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Invited Review

Effects of obesity on depression: A role for inflammation and the gut microbiota

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ABSTRACT

Depression is a mental disorder associated with environmental, genetic and psychological factors. Recent studies indicate that chronic neuro-inflammation may affect brain physiology and alter mood and behavior. Consumption of a high-fat diet leads to obesity and chronic systemic inflammation. The gut microbiota mediates many effects of a high-fat diet on human physiology and may also influence the mood and behavior of the host. We review here recent studies suggesting the existence of a link between obesity, the gut microbiota and depression, focusing on the mechanisms underlying the effects of a high-fat diet on chronic inflammation and brain physiology. This body of research suggests that modulating the composition of the gut microbiota using prebiotics and probiotics may produce beneficial effects on anxiety and depression.

Contents

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1. Introduction

The prevalence of obesity has increased worldwide in recent decades, mainly due to high-calorie diets and sedentary lifestyles (Drewnowski, 2000). The World Health Organization estimates that 39% of the human adult population is overweight and 13% is obese (WHO, 2016). Obesity is not only associated with significant diseases such as type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease and cancer, but also reduces longevity and quality of life (Scully, 2014).

Global surveys indicate that ~5% of the world population (approximately 300 million people) suffers from mood disorders (WHO, 2017). Depression is a leading cause of disability worldwide and can lead to suicide, which represents the second leading cause of death in people aged between 15 and 29 years (WHO, 2017). Epidemiological data indicate that individuals with obesity have an increased risk of developing mood disorders such as major depressive disorder (MDD), which represents the most prevalent type of depression (Mansur et al., 2015). The relationship between obesity and depression is bi-directional: individuals with depression have a 50% higher risk of developing obesity and, conversely, people with obesity have an increased risk of developing depressive symptoms and manic episodes. Despite the introduction of new antidepressant drugs, many obese patients treated for depression respond poorly to therapy, suggesting that obesity may reduce the efficacy of anti-depression treatment (Woo et al., 2016).

While depression is a multifactorial disease associated with factors such as stress, genetic predisposition and traumatic life events, recent studies indicate that chronic inflammation caused by a high-fat diet (HFD) may play a major role in inducing neuroinflammation and depression. Notably, the gut microbiota mediates several of the effects of HFD on human physiology, and influences the mood and behavior of the host. We review here recent studies that suggest an association between obesity, the gut microbiota and depression. While the role played by neurological and hormonal systems has been described in previous reviews (Sarkar et al., 2016; Wang and Kasper, 2014), we focus here on the mechanisms underlying the effects of HFD on the immune system and brain physiology.

2. Obesity and inflammation

Obesity is associated with chronic, low-grade inflammation in peripheral tissues and blood circulation (Gregor and Hotamisligil, 2011). This association was first reported over two decades ago when the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) was found to be elevated in the blood and adipose tissues of obese individuals (Hotamisligil et al., 1995). Reduction of body weight in these subjects improved insulin sensitivity and reduced TNF-α expression in adipose tissues (Hotamisligil et al., 1995). Recent studies show that an increase of fat mass enhances the secretion of pro-inflammatory cytokines (or adipokines) such as TNF-α and interleukin (IL)-6 from adipocytes (Ouchi et al., 2011). In contrast, the adipocytes of lean individuals secrete higher amounts of anti-inflammatory adipokines such as adiponectin, which increases insulin sensitivity and protects against type 2 diabetes mellitus and cardiovascular disease (Ohashi et al., 2014).

