes in response to microbial products (Kleerebezem, 2018).

In the distal ileum, bacteria can deconjugate bile acids to avoid its uptake allowing its entry in the colon to be metabolized into secondary bile acids (Portune et al., 2017). Bile acids have a selective antimicrobial activity in the small intestinal, and, therefore, it could mediate the fat-induced effects on the gut microbiota (Torre-Fuentes et al., 2017). To cope with bile salts, a wide variety of intestinal microbes have genes encoding bile salt hydrolases, which allow them to overcome this inhibitory impact via deconjugation (Zoetendal and Vos, 2014). Thus, secondary bile acids may alter microbiota composition, preferring certain groups of bacteria, such as *Bilophila wadsworthia*, which increases organic sulfur availability and alters the microbial environment, favoring the installation of an inflammatory process (Devkota et al., 2012; Portune et al., 2017). This participation of the microbiota can modify the solubilization and absorption of dietary lipids and increase the bile excretion in the feces (Portune et al., 2017).

Table 1. Dietary intervention studies which compare the effect of high-fat (HFD) and high-sugar diets (HSD) on changes in gut-microbiota and/or neuroinflammation.

Author	Study design and aim	Main findings
Fava et al. (2013)	• 88 subjects (43 men and 45 women; mean age, 55.9 years; mean BMI, 28.8 kg/m^2) at increased MetS risk received high-SFA diet (HSFA) for 4 weeks (baseline), then randomized for 5 experimental diets for 24 weeks: HSFA; high-MUFA/high-glycemic index (GI) (HM/HGI); high-MUFA/low-GI (HM/LGI); high-carbohydrate (CHO)/high-GI (HC/HGI); and high-CHO/low-GI (HC/LGI). • To determine the effects of the amount and type of dietary fat and carbohydrate on fecal bacteria and SCFA concentrations.	• High-MUFA diets ↓ total cholesterol and LDL-cholesterol; • ↓ total bacteria, but not affect individual bacterial population number; • HC diets ↑ *Bifidobacterium*; • HC/HGI ↑ *Bacteroides;* • HC/LGI and HSFA ↑ *Faecalibacterium prausnitzii;* • Changes in *Bacteroides* numbers were correlated inversely with body weigh;. • HSFA increased fecal SCFA concentrations.
Beilharz et al. (2016)	• Male Sprague-Dawley rats were fed matched purified diets for 2 weeks: control, sugar (sucrose), SFA (lard), or PUFA (sunflower oil). • To investigated how these macronutrients affect memory, neuroinflammation and neuroplasticity markers, and gut microbiota.	• Microbial composition was affected in distinct ways: the relative abundance of 89 taxa (OTUs) differed significantly between the macronutrients. The majority changes were *Alloprevotella* (control), *Clostridium* sensu stricto (SFA), *Ruminococcaceae* unclassified (PUFA), and *Porphyromonadaceae* unclassified (Sugar). • These altered taxa were correlated with impairment memory and inflammation-related hippocampal genes. • There are no differences in appetite regulating genes and inflammatory markers in hypothalamus.
Nakayama et al. (2017)	• 43 Philippines' children (7 – 9 years) from rural (24) and urban (19) cities. • To correlate bacterial composition and diet.	• Fat intake accounted for 27.2% of the total energy intake by urnbans' children; • Higher carbohydrate consumption correlated with ↑ Prevotellaceae and with some succinate-producing bacteria: *Dialister succinatiphilus, Prevotellaceae, Veillonellaceae*, and *Erysipelotrichaceae;* • Higher fat consumption correlated with ↑ F/B ratio and Bacteroidacea, and ↓ *Prevotella.* It was most predominant in urbans' children with obesity; • Predicted metagenomics showed that Bacteroidaceae-type microbiota is well nourished and metabolically more active with simple sugars, amino acids, and lipids; while Prevotellaceae-type community is more involved in digestion of complex carbohydrates.
Rosas-Vilegas et al. (2017)	• Adults Male Wistar rats were fed with HFS – HFD + sucrose (5% in drinking water) or HFF – HFD + fructose (5% in drinking water) or a control diet (C) for four months. Half of the HFS or HFF groups were maintained with the same diet and the other half were switched to the consumption of C. • To evaluate the effect of sucrose or fructose in a HFD on gut microbiota and renal oxidative stress.	• HFS and HFF ↑ body weight; • HFS ↑ body fat mass, metabolic inflexibility, glucose intolerance, LPS, insulin, ROS, MDA, Nadphox, Srebp-1; • HFS ↓ antioxidant enzymes and lean body mass; • The type of carbohydrate differentially modified the microbiota composition, however, both groups significantly decreased *C. eutactus;* • HFS ↓ *Aggregatibacter*, *Bilophila*, *Sphingomonas*, *Turicibacter*, and *Klebsiella;* • HFF ↑ *L. reuteri* and *B. fragilis.*
Roytio et al. (2017)	• 100 overweight and obese (mean BMI, 30.7 ± 4.4 kg/m^2 and mean age, 30.1 ± 4.7 years) women in early pregnancy (≤17 weeks). They were grouped according to food intake: low-fiber/moderate-fat (< 25 g and 25-40 %); high-fiber/moderate-fat (≥ 25 g and 25-40 %); low-fiber/high-fat (< 25 g and ≥ 40 %, > 10% of SFA). • To verify the effect of the habitual diet and adherence to the dietary reference values on gut microbiota and associate with serum lipidomics and low-grade inflammation.	• High-fiber/moderate-fat (recommended dietary intake of fiber and fat) was related to higher gut microbiota richness and ↓ Bacteroidaceae. It was correlated with beneficial lipidomic profile and ↓ low-grade inflammation marker (GlycA). • Dietary fat quality appeared to manifest diverse impact to microbiota. SFA were negatively associated with dysbiosis indexes, whereas n-3 PUFA showed no correlation.
Sen et al. (2017)	• Male Sprague-Dawley rats were fed with HF/HSD, low-fat/high-sugar diet (LF/HSD), or control low-fat/low-sugar diet (LF/LSD) for 4weeks. • To investigate the effects of HF/HSD and LF/HSD on microbiota composition, gut inflammation, gut brain vagal communication and body fat accumulation.	• Both HF/HSD and LF/HSD ↓ gut bacterial diversity, ↑ F/B ratio, ↑ Clostridia and Bacilli, and ↓ *Lactobacillus* spp.; • LF/HSD ↑ *Sutterella* and *Bilophila;* • Both HF/HSD and LF/HSD ↑ body weight and body fat; • ↑ LPS, expression of IL-6, IL-1β and TNFα in the cecum and ↓ occludin; • Promoted withdrawal of vagal afferents from the gut and at their site of termination the NTS.

F/B: Firmicutes-to-Bacteroidetes ratio; GlycA: glycoprotein acetylation; HFD: high-fat diet; HSFA: high-saturated fatty acids; LPS: lipopolysaccharide; MDA: malondialdehyde; MetS: Metabolic syndrome; MUFA: monounsaturated fatty acid; Nadphox: Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; NTS: nucleus tractus solitarius; PUFA: polyunsaturated fatty acid; ROS: renal reactive oxygen species; SCFA: short-chain fatty acids; SFA: saturated fatty acid; Srebp-1: sterol regulatory element-binding protein 1.

