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REVIEW ARTICLE

Gut-brain Axis: Role of Lipids in the Regulation of Inflammation, Pain and CNS Diseases

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Abstract: The human gut is a composite anaerobic environment with a large, diverse and dynamic enteric microbiota, represented by more than 100 trillion microorganisms, including at least 1000 distinct species. The discovery that a different microbial composition can influence behavior and cognition, and in turn the nervous system can indirectly influence enteric microbiota composition, has significantly contributed to establish the well-accepted concept of gut-brain axis. This hypothesis is supported by several evidence showing mutual mechanisms, which involve the vague nerve, the immune system, the hypothalamic-pituitary-adrenal (HPA) axis modulation and the bacteria-derived metabolites. Many studies have focused on delineating a role for this axis in health and disease, ranging from stress-related disorders such as depression, anxiety and irritable bowel syndrome (IBS) to neurodevelopmental disorders, such as autism, and to neurodegenerative diseases, such as Parkinson Disease, Alzheimer's Disease *etc.* Based on this background, and considering the relevance of alteration of the symbiotic state between host and microbiota, this review focuses on the role and the involvement of bioactive lipids, such as the N-acylethanolamine (NAE) family whose main members are N-arachidonoylethanolamine (AEA), palmitoylethanolamide (PEA) and oleoilethanolamide (OEA), and short chain fatty acids (SCFAs), such as butyrate, belonging to a large group of bioactive lipids able to modulate peripheral and central pathologic processes. Their effective role has been studied in inflammation, acute and chronic pain, obesity and central nervous system diseases. A possible correlation has been shown between these lipids and gut microbiota through different mechanisms. Indeed, systemic administration of specific bacteria can reduce abdominal pain through the involvement of cannabinoid receptor 1 in the rat; on the other hand, PEA reduces inflammation markers in a murine model of inflammatory bowel disease (IBD), and butyrate, producted by gut microbiota, is effective in reducing inflammation and pain in irritable bowel syndrome and IBD animal models. In this review, we underline the relationship among inflammation, pain, microbiota and the different lipids, focusing on a possible involvement of NAEs and SCFAs in the gut-brain axis and their role in the central nervous system diseases.

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1. INTRODUCTION

The human body, primarily the gastrointestinal (GI) tract, is widely colonized by several species of bacteria (about 10^{14} bacterialcells and 500-1,000 species), collectively termed as the "human microbiota". Their whole genome is called "human microbiome" [1, 2]. Before birth, the human fetal gut is sterile, but few hours after delivery, all the external stimuli, such as environment, diet, maternal transfer or even the early introduction of antibiotics, start to influence the coloni-

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zation process leading, in each different infant, to an adult-like gut microbiota profile, that will reach a certain stability in composition and number at 1 year of age [3]. Given the high variability of bacterial communities among individuals, lately subjects have been classified into three distinct clusters -enterotypes- based on the prevalence of key bacterial genera in their gut microbiota composition (i.e. Bacteroides, Prevotella or Ruminococcus genes). However, different sampling analysis and methods influence the detection of enterotypes, with divergent interpretation of results [4].

It is worth noting that the relationship established by commensal bacteria with the host seems to be more mutually symbiotic rather than a parasitism with human host [5]. In fact, the gut microbiota contributes to the development of immune system, behavior and cognition [6] and, remarkably, concur to maintain normal homeostasis through three major functions: (i) it helps and protects the host against pathogen colonization by nutrient competition and production of active antimicrobial agents, such as hydrogen peroxide, acidophylin, acidolin, lactallin, *etc.* (ii) It stimulates the innate immunity and limits production of toxins and penetration of pathogenic microorganism into gut tissues adjusting the sensitization and/or the tolerance (iii) It facilitates nutrient absorption by metabolizing indigestible dietary fibers, or tri/tetrasaccharides, to monosaccharides producing B-group vitamins.