Immune cells found in adipose tissue play a large role at the early stage of HFD-induced inflammation. Pro-inflammatory adipokines induce macrophage infiltration of adipose tissues and promote systemic insulin resistance (Xu et al., 2003). Accordingly, mice that are deficient in the pro-inflammatory cytokine monocyte chemoattractant protein-1 (MCP-1) show reduced macrophage accumulation in adipose tissues and reduced insulin resistance when fed a HFD (Kanda et al., 2006). Increased expression of macrophage-related genes occurs in adipose tissues within three weeks of HFD feeding in mice (Xu et al., 2003). Macrophages that accumulate in adipose tissues of obese mice belong to the M1 macrophage phenotype (or "classical activation," which is involved in inflammation and tissue damage). In contrast, macrophages isolated from adipose tissues of lean mice mainly express genes associated with the M2 macrophage phenotype (or "alternative activation," which is involved in resolution of inflammation and tissue repair) (Lumeng et al., 2007). Yet it is important to note that the chronic inflammation observed in adipose tissues of obese individuals is non-resolving and occurs over a long period of time (months to years), indicating that the macrophage population may continuously evolve based on the signals that modulate the activity of these cells, and factors that induce macrophage death/survival or replenishment from the pool of monocytes (Murray, 2017).

Various T cell subsets present within adipose tissues can modulate local and systemic inflammation. For example, $CD8^+$ T cells enhance inflammation and precede M1 macrophage accumulation in adipose tissues of HFD-fed mice (Nishimura et al., 2009). In addition, anti-inflammatory $CD4^+$ regulatory T cells (T_{reg}) are more abundant in adipose tissues of lean mice compared with obese mice (Feuerer et al., 2009). Furthermore, after a few days of HFD feeding, neutrophils accumulate in adipose tissues and produce the proteolytic enzyme elastase, which contributes to the development of insulin resistance (Talukdar et al., 2012). Another cell type involved in HFD-induced inflammation includes perforin-positive dendritic cells (perf-DCs), a subpopulation of DCs that protect the host against metabolic syndrome and obesity by reducing the number of pro-inflammatory T cells in adipose tissues (Zlotnikov-Klionsky et al., 2015). Accordingly, mice that lack perf-DCs show expansion of T cells in adipose tissues and develop metabolic syndrome and obesity, a phenomenon that can be amplified by a HFD.

Some food nutrients are pro-inflammatory, especially saturated fatty acids (Lyons et al., 2016) which activate Toll-like receptor-4 (TLR4) expressed by adipocytes and macrophages, leading to release of pro-inflammatory cytokines and disruption of cellular metabolism (Ohashi et al., 2014; Shi et al., 2006). The seminal work of Cani and co-workers revealed that HFD feeding for four weeks increases plasma lipopolysaccharide (LPS) levels by two to three fold in mice, leading to a condition termed "metabolic endotoxemia" (Cani et al., 2007, 2008). Bacterial LPS originating from the gut microbiota may thus represent an early factor that triggers chronic inflammation in obese individuals. Accordingly, repeated injections of LPS subcutaneously into mice for four weeks induce low-grade inflammation, insulin resistance and weight gain in a manner similar to HFD feeding (Cani et al., 2007).

In humans, the plasma LPS concentration increases by ~50% (from 8.2 to 12.3 pg/ml) following ingestion of a single high-fat meal (Erridge et al., 2007). Similarly, healthy individuals fed for one month with a Western-style diet containing 40% fat show a 71% increase in plasma LPS (Pendyala et al., 2012). On the other hand, a study showed that overfeeding for eight weeks (+760 kcal/-day) increases LPS endotoxemia in healthy non-obese individuals, but blood IL-6 levels increase only in a few individuals, possibly

due to LPS-binding proteins or other mechanisms which may protect against systemic inflammation (Laugerette et al., 2014).