It has been emphasized that dietary fat cannot be metabolized under anaerobic conditions. Since most resident bacteria of the gastrointestinal tract are strict anaerobes (for instance, Clostridia, *Bacteroides, Eubacterium, Peptostreptococcus,* and *Bifidobacterium*), fatty acids could not serve as an energy source for gut microbiota growth (Blaut and Klaus, 2012). Therefore, it should not be a prominent mechanism for explaining high-fat induced

dysbiosis (Cândido et al., 2018). Also, the gastrointestinal tract of mice and ruminants houses lipid-degrading bacterial species capable of biohydrogenating certain PUFAs such as linoleic acid to SFA vaccenic acid and stearic acid (Kishino et al., 2013; Druart et al., 2015). In vivo, similar biotransformation of linoleic acid has been observed in numerous strains of human gut bacteria, mainly the species *Roseburia spp.* and *Enterobacter aerogenes* (Cipinyté et al., 2009). High concentrations of linoleic acid were found to decrease butyrate production and *Faecalibacterium prausnitzii* numbers dependent on PUFA acid biohydrogenation to SFA (De Weirdt et al., 2017).

Fatty acids and their metabolites act directly and indirectly to regulate mammalian metabolism (Laugeretti et al., 2012). Dietary fatty acids appear to be not equal in their participation in the gut microbiota. The presence of higher amounts of fatty acids in the intestine has been associated with signals of dysbiosis since high-SFA intake reduced microbial diversity and increased Firmicutes/Bacteroidetes ratio, and high-MUFA intake reduced the total bacteria in fecal content (de Wit et al., 2012; Fava et al., 2013). Bacteria from the phylum Firmicutes increased the number of lipid droplets, while lipid droplet size was associated with other bacterial types, thereby supporting some evidence for distinct mechanisms of microbial species in regulating fatty acid absorption in the host (Semova et al., 2012).

Long-chain SFA facilitates the LPS translocation across the intestinal epithelium, favoring TLRs activation (Lancaster et al., 2018), either through an increase in paracellular diffusion or by incorporation into chylomicrons during fat absorption (Sen et al., 2017). This fact could be due to the tendency of SFA to form lipid rafts in the cellular membranes of enterocytes, thereby decreasing membrane fluidity (Bailey and Holseher, 2018). Furthermore, SFA has been related to the declined integrity of gut epithelial tight-junction proteins (Caesar et al., 2015) and mucus layer thickness reduction through the decrease in the abundance of the mucus-degrading bacterium *Akkermansia muciniphila* (Everard et al., 2013; Marques et al., 2016).

High-SFA diet can increase the proportion of gram-negative bacteria in the intestine and decrease the abundance of some gram-positive bacteria in animals and humans (Cani et al., 2007; Agus et al., 2016; Nakayama et al., 2017). This shift may occur because gram-negative bacteria are generally more tolerant of bile, probably because of the protective qualities that LPS provides. Bacteria lacking the O-antigen portion from the LPS structure are shown to have reduced bile acid–tolerance (Bailey and Holseher, 2018). However, it is worth noting that dietary lipids are mostly absorbed in the proximal small intestine and the largest source of LPS is resident in the distal small intestine and colon. This apparent paradox is due to endotoxemia that may be the result of the small intestine bacterial overgrowth (SIBO), which has been widely reported in obesity (Roland et al., 2018).

Dysbiosis induced by SFA-rich diet is characterized by increased abundance of *Bilophila wadsworthia* and other Proteobacteria species, Firmicutes and Actinobacteria, followed by a reduction in the abundance of Bacteroidetes. Reductions in fiber-fermenting bacteria, such as *Bifidobacterium, Roseburia spp.*, *Eubacterium rectale*, and *Akkermansia muciniphila* were also observed in mice submitted to HFD (Devkota et al., 2012; Everard et al. 2013; Daniel et al., 2014). However, there is usually a lower content of other dietary compounds such as carbohydrates and fibers, reducing energy substrates for beneficial bacteria growth once the dietary fat content is increased, (Daniel et al., 2014), which could bias the outcome.

In contrary to the reported results with high-SFA diets, the effects of MUFA-rich diets are less consistent. MUFA may have no effect on gut microbiota or may negatively affect total bacterial numbers (Wolters et al., 2018). In humans, a high-MUFA intake appears no affect bacterial diversity (Roytio et al., 2017). Nonetheless, high-MUFA diets ingested for 30 days was positively associated with the abundance of Enterobacteriaceae (Proteobacteria phylum), with no effect on the Firmicutes/Bacteroidetes ratio (Pu et al., 2013), as confirmed in previous study in mice (de Wit et al., 2012). Otherwise, MUFA supplementation reversed the damage caused by diet-induced obesity in mice, decreasing Enterobacteriales and Clostridium cluster XIV and increasing *Bifidobacterium* (Mujico et al., 2013).

Microbial interactions with dietary lipids may also play an essential role in the local, systemic and peripheral inflammation as well as for promoting metabolic changes. Marques and colleagues (2016) have hypothesized that changes in the gut microbiota could occur first and then trigger an inflammatory pathway from the gut to the brain. While MUFA appears to act on jejunal afferent nerves through gastrointestinal hormones-mediated mechanism to send satiety signs to the brain (Bonaz, Bazin, and Pellisier, 2018), SFAs, especially palmitic acid, desensitize the afferent vagus nerve and can activate inflammatory host response in the hypothalamus by TLR4 activation in the microglia (Milanski et al., 2009; Laugeretti et al., 2012). In concert with its flux into the brain, milk fat (mostly palmitic and stearic acids) gavage for 3 days also induced accumulation of mediobasal hypothalamic microglia but did not increase systemic inflammation. By contrast, isocaloric gavage with olive oil (primarily oleic acid) did not induce hypothalamic inflammation (Valdearcos et al., 2014). It suggests microglia as sensors that dictate the intensity of neuroinflammation and mediate key changes in hypothalamic function that occur in response high-SFA diet (Thaler et al., 2012; Valdearcos et al., 2014).

High-SFA diet has been associated with increased expression of several pro-inflammatory markers and apoptotic genes, and decreased BDNF levels in the brain (Meireles et al., 2015; 2016) both in vivo and in vitro, even in short-term (<10 days) (Nakandakari et al., 2019). Additionally, prolonged high-SFA diet consumption reduces the number of neurons and affects their capacity to respond adequately to satiety signals, causing hyperphagia (Sears and Perry, 2015; Hamilton and Raybould, 2016).

Thaler et al. (2012) have elegantly shown the time-course of hypothalamic inflammation induced by HFD in rodent

models. Within 24 h of HFD exposure, occurs evident gliosis involving recruitment of both microglia and astrocytes. These neuroadaptations were transient. However, with continued HFD exposure, after 1 week, the inflammation and gliosis return and become established. In the same study, the authors also report increased gliosis in the mediobasal hypothalamus in individuals with obesity. These alterations contribute to leptin resistance and weight gain. In response to more chronic exposure, high-SFA diets can damage the BBB which may lead to increased neuroinflammation via blood-to-brain leakage of peripheral proteins (Takechi et al., 2013). Changes in BBB permeability may be evident after 90 days of high-SFA exposure (Hargrave et al., 2016). Moreover, it increases the hypothalamic production of palmitic acid-enriched ceramides (Moraes et al., 2009).

The composition of the fat in the diet may modulate the onset of low-grade inflammation through the endotoxin receptors. Comparing diets rich in palm oil (SFA) or rapeseed oil (n-6 and n-3 PUFAs and MUFA) in metabolic endotoxemia, it was observed that the palm oil-based diet resulted in higher active transport of LPS toward the peripheral tissues via high LBP (considered the major pro-inflammatory LPS transporter in plasma) and proinflammatory cytokines expression, and lower CD14 expression. In contrast, rapeseed oil-based diet induced a higher CD14 concentration associated with lower peripheral inflammation, despite higher plasma LPS, but with lower inflammatory potential (Laugerette et al., 2012). Nonetheless, high-SFA diet generally leads to more inflammation than unsaturated fats due to the ability of saturated fats to stimulate TLR4 directly (Shi et al., 2006; Laugerette et al., 2012).