Microbiota and central nervous system (CNS) comunication, known as microbiota-gut-brain axis, is able to influence neurotransmission and behavior and occurs through different pathways [7, 8]. In particular, visceral afferent activity is known to modulate behavioral and cognitive process through brainstem nuclei and cholinergic and noradrenergic projections, to cortex/cognitive process [9]. This relationship is strongly strenghtened by the high comorbidity between GI alterations and psychiatric disorders. Interestingly, imbalance of the gut microbiota (dysbiosis) can contribute, among others, to the pathogenesis of inflammatory bowel disorders (IBD) [10] and irritable bowel syndrome (IBS) [11], commonly described as gut-brain axis disorders. These pathologies are characterized by abdominal pain and/or discomfort associated with altered bowel habits. In more than one case, chronic inflammation or immune activation, in IBD and IBS, can contribute to predispose individuals to neurological and neurodegenerative diseases through the cytokines release into the bloodstream [12,13]. Specific changes in the inflammatory process, in pain threshold and in the intestinal innate immune system have been supposedly linked to be under lipid regulation and host metabolism. A large body of evidence underlines the correlation between lipids and microbiota [14] identyfing endocannabionids, N-acylethanolamines (NAEs) and butyrate among the main compounds having a key role in several pathologies associated to gut inflammation, pain and central disorders. As reported by Rousseaux et coworkers [15], systemic administration of *Lactobacillus acidophilus* strain reduces abdominal pain through the involvement of cannabinoid receptor (CB); moreover, it has been reported that an indirect cannabinomimetic acylethanolamide, palmitoylethanolomide (PEA), reduces inflammation in a mouse model of IBD [16]. On the other side, butyrate, a short chain fatty acid (SCFA) produced in the colon and nowadays considered an active postbiotic, has proved to be highly effective in reducing pain discomfort in IBS and IBD, controlling inflammation and peripheral nerves sensitization [17].

The multiplicity of different lipids involved in pathological status, as well as in spontaneous recovery or therapeutic approach, underlines the role of these molecules in cellular trafficking and signalling, in structure and in energy storage, thus indicating their possible role as risk markers in distinct cellular physiopathological functions. Here we analyze how the gut microbiota and lipidic transmitters are able to modulate the inflammatory diseases of the intestinal tract which represent the “primo movens” to CNS diseases (Fig. **1**).

2. GUT-BRAIN AXIS

Many evidences have shown that gut microbiota influences human brain development and its function. The exchange of regulatory signals through an integrative and bidirectional communication between the gastrointestinal tract and the CNS represents the gut-brain axis. The complexity of these interactions suggested, for the first time in the 1880s, the term gut-brain axis by William James andCarl Lange, refined later by Walter Cannon [18]. Specifically, this network includes the CNS, both brain and spinal cords, the autonomic nervous system, the enteric nervous system (ENS) and the HPA. This crosstalk has revealed a complex communication system that not only ensures the proper maintenance of GI homeostasis, but also is likely to have multiple effects influencing brain development, mood and cognitive functions. Indeed, emerging data supports the role of microbiota in anxiety and depressive-like behaviors [19, 20] and, more recently, in autism too [21].