Mice fed a HFD show reduced expression of zonula occludens-1, a tight-junction protein that maintains intestinal integrity (Cani et al., 2008), suggesting that bacterial LPS may cross the gut barrier via the paracellular pathway. This elevated intestinal permeability observed in animal models of diet-induced obesity has been called "leaky gut" (Cani et al., 2008). In contrast, other *in vitro* studies showed that LPS can translocate in a transcellular manner from the apical to the basal side of intestinal epithelial cells cultured in monolayers (Beatty et al., 1999). Using an animal model and cultured intestinal cells, Ghoshal and co-workers reported that LPS is internalized by gut cells and transported into the circulation via chylomicrons, suggesting that the endotoxin may translocate through the transcellular pathway (Ghoshal et al., 2009). The scavenger receptor family of receptors, which were first identified for their ability to bind and internalize lipoproteins and lipids (Thuahnai et al., 2001), represents a candidate to mediate translocation of LPS via the transcellular pathway. The scavenger receptor B1 (SR-BI) mediates LPS binding and internalization by macrophages (Bocharov et al., 2004). This receptor is also expressed on the apical membrane of intestinal epithelial cells and mediates cholesterol and triglyceride absorption (Levy et al., 2004), but its possible role in LPS translocation remains to be investigated.

3. Inflammation and depression

Mood disorders are usually classified as depressed or elevated moods (mania), which may occur alone or together, as in bipolar disorder (Angst et al., 2015). Mood disorders such as depression and bipolar disorder are often accompanied by chronic anxiety and stress. While the cause of mood disorders is multifactorial, alterations in specific regions of the brain have been detected in some individuals, including the prefrontal cortex (PFC), amygdala (AMG), hypothalamus (HYP) and hippocampus (HPC) (Furtado and Katzman, 2015; Snyder, 2013). Extensive research has shown that monoaminergic transmission involving serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE) and dopamine (DA) exerts a large role in mood regulation. Deficiencies in some of these neurochemicals have been detected in most MDD patients (Ban, 2001).

Several lines of evidence indicate that inflammation is also involved in the development of MDD. More than three decades ago, a seminal study revealed that cancer patients treated with the cytokine interferon-alpha (IFN-α) show behavioral changes and mild-to-moderate cognitive, affective and personality abnormalities (Adams et al., 1984). Pro-inflammatory cytokines released during infection can be transported across the blood-brain barrier (BBB) and reach the brain where they affect mood and behavior in a manner similar to depression (Dantzer et al., 2008)—a condition referred to as sickness behavior which often includes fever, lethargy, anxiety, sleepiness and loss of appetite. Pro-inflammatory cytokines may also disrupt the BBB, a phenomenon observed in various mood disorders (Almutairi et al., 2016). Similarly, pro-inflammatory molecules like LPS may affect the functions of the BBB due to the presence of TLR4 receptors on the surface of brain endothelial cells (Banks, 2015).

Both neuronal and non-neuronal brain cells express receptors for pro-inflammatory mediators, and produce cytokines constitutively or in response to inflammatory stimuli (Vezzani and Viviani, 2015). Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis induced by pro-inflammatory cytokines is often observed in clinical depression (Dantzer et al., 2008). Numerous studies have demonstrated that cytokines such as IL-1β, IL-6, TNF-α and IFN-α can activate the HPA axis and may induce symptoms of depression (Rosenblat et al., 2014).

Cytokines can also affect neurotransmitter metabolism in the brain. Tryptophan is an essential amino acid actively transported into the brain for 5-HT synthesis. Treatment with IL-2 or IFN-α reduces tryptophan plasma levels and is associated with depression symptoms in cancer patients undergoing cytokine therapy (Capuron et al., 2002). This reduction could be due to activation of two major enzymes that metabolize tryptophan, i.e., tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). Accordingly, IDO activation has been observed in mice treated intraperitoneally with LPS, which increases IFN-γ and TNF-α levels and induces depression symptoms (O'Connor et al., 2009). In addition, IL-1β and TNF-α stimulate 5-HT uptake by neuronal cells (Zhu et al., 2006), while IFN-α decreases the expression of 5-HT receptor 1A (Cai et al., 2005).

Systemic inflammation may induce accumulation of peripheral monocytes into the brain, a process implicated in the development of mood disorders (Wohleb et al., 2015). In mice, chronic psychological stress stimulates the production of MCP-1 in HYP neurons, and migration of monocytes to the brain is associated with anxiety and depressive behavior (Ataka et al., 2013). Wohleb and colleagues reported that trafficking of myeloid cells into the brain in response to stress coincides with activation of resident microglia, production of pro-inflammatory cytokines, and appearance of anxiety and depression-like behavior (Wohleb et al., 2014). Accordingly, elevated numbers of macrophages have been observed in various brain areas, including the PFC, AMG, HYP and HPC.