Both n-3 and n-6 PUFAs are not synthesized in mammalian cells, even being considered essential fatty acids, they must be obtained from the diet (Robertson et al., 2017). Overall, unsaturated fatty acids are considered healthier than SFAs, but it has been assumed that especially the n6/n3 ratio would determine health status, once the "westernization" of modern diets has led to a drastic n-3 intake in place of n-6.

Elderly mice fed with high-n-6 diets (40% energy) presented bacterial overgrowth, increased Firmicutes/Bacteroidetes ratio and bacterial infiltration into the intestinal epithelium. This was correlated with increased body mass and infiltration of macrophages and neutrophils. However, the addition of 1% fish oil (n-3 PUFA like DHA and EPA) in high-n-6 diet restored the bacterial content of the microbiota, the inflammatory cell infiltration, and promoted regulatory immune cell recruitment. Otherwise, this combination was associated with increased oxidative stress in the ileum (Ghosh et al., 2013). In this sense, the improvement of unbalanced dietary fatty acid intake (n6/n3) may provide an important strategy for preventing complications in patients with metabolic alterations by decreasing Firmicutes/Bacteroidetes ratio and by reducing the expression of proinflammatory cytokines (Lee et al., 2019).

Results on diets rich in n-3 PUFA are controversial. Recent studies have demonstrated that high-n-3 diets do not affect the microbial diversity compared to control diets in humans (Rajkumar et al., 2014; Balfego et al., 2016) and mice (de Wit et al., 2012). In contrast, the supplementation with 4 g/d of n-3 PUFA for 8 weeks did not change bacterial diversity or phyla composition but increased abundance of beneficial bacteria such as *Bifidobacterium, Lactobacillus,* and *Roseburia* (Watson et al., 2018). The consumption of diets rich in n-3 has been associated with the increase of several SCFA-producing bacteria and consequently dampening inflammatory responses associated with metabolic endotoxemia both in animals (Kaliannan et al., 2015) and in humans (Watson et al., 2017). However, an intervention with high-MUFA oil n-3-enriched for 30 days increased Firmicutes which was positively correlated with total cholesterol levels and also increased *Lachnospiraceae* (Pu et al., 2013) which has been reported to be abundant in animals fed with high-fat diets (Zhang et al., 2012; Lecomte et al., 2015). However, the nutritional status seems to contribute to the impact of the microbial diversity together with the high consumption of MUFA and PUFA. High-MUFA increased *Parabacteroides* and decreased *Isobaculum* in individuals with obesity, but not overweight. Subjects, and both high-MUFA and high-PUFA diets reduce taxonomical levels mainly in subjects with obesity (Pu et al., 2016). In comparison to high-SFA diets, high-n-3 or n-6 diets occasioned lower decreases in *Bacteroidetes* in mice (Liu et al., 2012).

Linoleic acid (n-6) may mediate various sex-dependent effects via the gut-brain axis. In males, a long-term high-fat diet enriched with n-6 was able to change microbiota composition and reduced butyrate production, leading to hypothalamic leptin resistance via microglia accumulation. However, this is not seen in females, being restored butyrate-producing bacteria, contributing to the hypothalamic inflammation control via GPR41 and GPR109A up-regulation (Zhuang et al., 2017).

Moreover, n-6 and n-3 seem to regulate the hypothalamic fatty acid profiles, gene expression, and insulin signaling differentially; being n-6 more expressive in changes for the whole-body energy homeostasis (Fernandes et al., 2018). The hypothalamus contains receptors specific for n-3 – GPR120, primarily present in microglia, whereas GPR40 is expressed in neurons – which act in concert in the hypothalamus to reduce energy efficiency and regulate the inflammation (Dragano et al., 2017). Thus, the presence of suitable levels of n-3 in the diet can decrease hypothalamic inflammation (Cintra et al., 2012).

Mice with n-3 deficiency displayed high Firmicutes/Bacteroidetes ratio and systemic LPS responsiveness, and it was linked with neurobehavioural alterations, but not with microglial activation (Robertson et al., 2017). Nevertheless, prolonged ingestion ($\geq$9 weeks) of a hyperlipidic diet enriched with 12% fish oil impaired hypothalamic mechanisms related to hypophagia and energy expenditure in rats (Watanabe et al., 2010). High-linoleic acid diet (22.5%) also augmented the expression of arcuate appetite-regulating neuropeptides, produced greater body weight gain and insulin resistance, and suppressed activity more than the SFA (Mamounis, Yasrebi, and Roepke, 2017).

The improvement of dietary fatty acids profile is proposed to treat and prevent several disorders. Thus, the

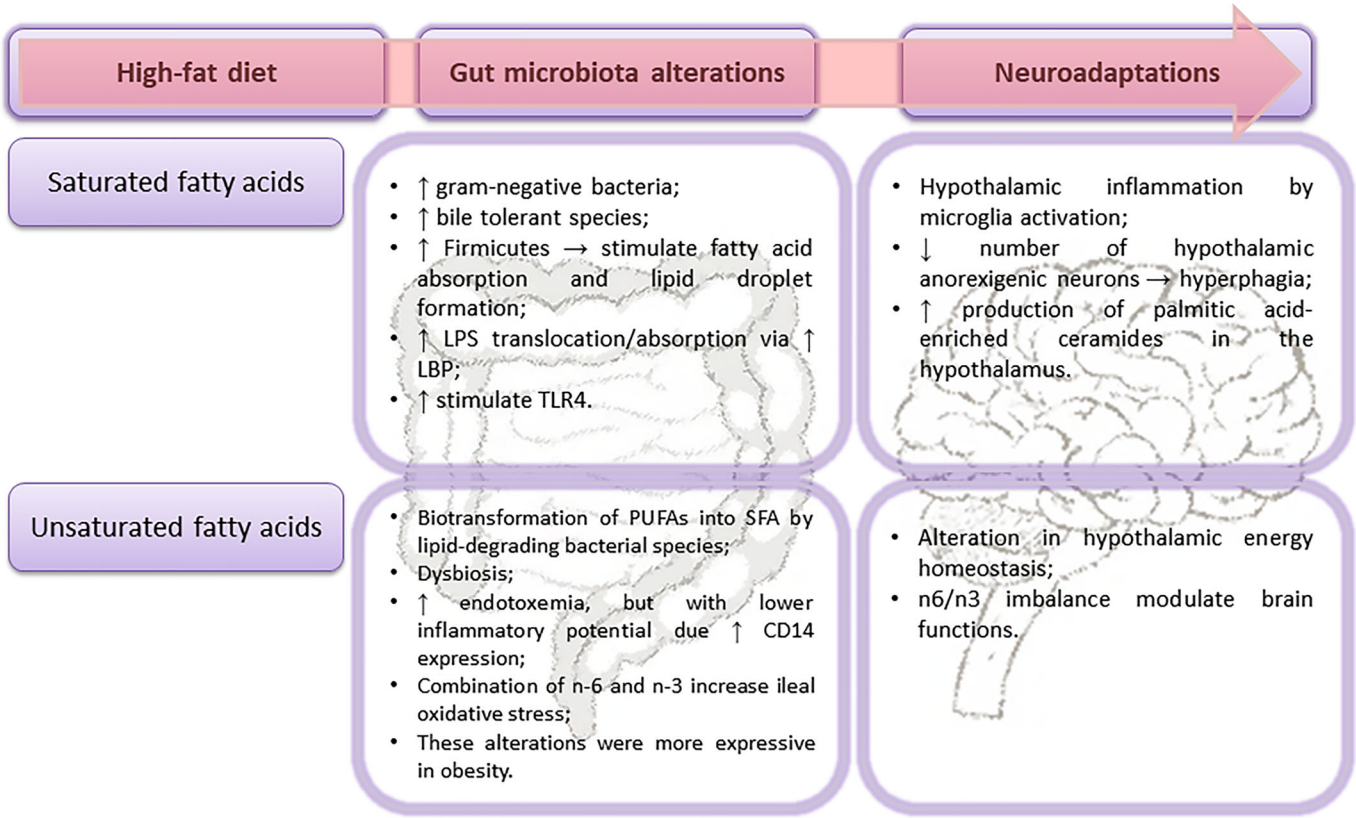

Figure 2. High-fatty acids diets as the trigger in the changes of the gut microbiota and central nervous system. This figure summarizes the results found regarding the alterations caused in the gut microbiota and the central nervous system by different types of fatty acids when consumed in excess. CD14: CD14 co-receptor; LBP: LPS-binding proteins; LPS: lipopolysaccharide; n-3: omega fatty acid; n-6: omega 6 fatty acid; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; TLRs: toll-like receptors.