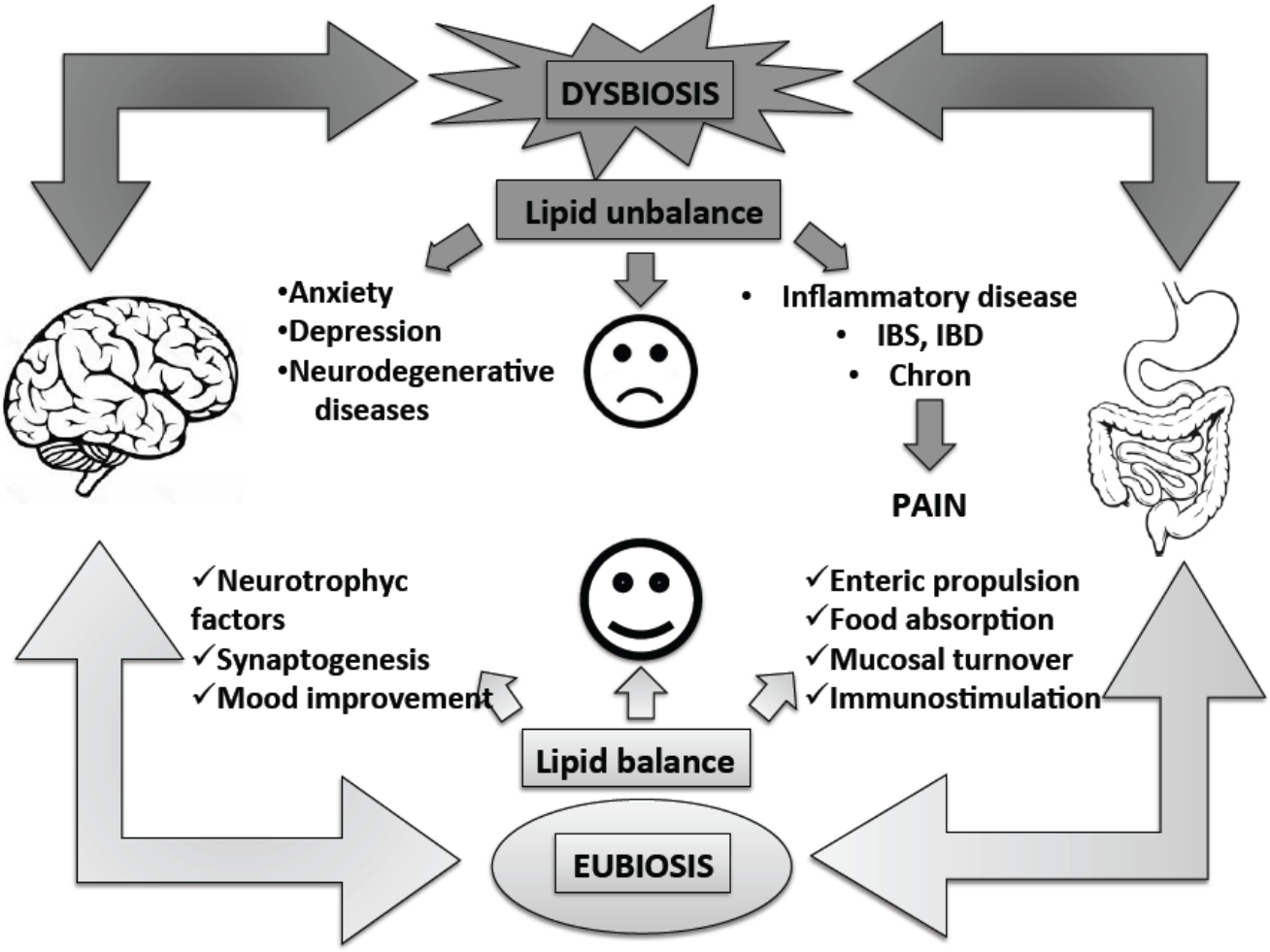

Fig. (1).

Furthermore, the direct or indirect release of signaling molecules, such as serotonin, norepinephrine and dynorphins, cytokines and antimicrobial peptides into the gut lumen, underlines that the CNS has an immediate influence on gut microbiota [22]. Indeed, disregulation of serotonin in the human gut has been implicated in anassorted group of GI disorders, such as IBD and IBS. Moreover, norepinephrine and dynorphins are released into the gut lumen during perturbation of GI homeostasis [23]. Recently, it has been suggested that there is a direct interaction between gut microbiota and ENS. Kunze *et al.* [24] observed that *Lactobacillus reuteri* enhanced the excitability of colonic neurons in naive rats and, more recently, it has been found that both *Lactobacillus rhamnosus* and *Bacteroides fragilis* are able to activate intestinal afferent neurons [25].

In the recent years, most studies using germ-free (GF) and probiotic- or antibiotic-treated animals indicate that enteric microbiota strongly impacts gut-brain axis. Accordingly, in the absence of gut bacteria, as happens in GF rodents, the HPA axis abnormally develops, leading to altered stress response, reducing hippocampus levels of brain derived neurotrophic factor (BDNF)-mRNA and protein [26]. In addition, GF mice also show immune defects at both structural and cellular levels [27, 28]. During early stages of life, the colonization of the body by different microorganisms offers abundance of antigens, which are critical for a healthy maturation of the immune system [29,30].

As above mentioned, vagal activation is necessary for a series of physiological effects and, with its approximately 80% afferent fibers, it relays signals from peripheral organs -including GI tract- to the CNS, modulating with a still unclear mechanism cognition and behavior. Although vagotomy abolished some of these effects, as reported in the studies on mice fed with probiotics or pathogens [31-33], others revealed that behavior modification are independent from vagus