4. HFD, brain inflammation and depression

Long-term HFD feeding is known to produce systemic, chronic inflammation in animals and humans (Buckman et al., 2014; Gregor and Hotamisligil, 2011). Rats fed a HFD for 16 weeks show an increased expression of IL-1β, IL-6 and TNF-α in the HYP compared with animals fed a normal diet (De Souza et al., 2005). Notably, HFD feeding reduces expression of tight junction proteins in the choroid plexus and BBB in rats, and may affect brain function by disrupting BBB integrity (Kanoski et al., 2010). Brain microglia isolated from HFD-fed mice release more TNF-α than the microglia of control mice, suggesting a specific response of brain myeloid cells to HFD (Puig et al., 2012). Buckman and colleagues demonstrated a significant increase in the ratio of $CD11b^{+}CD45^{high}$ cells to $CD11b^{+}CD45^{low}$ cells in the brain of HFD-fed mice compared with lean mice, indicating increased migration of circulating monocytes (Buckman et al., 2014).

The induction of inflammation in the brain in response to excess lipid consumption is faster than previously thought. After one day of HFD feeding, mice and rats show increased hypothalamic IL-1β and IL-6 levels, even before substantial weight gain can be detected (Thaler et al., 2012). Other studies suggest that overfeeding with glucose or lipids induces hypothalamic inflammation as early as a few hours after feeding (Cai and Liu, 2012).

Zemdegs et al. reported that HFD-fed mice show impaired serotonergic functions that lead to anxiety-like behavior (Zemdegs et al., 2016). In addition, treatment with an inhibitor of the P2X7 receptor reverses HFD-induced anxiety in rats (Dutheil et al., 2016). P2X7 is an ATP receptor expressed by almost all tissues in the body and known to activate the inflammasome and NF-κB signaling pathways (Burnstock and Boeynaems, 2014). Brain-derived neurotrophic factor (BDNF) has also been widely associated with depression. Decreased levels of BDNF in the HYP, PFC or serum correlate with depression in animals and humans (Bocchio-Chiavetto et al., 2010). In rodents, HFD feeding reduces hippocampal BDNF levels (Molteni et al., 2004; Pistell et al., 2010). On the other hand, elevated BDNF levels in the nucleus accumbens and ventral tegmental area produce depression-like symptoms (Sharma and

Fulton, 2013). An increased level of BDNF and a reduced level of tyrosine hydroxylase—the rate-limiting enzyme of DA synthesis—have been detected in the nucleus accumbens and ventral tegmental area of HFD-fed mice, which show signs of anxiety and depression-like behavior (Sharma and Fulton, 2013).

Environmental stressors to which individuals are exposed in daily life can also trigger depression. Aslani and co-workers used a chronic mild stress (CMS) protocol to assess the effect of HFD on the response to stress in a rat model. Rats treated with both HFD and CMS showed more aberrant behavior than HFD-fed mice, indicating that both CMS and HFD may trigger the development of depression-like behavior in animals (Aslani et al., 2015). Another study showed that rats treated with HFD and CMS show higher anxiety and depression-like behavior, compared with controls (Yang et al., 2016).

An experiment conducted with 34 healthy volunteers who received intravenous LPS injection showed increased anxiety and negative mood, along with higher levels of cortisol, NE and pro-inflammatory cytokines in the blood (Grigoleit et al., 2011). These effects appeared 3 h after LPS administration and were dose-dependent, supporting the hypothesis that LPS derived from the gut microbiota, perhaps via a leaky gut phenomenon, may mediate the effects of HFD on behavior and brain function.