reduction of SFA intake and the replacement of them by MUFA and PUFA is strongly recommended (USDA, 2015). Even though that most studies report the beneficial effects of MUFA and PUFA, their excessive consumption appears to affect bacterial diversity, being closely related to chronic diseases as well as high-SFA intake (Jamar et al., 2018). Although only a few studies have compared the effects of different dietary fat types, these dietary recommendations may need additional research.

In short, the detrimental effects of the high-SFA diet on the gut microbiota are well discussed in the literature, mainly in animals. Regarding unsaturated fatty-acids-rich diets, high-MUFA diets have shown a potentially negative effect on the intestinal microbiome and negative effects of high-PUFA diets seem to be more related to the n6/n3 imbalance (Figure 2). Therefore, it is mandatory to investigate the excessive and indiscriminate consumption of fish oil n-3-rich supplements in the microbiota-gut-brain axis (for more details of some studies that report the role of fatty acids in changes in gut microbiota and neuroinflammation see Table 2).

Sugar and microbiota-gut-brain inflammation

Sugar typically refers to a category of simple carbohydrates that includes monosaccharides like fructose and glucose, and disaccharides, like sucrose and lactose, which have different effects on the body and brain (Della Corte et al., 2018). The present review focuses primarily on added sugars – sucrose and fructose, predominate in the typical Western diet – due to their negative impact on health.

The carbohydrate digestion process uses numerous enzymes, being highly dependent on the specific type of carbohydrate ingested. The contribution of the gut microbiota to the degradation of carbohydrates is necessary since humans produce only 17 carbohydrate-active enzymes, whereas some bacterial species in the gut have more than 200 carbohydrate-active enzymes (Portune et al., 2017; Korpela, 2017). Microbial bacteria can contribute beneficially to sugar degradation, for example, *Bifidobacterium* benefit from the presence of lactose. Therefore, lactase-deficient individuals may tolerate dairy products in their diet, improving the symptoms of lactose intolerance (Bonder et al. 2016; Korpela, 2017).

The majority of digestible dietary carbohydrates are utilized and absorbed in the small intestine, whereas non-digestible carbohydrates (fibers) reach the colon and are fermented by acid-tolerant anaerobic bacteria, such as *Bifidobacterium*, *Ruminococcaceae*, and *Lachnospiraceae,* to produce several metabolic end products (Korpela, 2017; Portune et al., 2017).

Simple sugars present in the small intestine are detected by sweet taste receptor type 1 (T1Rs), expressed by L cells, that detect monosaccharides (Furness et al., 2013). Fast-growing bacteria such as *Prevotella, Streptococcus,* and *Veillonellaceae*, efficiently utilize simple sugars and amino acids, reflecting in accelerated intestinal transit (Zhernakova et al. al., 2016). Overconsumption of simple sugars can exceed the carbohydrate absorption capacity of the small

Table 2. Dietary intervention studies investigating the effect of high-fat diets (saturated, monounsaturated, or polyunsaturated fatty acids) on changes in gut-microbiota and/or neuroinflammation.

Author	Study design and aim	Main findings
Watanabe et al. (2010)	• Male Wistar rats were fed with chow or HFD (40%) enriched with either soy or fish oil (12%) for 9 weeks after wearning. • To examine the influence of different high-PUFA diets on serotonin-induced hypophagia, hypothalamic serotonin turnover, and hypothalamic protein levels of serotonin transporter (ST) and receptor (SR-1B and SR-2C).	• Fish oil developed heavier retroperitoneal and epididymal fat depots; • ↓ hypothalamic serotonin turnover and SR-2C level; • Impaired hypophagia mechanisms and affected energy expenditure.
de Lartigue et al. (2011)	• Sprague-Dawley rats with initial weight 180 g were fed with chow or HFD (45%t) for 8 weeks to induce obesity. • To verify if leptin resistance occurs in vagal afferent neurons in response to HFD.	• Vagal afferent neurons of HFD rats become leptin resistant; • LPS and SOCS-3 may play a role in the development of leptin resistance.
Thaler et al. (2012)	Animals´ study: • Weight-matched male Long-Evans rats (300–350 g) or male C57BL/6 mice (20–25 g) were fed with chow or HFD (60%) for 1 day to 8 months. • To identify the time course of HFD-induced hypothalamic inflammation. Humans´ study: • 34 participants (19 men and 15 women; mean age, 38 ± 12 years; mean BMI, 28.5 ± 6.7 kg/m^2). • Retrospective cohort study to assess for radiologic evidence of MBH gliosis and correlated with BMI levels and obesity.	• Hypothalamic inflammatory signaling was evident in both rats and mice within 1 to 3 days after HFD exposure, prior to substantial weight gain; • Gliosis and neuron injury were evident in the hypothalamic arcuate nucleus of rats and mice within the first week of HFD; with continued HFD feeding, inflammation and gliosis returned permanently to the MBH; • Individual with obesity presented ↑ gliosis in the MBH; • In both humans and rodent models, obesity is associated with neuronal injury in a brain area crucial for body weight control.
Laugeretti et al. (2012)	• C57/Bl6 mice were fed with chow or isocaloric isolipidic diets enriched with different fatty acid: milk fat, palm oil, rapeseed oil, or sunflower oil for 8 weeks; • In vitro, adipocytes (3T3-L1) were stimulated or not with LPS and incubated with different fatty acids. • To test the impact of HFD on endotoxin metabolism and inflammation.	• Palm oil ↑ IL-6 in plasma, IL-1β in adipose tissue, and LPS-sensing TLR4 and CD14. It was correlated with a greater ratio of LBP/sCD14 in plasma. • Rapeseed oil ↑ sCD14. It was associated with ↓ inflammation in both plasma and adipose tissue despite ↑ plasmatic LPS. • Palm oil resulted in the most active transport of LPS toward tissues via ↑ LBP and ↓ sCD14 and the greatest inflammatory outcomes. • Rapeseed oil resulted in an endotoxin metabolism driven toward less inflammatory pathways.
de Wit et al. (2012)	• C57Bl/6J mice were fed purified HFD (45%) containing palm oil (HF-PO), olive oil (HF-OO), or safflower oil (HF-SO) for 8 weeks. • To verify the effect of dietary fat type on development of obesity, hepatic steatosis, and insulin resistance and the potential contribution of the intestine.	• HF-PO ↑ body weight gain and liver triglyceride content; • ↑ PPARɣ in small intestine; • ↓ microbial diversity and increased the F/B ratio, with ↑ Bacilli and *Clostridium* clusters; • Favored overflow of palm oil to the distal intestine.
Valdearcos et al. (2014)	• 10 week-old Male C57BL/6 mice were fed with chow or HFD (42% fat from milk, mostly palmitic and stearic acids) for 1, 4, and 16 weeks. • Wild type and CD11b-DTR mice to slice studies and bone marrow transplants, which were used to deplete CD11b-expressing cells; • CX3CR1-GFP mice to confirm the effect of CSF1R (a specific BBB-permeable colony-stimulating factor 1 receptor) antagonism on microglial depletion *in vivo*. • Primary microglia and astrocytes were from Wild type mice; • To show that microglia mediate inflammation, gliosis, and neuronal stress in the MBH in response to consuming excess SFA and its functional impact.	• HFD accumulated microglia and astrocytes in the MBH (reaching a plateau by 4 weeks); • Only the microglia undergo inflammatory activation (increased TNFα) specifically in the hypothalamus, where occurred SFA accumulation; • Enteric gavage with SFAs for 3 days reproduces microglial activation and neuronal stress in the MBH; • In culture, SFA treatment activated microglia, but not astrocytes; • Depleting microglia from the MBH annuls inflammation and neuronal stress induced by excess of SFA and, consequently, enhances leptin signaling and reduces food intake.
Daniel et al. (2014)	• Male C57BL/6NCrl mice were fed with carbohydrate diet (66% glucose) or HFD (60%) for 12 week. • To provide novel insights into biochemical alterations of the gut microbiota in response to HFD.	• HFD increased body weigh; • Altered microbial diversity and composition: ↑ F/B ratio, ↓ *Ruminococcaceae* and ↑ *Rikenellaceae*, *Lactobacilli*, *Alistipes* and *Clostridium cluster* XIVa; • Altered the gut bacterial metaproteome, mainly by changes in the abundance of *Bacteroidales* and *Lachnospiraceae*, leading to alterations most pronounced for pathways of amino acid metabolism; • Affected cecal metabolic pathways: eicosanoid, steroid hormone, macrolide, bile acid and bilirubin metabolism.
Bruce-Keller et al. (2015)	• Adult male C57BL/6 mice received chow diet and were subjected to a microbiome depletion/ transplantation paradigm using microbiota isolated from donors on either HFD (60%) or control diet for 10 weeks. • To verify if obesity-associated changes in gut microbiota are intrinsically able to impair neurocognitive behavior in mice.	• HFD microbiota ↓ *A. muciniphila* and ↑ *Bilophila* sp. and *Clostridiales*; • Disrupted markers of barrier function (ZO-1, occluding, and claudin) in jejunum, colon, and in the medial prefrontal cortex; • ↑ circulating LPS and systemic inflammatory markers, neuroinflammatory markers and disrupted cerebrovascular. • There were no significant differences in soluble BDNF between groups.