5. A role for the gut microbiota in obesity-induced depression

The human gastrointestinal tract is inhabited by trillions of microorganisms (Lin et al., 2014). More than 1500 species of bacteria have been identified so far in the human gut, with *Bacteroidetes* and *Firmicutes* representing the two predominant phylotypes (Gill et al., 2006). Different studies indicate consistently that the composition of the gut microbiota is different in lean and obese animals (Ley et al., 2005). HFD affects gut microbiota composition, increasing the *Firmicutes*/*Bacteroidetes* ratio (Lin et al., 2014). The level of *Bifidobacterium*, *Lactobacillus* and *Akkermansia muciniphila* is also reduced in HFD-fed animals (Schneeberger et al., 2015).

The composition of the gut microbiota is a determining factor in the development of obesity. Transfer of the gut microbiota of obese mice to germ-free (GF) mice, which are raised in sterile conditions and therefore lack a gut microbiota, causes the recipients to gain more weight compared with animals that receive the gut microbiota of lean mice (Turnbaugh et al., 2006). The obesity phenotype is also transmissible via transfer of the fecal microbiota from obese humans to GF-mice fed with a normal diet (Ridaura et al., 2013).

To determine whether the gut microbiota of obese mice may affect host behavior in the absence of obesity, mice were maintained on a normal diet but subjected to microbiota depletion using antibiotic treatment, followed by adoptive transfer of cecal plus colonic contents collected from donor mice fed either a HFD or control diet (Bruce-Keller et al., 2015). Mice that had received the microbiota of HFD donors showed increased anxiety-like behavior when compared with HFD-fed mice that received the microbiota of mice fed a normal diet. Although the body weight, blood glucose and lipid levels of both groups were similar, the mice treated with the microbiota of HFD-fed animals showed increased intestinal inflammation and permeability, as well as increased levels of plasma endotoxins. In addition, expression of TLR2 and TLR4 also increased in the PFC of mice that received the microbiota of HFD mice (Bruce-Keller et al., 2015).

Thus, a microbiota–gut–brain axis is increasingly viewed as a bidirectional neurohumoral communication system that integrates brain and gastrointestinal function. The gut microbiota also produces metabolites that affect host behavior. Short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate, which are produced by bacterial fermentation of dietary fiber, modulate the immune response of the host, notably by reducing the secretion of pro-inflammatory cytokines and inducing T_{reg} cell development and IL-10 secretion (Sun et al., 2017). On the other hand, SCFAs may also induce migration of neutrophils and activate NF-κB in epithelial cells (Sun et al., 2017). A fraction of circulating SCFAs may also cross into the central nervous system and affect brain function, but it remains unclear to what extent these molecules contribute to depression (Sarkar et al., 2016). Long-term consumption of a Western-style HFD, which is low in fiber, may possibly result in reduced production of SCFAs by the gut microbiota and lead to systemic inflammation, including in the brain. In addition to SCFAs, some bacteria also have the capacity to generate neurotransmitters and neuromodulators, including gamma-aminobutyric acid (GABA), NE, 5-HT, DA and acetylcholine (Lyte, 2011). These neuroactive compounds may regulate brain function and influence host behavior (Lyte, 2011). However, the role played by these metabolites on mood and behavior remains mostly unexplored.

The contribution of the gut microbiota to diet-induced neuroinflammation and depression has been examined using various animal models, including GF animals. An early study performed in 2004 showed that GF mice exhibit increased physiological reaction to stress (Sudo et al., 2004). In 2011, two research teams showed that GF mice exhibit lower levels of anxiety compared with specific pathogen-free (SPF) mice (Diaz Heijtz et al., 2011; Neufeld et al., 2011). These conflicting results have been attributed to differences in animal strains, sex, acclimatization or euthanasia protocols (Luczynski et al., 2016). Notably, anxiety-like behavior can be induced in low-anxiety GF NIH Swiss mice by transfer of the gut microbiota from high-anxiety Balb/C mice. Reciprocally, transfer of gut microbiota from low-anxiety NIH Swiss mice into high-anxiety Balb/C mice attenuates the anxious phenotype of the recipient mice (Luczynski et al., 2016). Similarly, colonization with pathogenic bacteria such as *Campylobacter jejuni* increases anxiety-like behavior in recipient mice (Goehler et al., 2008).

Asano and co-workers examined the role of the gut microbiota in bio-transformation of luminal catecholamines using a GF mouse model (Asano et al., 2012). In GF mice, >90% of DA and 40–50% of NE is found to be present as a biologically inactive, conjugated form. In contrast, 90% of DA and NE is present in an active, free form in SPF mice. Transfer of fecal microbiota from SPF to GF mice results in a drastic elevation of free DA and NE, suggesting that the gut microbiota plays a critical role in generating free catecholamines in the gut lumen (Asano et al., 2012). Moreover, GF mice show elevated plasma tryptophan and hippocampal 5-HT concentrations compared with SPF animals (Clarke et al., 2013). These studies indicate that the gut microbiota produce several neuroactive molecules that may affect brain physiology.

MDD patients exhibit significant alterations in the gut microbiota. Analysis of fecal samples from MDD patients revealed that the relative proportion of *Bacteriodetes* is increased compared with the control group, whereas *Firmicutes* is reduced (Jiang et al., 2015; Zheng et al., 2016). Another study showed that depressed patients have higher levels of blood antibodies that bind to LPS from commensal gut bacteria (Maes et al., 2012), providing further support to the concept that leaky gut may be involved in chronic depression. In addition, fecal transplantation from patients with MDD to GF mice increases depression and anxiety-like behavior in recipients (Zheng et al., 2016).

Irritable bowel syndrome (IBS) is an intestinal disorder characterized by chronic abdominal pain and altered bowel habits, and by anxiety and depressive behavior (Holtmann et al., 2016). Notably, the *Firmicutes/Bacteriodetes* ratio of IBS patients is elevated compared with healthy controls, a condition also observed in obese and depressed patients (Jeffery et al., 2012). Furthermore, De Palma and co-workers reported that GF mice that received fecal

microbiota from IBS patients displaying anxiety also developed anxiety-like behavior (De Palma et al., 2017).

6. Prebiotics and probiotics

Probiotics are living microorganisms that exert beneficial effects on the host (Delzenne et al., 2011). A large body of animal and clinical studies indicate that probiotics reduce body weight gain and inflammation in HFD-induced obesity (Kobyliak et al., 2016). Most of these studies were conducted using bacteria belonging to the genus *Lactobacillus* and *Bifidobacterium*.

In 2005, Logan and Katzman proposed the use of probiotics as adjunct therapy in the treatment of depression (Logan and Katzman, 2005). Since then, many studies in animals and humans support the possibility that probiotics could act as psychotropic agents, for which the term "psychobiotics" was recently introduced (Dinan et al., 2013). The probiotics tested for anti-depressive effects are often the same species that possess anti-obesity properties (Dinan et al., 2013), suggesting that modulation of the microbiota composition may be beneficial for both obesity and depression. Accordingly, many studies indicate that probiotics can reduce inflammation (Sarkar et al., 2016).

The ability of probiotics to alter behavior by modulating the gut microbiota was demonstrated in a study using the lactic acid-producing bacterium *Lactobacillus helveticus*. This probiotic not only restores the *Firmicutes*/*Bacteriodetes* ratio in HFD-fed mice but also reduces HFD-induced anxiety-like behavior (Ohland et al., 2013). In two recent studies, Abildgaard and colleagues showed the effects of a probiotic cocktail containing eight different species of *Bifidobacterium* and *Lactobacillus* on depressive-like behavior induced by HFD in rats (Abildgaard et al., 2017a,b). The first study showed that the anti-depressant effects of the probiotic cocktail is accompanied by reduced serum levels of IL-6 and TNF-α; however, no decrease in serum LPS is observed in HFD-fed rats treated with the probiotics (Abildgaard et al., 2017b). In the second study, the authors used rats from the Flinders sensitive line (FSL), a genetic animal model of depression which presents increased levels of depressive-like behavior. In this model, the probiotic cocktail reduces the levels of $CD4^+$ relative to $CD8^+$ T cells in the brain, and also reduces HFD-induced depressive behavior (Abildgaard et al., 2017a). Notably, recent clinical studies indicate that probiotics also reduce depression symptoms in humans (Huang et al., 2016; Wallace and Milev, 2017). On the other hand, optimal bacterial strains, dosing and duration of treatment remain to be determined.