(*continued*)

Table 2. Continued.

Author	Study design and aim	Main findings
Pu et al. (2016)	• 25 volunteers with risk of MetS were randomized to receive 60g of: high-MUFA diets - (1) conventional canola oil; (2) DHA-enriched high-oleic canola oil; (3) high-oleic canola oil; and high-PUFA diets - (4) a blend of corn/safflower oil; (5) a blend of flax/safflower oil. • To investigate effects of different oil blends on gut microbiota, obesity, and biomarkers of MetS.	• High-MUFA ↑ *Parabacteroides, Prevotella, Turicibacter*, and Enterobacteriaceae; • High-PUFA ↑ *Isobaculum;* • These alterations were more evident in individuals with obesity, but not overweight, accompanied by ↓ taxonomical levels (OTUs).
Kreutzer et al. (2017)	• 57 subjects with obesity (mean age, 43 years; mean BMI, 43.7 kg/m^2) and 54 age- and sex- matched non-obese controls (mean age, 46 years; mean BMI, 22.2 kg/m^2). • Retrospective analysis of the MBH by brain magnetic resonance imaging to verify hypothalamic inflammation, combining food intake analysis and gut microbiota.	• Obese subjects exhibited hyperintensity in the left MBH. It was associated with systemic low-grade inflammation. • N° of neurons in the left hypothalamic region were similar between groups. It suggest functional but not structural impairment due to the inflammatory process. • The overconsumption of fat ↓ *Parasutterella sp.* It was correlated to MBH-hyperintensity. • These environmental factors we found subjects carrying common polymorphisms in the JNK or the MC4R gene to be more susceptible to hypothalamic inflammation.
Mamounis et al. (2017)	• Male C57BL6/J mice were fed with control or 3 HFD (45%) + LA (1%, 15% and 22.5%) diets for 12 weeks. • To determine the obesogenic potency of LA and the involvement of hypothalamic inflammation.	• 22.5% LA ↑ body weight gain and ↓ insulin resistance; • ↑ neuropeptides gene (POMC, CART, AgRP); • All HFD groups had similar ↑ in leptin and ghrelin levels; • There was no consistent pattern of inflammation between diets.
Robetson et al. (2017)	• Pregnant female C57BL/6 mice and their male offspring were fed with chow, n-3 supplemented (O3+: ∼1g EPA + DHA/100g diet) or n-3 deficient (O3-) diet. • To examine the effects of n-3 PUFA deficiency or supplementation, *in utero* and early life, on depressive, cognitive and social behaviors during adolescence and adulthood and correlate with inflammation, gut microbiota, and HPA axis activity.	• n-3 interventions induced changes in offspring early-life and adolescent behaviors, which were further evident in adulthood; • O3- ↓ communication, social, and depression-related behaviors; ↑ F/B ratio and systemic LPS; • O3+ ↓ cognition; ↑ *Bifidobacterium* and *Lactobacillus;* ↓ HPA-axis activity.
Zhuang et al. (2017)	• Young C57BL/6J mice were fed with HFD (45%) for 10 weeks to induce obesity, and then fed with HFD + AA (10g/kg) or a continuous HFD in the following 15 weeks. • To investigate the effects of AA in obesity through associating microbiota-driven inflammation with hypothalamus-adipose-liver axis.	• AA aggravates obesity for both genders whereas sex-dependently affects gut microbiota composition: ↓ F/ B ratio and altered microbial diversity and abundance; • ↑ pro-inflammatory microbiota and ↓ butyrate production; • In male, ↓ circulating serotonin and triggered hypothalamic leptin resistance via microglia accumulation; • In female, ↓ obesity-related disorders via rescuing anti-inflammatory and butyrate-producing microbiota, up-regulating GPR41 and GPR109A and controlling hypothalamic inflammation.
Nakandakari et al. (2019)	• Young male C57BL/6J mice were fed with chow or HFD (35.2%) for 3, 7, and 10 days; • Neuronal (N2a) and microglial (BV2) mouse cells were cultivated and supplemented palmitate acid low concentration. • To investigate the effects of short-term HFD in Alzheimer markers and neuroinflammation in the hippocampus.	• HFD ↑ fasting glucose and HOMA-IR; • ↑ activation of inflammatory, ER stress and apoptotic signals in the hippocampus; • N2a and BV2 cells presented ↑ expression of inflammatory and apoptotic genes when stimulated with palmitate.

AA: arachidonic acid; AgRP: Agouti-related protein; BBB: blood-brain barrier; BDNF: derived neurotrophic factor; BMI: body mass index; CART: Cocaine- and amphetamine-regulated transcript; sCD14: CD14 co-receptor; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ER: endoplasmatic reticulum; F/B: Firmicutes-to-Bacteroidetes ratio; GPR: G protein-coupled receptors; HFD: high-fat diet; HOMA-IR: homeostasis model Assessment for insulin resistance; HPA: hypothalamic-pituitary-adrenal; Iba-1: Allograft inflammatory factor 1; JNK: Jun N-terminal Kinase; LA: linoleic acid; LBP: LPS-binding proteins; LPS: lipopolysaccharide; MBH: mediobasal hypothalamus; MC4R: melanocortin-4 receptor; MetS: Metabolic syndrome; MUFA: monounsaturated fatty acids; n-3: omega-3; POMC: Pro-opiomelanocortin; PPARγ: Peroxisome proliferator-activated receptor PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; SOCS-3: Suppressor of cytokine signaling 3; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-alpha.

intestine providing easily accessible substrates for bacterial growth in the distal small intestine and the colon (Jang et al., 2018). Furthermore, high-carbohydrate diets cause a dramatic loss of microbial diversity, coinciding with a bloom in fecal saccharolytic bacteria which are normally not present in the distal colon regardless of the glycemic index (Turnbaugh et al., 2008; Fava et al., 2013).