Prebiotics are food ingredients that produce beneficial effects on the gut microbiota and the host even though they are not digested by human enzymes of the gastrointestinal tract (Delzenne et al., 2011). Fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) are water-soluble fibers, which are fermented by the gut microbiota into SCFAs (De Vadder et al., 2014). Administration of FOS to HFD-fed mice increases the levels of propionate in plasma and reduces the *Firmicutes*/*Bacteroidetes* ratio in the gut microbiota (De Vadder et al., 2014). Administration of bimuno-GOS (a GOS preparation treated with galactosidase enzyme isolated from *Bifidobacterium bifidum*) to healthy volunteers reduces anxiety-like behavior and decreases salivary cortisol levels, suggesting that prebiotics may modulate HPA-associated activity (Schmidt et al., 2015). Bimuno-GOS also increases *Bifidobacterium* and *Lactobacillus* in the gut microbiota (Grimaldi et al., 2016), suggesting that these bacteria may be involved in the phenotype observed. Similarly, rats treated with FOS fibers

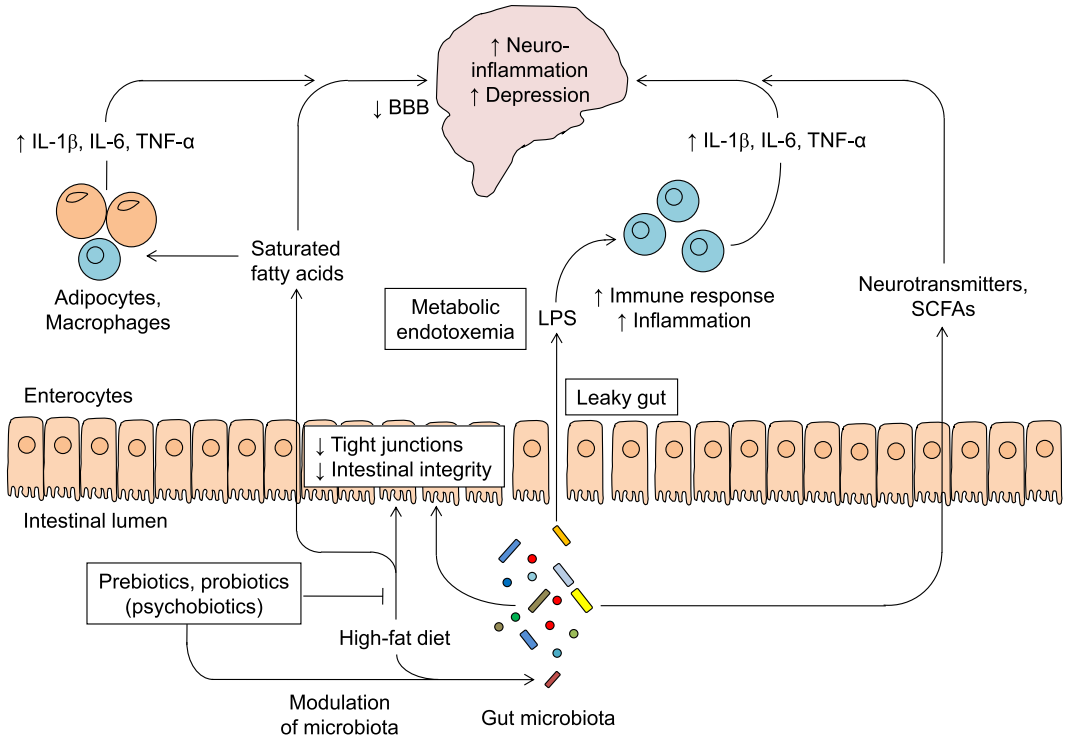

Fig. 1. Effects of a high-fat diet on the gut microbiota, inflammation and depression. A high-fat diet reduces expression of tight junction proteins in the intestinal epithelium, thereby disrupting the intestinal integrity and producing a leaky gut. Bacterial molecules such as lipopolysaccharide (LPS) may leak into the blood and produce metabolic endotoxemia, leading to activation of immune cells and secretion of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α). Excess saturated fatty acids induce secretion of pro-inflammatory cytokines by adipocytes and macrophages, and affect the integrity of the blood-brain barrier (BBB), allowing pro-inflammatory cytokines and immune cells to reach the brain. The gut microbiota may ferment dietary fiber to produce short-chain fatty acids (SCFAs). These phenomena produce neuro-inflammation and may affect mood and behavior. Psychobiotics consisting of prebiotics and probiotics reduce inflammation and may produce beneficial effects in depressed individuals.

show higher HPC levels of BDNF and an increased amount of *Bifidobacterium* in feces compared with controls, suggesting that prebiotics may modulate the gut microbiota and affect brain function (Savignac et al., 2013). Recently, Burokas and co-workers showed that treatment with FOS, GOS or both for three weeks alters the gut microbiota of mice and reduces anxiety and depression-like behavior compared with controls (Burokas et al., 2017). These researchers also reported an increase of *Bacteroides*, *Parabacteroides* and *Akkermansia* in prebiotics-treated mice; previous studies showed that these bacteria are negatively correlated with obesity (Chang et al., 2015; Lin et al., 2014; Schneeberger et al., 2015).

Our laboratory showed that high-molecular weight polysaccharides isolated from *Ganoderma lucidum*—a mushroom used in traditional Chinese medicine—reduces body weight, inflammation, endotoxemia and insulin resistance in HFD-fed mice by modulating the gut microbiota (Chang et al., 2015). Similarly, a water extract of the medicinal mushroom *Antrodia cinnamomea* produces anti-obesogenic, antidiabetic and anti-inflammatory effects by modulating the gut microbiota in HFD-fed mice (Chang et al., 2017). Given that treatment with such polysaccharides or mushroom extracts also reduce the *Firmicutes*/*Bacteroidetes* ratio and increase the levels of bacteria associated with anti-inflammatory effects in the gut microbiota (e.g., *Bacteroides*, *Parabacteroides*), it is tempting to speculate that these polysaccharides and mushroom extracts may also produce beneficial effects on HFD-induced depression-like behavior, a possibility that remains to be examined. In addition, several plants and mushrooms used in traditional Chinese medicine and as nutraceuticals may alter the gut microbiota composition and produce anti-obesity and anti-inflammatory effects in animals and humans (Martel et al., 2017). These plants and mushrooms, which produce relatively few or no side effects (Marteau and Seksik, 2004), represent potential candidates to treat HFD-induced inflammation and depression.

7. Perspectives and concluding remarks

The studies presented here suggest that reducing obesity-induced neuro-inflammation may lead to beneficial effects on depression (see Fig. 1 for a summary of the pathways linking HFD, the gut microbiota, neuro-inflammation and depression). Modulation of the gut microbiota may thus represent a novel strategy for treating neuro-inflammation and depression. Probiotics, prebiotics, nutraceuticals and other plant and mushroom extracts may be used for the prevention and treatment of obesity and depression. Further studies are needed to optimize the use of these substances in humans.

Conflict of interest statement

YFK is President of Chang Gung Biotechnology Corporation. JDY is Chairman of the Board of Chang Gung Biotechnology Corporation. The authors (except for JS) have applied for patents related to the use of medicinal mushrooms and probiotics to treat human disease.

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