Recent studies suggest that a sucrose-rich diet and a fructose-rich diet affected the intestinal microbiome in different ways (Rosas-Vilegas et al., 2017; Volynets et al., 2017; San et al., 2017).

Yin and coworkers (2018) verified that sucrose-diet rich alters the activity of *Lactobacillus plantarum* in the digestive tract. The authors concluded that probiotics could differentially influence gut metabolomes through their carbohydrate consumption capacities. Sucrose-induced dysbiosis is characterized by a bloom in Clostridia and Bacilli; a marked decrease in *Lactobacillus* spp., *Sphingomonas,* and *Klebsiella;* and by increasing some bacterias, such as Firmicutes phylum (*Faecalibacterium* and *Streptococcus*) and Proteobacteria phylum (*Sutterella* and *Bilophila*) (San et al., 2017; Rosas-

Vilegas et al., 2017; Yin et al., 2018). The reduction of microbial diversity may occur after 1 week of consumption of a diet rich in sucrose, regardless of the fat content (San et al., 2017).

In various animals' species and humans, chronic excessive fructose consumption promotes loss of tight junction proteins in the duodenum accompanied with loss of mucus thickness and endotoxin translocation. It reduces the production of defensins – an antimicrobial peptide – in the ileum and colon, and induces systemic inflammation (Jin et al. 2014, Kavanagh et al. 2013; Volynets et al., 2017), especially combined with a Western diet (Rosas-Vilegas et al., 2017). These outcomes may also occur independently of total energy intake or fat content in the diet (Volynets et al., 2017). A recent study showed that monosaccharides (glucose or fructose) could similarly affect the gut microbiota, gut permeability, and inflammation without altering weight gain (Do et al., 2018).

Although the overconsumption of simple sugars affects gut microbes and increases the paracellular transport of LPS generating a chronic state of inflammation, sucrose seems to be more related to weight changes and metabolic parameter alterations, whereas fructose results in a more compromised gut barrier and subclinical inflammation. These consequences are more pronounced in combination with a high-fat diet (Volynets et al., 2017; Rosas-Vilegas et al., 2017). It is noteworthy to mention that during the process of intestinal absorption of sucrose, there is an increase in paracellular activity to favor the bioavailability of fructose (Korpela et al., 2017).

Excessive fructose consumption has specific effects on tissues in the regulation of metabolic inflammation, once it can lead to an increase in the infiltration of macrophages, causing the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) (DiNicolantonio et al., 2018). Also, added fructose causes central leptin resistance – impairing energy homeostasis – and peripheral leptin resistance, which contributes to the release of reactive oxygen species and recruitment of monocytes that perpetuate more inflammation (Shapiro et al. 2011; Della Corte et al., 2018)

Excessive consumption of added sugars seems to impact the CNS negatively with different impacts on the brain. It has been associated with dysbiosis, gut inflammation, and alterations in gut-brain vagal communication.

The differential effects of the two monosaccharides may be attributed initially to the availability to supply energy to the brain. Neurons have an especially high energy demand for generating postsynaptic potentials and action potentials, being glucose from the bloodstream the main source of energy for the brain. Glucose transporters in astrocytes and the epithelial cells of the BBB are responsible for transporting glucose into neurons. In contrast, fructose cannot directly supply the brain with energy as it crosses the BBB to a much lesser degree than glucose (Freeman et al., 2018). It was demonstrated that fructose administered intraperitoneally in rodents crossed the BBB and triggered neuronal activation (Ochoa et al., 2015). Additionally, studies in animal models showed that fructose load does not decrease the hunger sensation as compared to glucose, once the intracerebral injection of fructose stimulates food intake (Lowette et al., 2015; Wu et al., 2015). There also appears to be evidence of insufficient down-regulation of appetite following caloric intake in adult obese individuals (Wang et al., 2014). However, fructose's ability to cross the BBB has not yet been studied in humans (Freeman et al., 2018). This alteration in energy homeostasis has been associated with cravings and addictive-like eating symptoms for sweets and carbohydrates after 12 h of sugar overconsumption (Eikelboom & Hewitt, 2016).

High-sucrose diet activates microglia in the nodose ganglion (San et al., 2017), induces hypothalamic inflammatory responses, and leads to neuronal dysfunction in the control of energy metabolism (Gao et al., 2018). San and colleagues (2017) also showed an increase in body fat mass correlated with dysbiosis and gut-brain communication; and concluded that this condition possibly provides the basis for the obesity pathogenesis.

Excessive consumption of high-fructose corn sirup, used worldwide in ultra-processed food, induce hypothalamic microglial activation with neuroinflammation through the activation of the TLR4/NF-κB signaling, resulting in the reduction of neurogenesis (Li et al., 2015; Xu et al., 2016) in animals, even during the period of development of the CNS (Hsu et al., 2015). However, the mechanism by which fructose causes the activation of glial cells and the development of neuroinflammation is poorly understood so far.

In the brain, either by BBB fructose uptake or by endogenous glucose formation through the polyol pathway, it stimulates an increased release of cortisol, causing hepatic gluconeogenesis, leading to peripheral and central insulin resistance and, consequently, greater adiposity (DiNicolontonio et al., 2018). A study with neonatal nutrition in rats suggests that increased adiposity induced by a high- carbohydrate diet is not associated with hypothalamic gliosis. Thus, the activation of hypothalamic inflammatory processes and gliosis depend not only on weight gain but also on the type of diet that induces weight gain and early nutritional status (Fuente-Martin et al., 2013). In this sense, Andre et al. (2017) affirmed that the induction of obesity by the high-fat diet is determined by the amount of carbohydrate contained in the diet. Besides that, the microglial expansion in the hypothalamus requires the adequate presence of both fats and carbohydrates, once a high-fat/low-carbohydrate diet did not affect microglial proliferation (Andre et al., 2017). These diverse inflammatory processes induced by an obesogenic diet could indicate a differential disposition to pathologies development (Fuente-Martin et al., 2013).

Added sugar consumption has also been associated with mood changes and cognitive impairments, especially worsened hippocampal memory function (Wu et al; 2015; Beilharz et al., 2016).

Non-digestible carbohydrates (fibers) are known to produce beneficial effects from their degradation as it is the preferred carbon source by the microbiota in the large intestine. However, specific effects vary widely depending on the type of

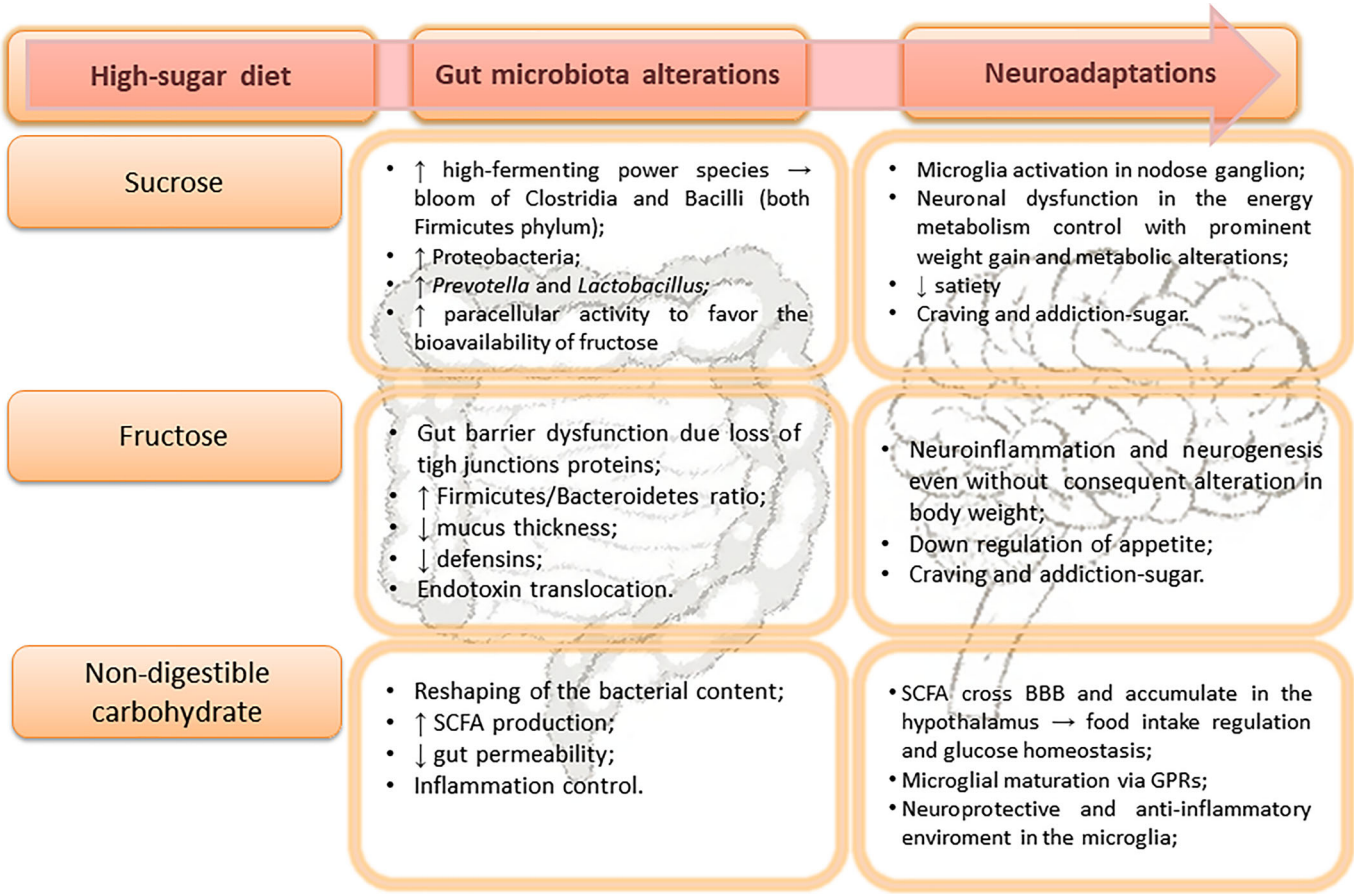

Figure 3. High-sugar diets as the trigger in the changes of the gut microbiota and central nervous system. This figure summarizes the results found regarding the alterations caused in the gut microbiota and the central nervous system by different types of sugar when consumed in excess. BBB: blood-brain barrier; GPR: G protein-coupled receptors; SCFA: short-chain fatty acids.

fiber evaluated, as well as the composition of the individual's microbiota (Portune, 2017). Generally, the high-fiber diet generates SCFA (products derived from the anaerobic fermentation) which can bind to specific receptors, such as G-protein coupled receptors FFAR2 and FFAR3, (also called GPR43 and 41). These receptors can also be expressed in the vagus nerve (De Vadder et al., 2014) and can contribute to the recruitment of immune cells, impacting the regulation of inflammatory pathways (Macia et al., 2012).

Oral administration of SCFAs mix showed to maturate the immature microglial phenotype observed in germ-free mice via GPR43 (Erny et al., 2015). It has been demonstrated that acetate can cross BBB and accumulate in the hypothalamus, altering gene expression of food intake regulating neuropeptides (Frost et al., 2014; Soliman et al., 2012). Furthermore, SCFA leads to an increase in butyrate-producing species in the distal colon (*Roseburia, Blautia, Eubacterium rectale, Faecalibacterium prausnitzii, Bifidobacterium,* and *Lactobacillus*) and variations in Bacteroidetes/Firmicutes proportions (Graf et al., 2015; Chung et al., 2016). Besides, it is associated with body weight control, central regulation of appetite and food intake, inflammation control and maintenance, and gut and glucose homeostasis (Blander et al., 2017; Torres-Fuentes et al., 2017). Butyrate has been extensively studied pharmacologically as a histone deacetylase inhibitor and serves as an attractive therapeutic product. Several reports using a high-fiber diet showed that the increase butyrate levels could reshape the gut bacteria, reduce gut permeability, and attenuate pro-inflammatory cytokine expression in microglia via a direct effect on vagal afferent terminals (Patnala et al., 2017; Matt et al., 2018).

Carbohydrate fermentation also results in the production of hydrogen and carbon dioxide, which can also be used as an energy source for a variety of microbes, including reductive acetogens, methanogens, and sulfate reducers, thus maintaining a balance in this ecosystem (Zoetendal, 2014). Colon bacteria are a significant source of anti-inflammatory histamine and polyamines, as putrescine and spermine. *Bifidobacterium* spp., which is involved in a probiotic action, increases gut histamine and polyamines concentrations and inhibits colon inflammation by suppressing cleavage of the protease caspase-1 and secretion of interleukin 18 (IL-18) (Blander et al., 2017). In contrast, a low-fiber diet promotes the proliferation of mucus-degrading bacteria; leading to colonic mucus erosion associated with alterations in the gut barrier, and increased susceptibility to gram-negative bacteria (Desai et al., 2016; Zoetendal, 2014).

Thus, SCFAs appear to play a protective role in the interaction between the microbiota and hypothalamus by decreasing intestinal permeability and interacting positively with the vagal afferent neurons, creating a neuroprotective

Table 3. Dietary intervention studies investigating the effect of high-sugar diets (fructose, sucrose, or glucose) and complex carbohydrates on changes in gut-microbiota and/or neuroinflammation.

Author	Study design and aim	Main findings
Fuente-Matín et al. (2013)	• Neonatal Wistar rats were induced to overnutrition (NON) or control. After weaning, they received chow diet and water or a solution of 33% sucrose in water for 2 months • To analyze the inflammatory and glial responses to a sucrose-enriched diet.	• Sucrose ↑ serum IL-1β and -6 and hypothalamic IL-6 mRNA levels in NON rats; • Sucrose ↑ hypothalamic TNF-α mRNA levels in control and NON rats; • Astrocyte marker glial fibrillary acidic protein was ↑ by NON but ↓ by sucrose; • Sucrose ↑ number of microglia and pIκB and JNK in control but not NON rats; • There was no effect on microglia activation markers by sucrose between groups; • Proteins highly expressed in astrocytes were ↑ increased by NON but not sucrose.
Jin et al. (2014)	• 58 adolescents with risk for NAFLD or not, presenting consumption of sweet beverages. • Retrospectively analysis of samples from three pediatric cohorts (1) to investigate whether endotoxemia is associated with the presence of hepatic steatosis; (2) to evaluate postprandial endotoxin levels in response to fructose beverage in an acute 24-hour feeding challenge, and (3) to determine the change of fasting endotoxin amounts in a 4-week randomized controlled trial comparing fructose to glucose beverages in NAFLD.	• Adolescents with hepatic steatosis had ↑ endotoxin levels compared to obese controls; • Endotoxin level correlated with insulin resistance and several inflammatory cytokines. • Adolescents with NAFLD had ↑ endotoxin levels after fructose beverages (consumed with meals) as compared to healthy children, in 24h and 2 weeks.
Wang et al. (2014)	• 19 healthy subjects (40–60 years old and BMI between 21–35 kg/m^2). They received in Day A: they received 75 g oral glucose drink; and Day B: oral placebo drink (artificial sweetener sucralose, 0.348 mg/ml that was of equal volume and sweetness level to the glucose solution). PET scan started at 10 minutes after the ingestion. A solution [^{11}C]raclopride was injected to measure dopamine. Days A and B were randomized across subjects and were separated between 2–42 days. • To verify if the dopamine response to calorie intake (independent of palatability) in striatal brain regions is attenuated with increases in weight.	• Blood glucose concentrations did not vary as a function of BMI at any time; • Changes in dopamine in the ventral striatum were significantly correlated with BMI; • Dopamine decreaed when glucose consumption was associated with obesity. • It was related with excessive food intake to compensate for the deficit between the expected and the actual response to food consumption.
Hsu et al. (2015)	• Adolescent or adult male Sprague-Dawley rats received low-fat chow and water (control), water + 11% sucrose solution, water + 11% high- fructose corn sirup (HFCS-55) solution for 30 days. • To examine the effects of sucrose and HFCS-55 intake during adolescence or adulthood on cognitive and metabolic outcomes.	• HFCS-55 impaired hippocampal-dependent spatial learning and memory in adolescent rats; • HCF-55 ↑ pro-inflammatory cytokines (interleukin 6, interleukin 1β) in the dorsal hippocampus in adolescent; • Interleukin 1β and plasma insulin levels were ↑ for both adolescent-exposed sugar groups; • HFCS-55 or sucrose in adults did not impact spatial learning, glucose tolerance, anxiety, or neuroinflammatory markers.
Chung et al. (2016)	• Three different human gut microbial communities in anaerobic, pH-controlled continuous-flow fermenters, added non-digestible polysaccharides as energy source (apple pectin or inulin) stimulated with SCFA. • To predict how diet composition, including the addition of prebiotics, can be used to manipulate microbiota composition.	• Apple pectin or inulin resulted in ↑ bacterial operational taxonomic units (OTUs), mainly in *Bacteroides;* • Inulin was more efficient in ↑ OTUs in several spices, with marked ↑ of *F. prausnitzii;* • Pectin was more effective in ↑ community diversity.
Desai et al. (2016)	• Germ-free male and female wild type Swiss Webster mice were colonized with a synthetic human gut microbiota composed of fully sequenced commensal bacteria at 8–9 weeks of age. On day 14 after colonization mice were randomized to receive sterilized fiber-free (FF); prebiotic (Pre - 2.1% of a purified polysaccharide mixture added along with 10% cornstarch); and fiber-rich (FR) diet for 39 to 42 days. • Kanamycin-resistant wild-type *C. rodentium* strain and a luciferase-expressing strain of *C. rodentium* (resistant to ampicillin) were used and gavaged with 0.2 ml of culture grown aerobically. Same culture was used to gavage all mice. • To investigate the mechanistic connections between chronic or intermittent dietary fiber deprivation on microbiota composition and physiology as well as the resulting effects on the mucus barrier.	• In chronic or intermittent dietary fiber deficiency (FF), the gut microbiota resorts to host-secreted mucus glycoproteins as a nutrient source, leading to erosion of the colonic mucus barrier; • Also promotes greater epithelial access and lethal colitis by the mucosal pathogen, *Citrobacter rodentium*.
Do et al. (2018)	• Adult male C57BL/6J mice were feed with control, high-glucose (HGD: 85% from glucose), or high-fructose (HFrD: 85% fructose) for 12 weeks.	• HGD and HFrD ↑ blood glucose and endotoxin levels, fat mass, dyslipidemia, and glucose intolerance without changes in body weight; • ↓ gut microbial diversity, characterized by a ↓ Bacteroidetes and Proteobacteria;

(*continued*)

Table 3. Continued.

Author	Study design and aim	Main findings
Matt et al. (2018)	• To examine the effects of diets high in monosaccharides on gut microbial diversity, gut permeability, metabolic endotoxemia, and lipid metabolism • Adult Balb/c male mice were injected i.p. with LPS or sodium butyrate (NaB); • Adult and aged Balb/c male mice were fed with low-fiber (1% cellulose) or high-fiber (1% cellulose + 5% inulin) diet for 4 weeks + injected i.p. with saline or LPS. • To determine the effects of NaB on microglia and immunity; and the effects of soluble fiber (inulin) in the microbiome, peripheral inflammation, and neuroinflammation.	• ↑ gut permeability due to alterations to the tight junction proteins caused by gut inflammation. • ↑ hepatic inflammation and lipid accumulation. • High-fiber altered gut microbiome (↓ *Ruminococcus* spp. and Rikenellaceae) and ↑ butyrate, acetate, and total SCFA production, and ↓ inflammatory infiltrate in aged mice; • High fiber promoted anti-inflammatory microglial in aged mice; • Low-fiber diet ↑ inflammatory infiltrate in aged mice; • Gene expression of inflammatory markers, epigenetic regulators, and the microglial sensory apparatus were altered by both diet and age.

and anti-inflammatory environment in the microglia (Mulders et al., 2018).

Summarily, the literature has shown the contribution of high-sugar diets in triggering remodeling negatively of the gut-brain axis (Figure 3 – Table 3). However, few studies compare the role of sugars in both the microbiome and neuroinflammation, mainly separated from the high-fat or Western diet. Further studies should be undertaken to determine the mechanisms that regulate gut microbiota-neuroinflammatory processes induced by high glucose, sucrose or fructose diet.

Concluding remarks

The gut microbiota influences endocrine and nervous routes, modulating energy homeostasis, production of gut peptides and hormones, and controlling the function of glial cells in the CNS. The diet-induced dysbiosis and microbiota encroachment play an essential role in the hypothalamic activity by vagal afferent nerve signaling. Nevertheless, hypothalamic inflammation and gliosis are proposed to participate in the pathogenesis of diet-induced obesity.

Each of the diets significantly altered the microbial composition in distinct ways, leading to neuroadaptations by different pathways. Consumption of both hyperlipidic (SFA and MUFA) and hyperglycidic (simple sugar) diets causes dysbiosis, whether in microbial quantity or diversity and, consequently, it can differently affect the neuroadaptations. Hyperlipidic diets increase LPS translocation and LBP activation, and it can stimulate TLR4 inflammatory pathway and modulate brain functions, mainly in the center of feeding. On the other hand, sucrose seems to be more detrimental for metabolic alterations, whereas fructose has a more pronounced effect on gut barrier dysfunction and subclinical inflammation; nevertheless, sucrose absorption favors fructose bioavailability, contributing to adiposity, insufficient down-regulation of appetite and sugar addiction. Additionally, the combined overconsumption of fat and sugar (Western diet) seems to be the great inductor of neuroinflammatory responses and eventually leads to neuronal dysfunction in the control of energy metabolism. In fact, there are few clinical trials that evaluate neuroadaptations in humans. Studies with high-SFA diet seem more consistent, besides to being more numerous, mainly in animals.

To our knowledge, this is the first review to explore the role of these macronutrients as initiators of inflammation on this axis. Further studies are needed to understand the exact mechanisms that regulate gut microbiota-neuroinflammatory process induced by dietary factors, since the precise role of each macronutrient, mainly regarding its type and quantity, is not yet well established. These findings illustrate the necessity for designing new experimental studies using different diets associated with bacterial products for better elucidating the pathways closely involved in the biological context.

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Conflict of interest

There is no conflict interest.

Abbreviations

JNK:	c-Jun N-terminal kinase
IL:	interleukin
NAFLD:	nonalcoholic fatty liver disease
NASH:	nonalcoholic steatohepatitis
pIκB:	phosphorylation of inhibitor of -κB
SCFA:	short-chain fatty acids
TNF-α:	tumor necrosis factor-alpha.

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