pathway [34]. Therefore, vagous nerve seems not to be the only mediator of microbiota-gut-brain interaction. An example of vagal-independent communication is given by the immune signaling, which plays a role in both normal brain function and neurodegenerative diseases [35]. The immune activation in the gut elicited by local microbes can cause an alteration of barrier function, activation of ENS and changes in sensory-motor function [36]. Several evidences demonstrated that probiotics can improve intestinal barrier function and decrease the immune cell activation both locally and systemically [37, 38]. Moreover, they can induce immune modulatory effects in gut-brain axis disorders characterized by "leaky gut." This hypothesis, is supported by the evidence that chronic stress is able to disrupt the continuity of intestinal barrier, making it "leaky" and increasing the permeability to ions and bacterial peptides [39], triggering the immune response. Other studies have shown that stress can influence microbial colonization, affecting pain pathways. In addition, treatment with antibiotics in early life is associated with visceral hypersensitivity [40]. Actually, mice exposed to a social disruption stressor showed an altered gut microbiota, as well as increased circulating levels of cytokines [41]. In particular, stress-induced reduction of *Lactobacillus reuteri*, a specific immunomodulatory species of bacteria, leads to an increased proinflammatory gene expression and monocyte differentiation [42, 43]. This results in an altered gut microbiota, which in turn can enhance the ability of enteric pathogens to colonize the intestine [44]. It has also been shown that stress is able to modulate the levels of intestinal secretory IgA, influencing intestinal homeostasis, inflammatory response and dysbiosis [45]. Furthermore, gut bacteria can stimulate circulating cytokines, which in turn can influence the brain function [46, 47]. This condition occurs for example, in the classic sickness behavior where pro-inflammatory cytokines, acting on the CNS, cause low motivation to eat, exaggerated pain response and slowed psychomotor functions [48].

3. ENDOCANNABINOIDS, ACYLETHANOLAMIDES AND SHORT CHAIN FATTY ACIDS (SCFAS)

N-arachidonoylethanolamine (anandamide or AEA), a member of a large group of bioactive lipids named N-acylethanolamine family, was the first endogenous agonist discovered for CB [49]. Another class of lipids active on CB are the fatty acid glycerol esters to which belongs the second ligand of CB, 2-arachidonoylglycerol (2-AG), identified for the first time in the intestine [50]. During the last decade, it has been pointed out that the physiological and pharmacological activities of endocannabinoids are the result of the modulation of several cellular systems. This is not only restricted on CB receptors, called cannabinoid receptor CB_1 and CB_2. They are also able to interact with peroxisome proliferator-activated receptors (PPAR)-types α and γ, G-protein-coupled receptor (GPR)55 [51], vanilloid receptor 1 [52], and through the modulation of calcium and potassium channels. CB receptors are the members of G-protein-coupled membrane receptors family: in particular, CB_1 is mostly abundant in different brain areas, as well as in peripheral nerve terminals, while CB_2 is mainly expressed in lymphoid tissues, myeloid cells and spinal cord, modulating immune response and pain [53]. The endocannabinoid system also contributes by multiple mechanisms to the regulation of both gut and adipose tissue functions. In particular, it modulates gastric emptying and motility [54], food intake, satiety and postprandial glycaemia [55, 56]. Moreover, it also has a major role in facilitating adipogenesis and adipose tissue expansion and in regulating inflammation [57, 58]. The modulation of visceral pain perception by bacteria through the endocannabinoid system was shown in patients with irritable bowel syndrome, who commonly have abdominal pain. Indeed, oral administration of specific *Lactobacillus acidophilus* strain modulates the expression of CB receptors, as well as μ-opioid receptor in intestinal epithelial cells, enhancing the analgesic pathways underlying these receptors [15]. Obesity is usually associated with changes in the composition of the gut microbiota, which in turn induce gut barrier dysfunction and increase gut permeability [59]. This leads to the increased levels of lipopolysaccharide serum (LPS). Several studies have shown that treatment with LPS influences the production of endocannabinoids by immune cells, suggesting a strong link between bacterial components and the endocannabinoid system [60, 61]. In addition, in obese mice, the gut microbiota modulates the endocannabinoid tone and adipose tissue, regulating key enzymes related to NAEs metabolism and activity as N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), CB_1 and fatty acid amide hydrolase (FAAH) expression, and AEA concentration [62]. The endocannabinoid system controls gut permeability and endotoxaemia in obesity and diabetes, through a CB_1-dependent mechanism. Specific CB antagonism decreases gut permeability, acting as 'gate keepers' [63]. Furthermore, it has been proven that specific deletion of NAPE-PLD in adipose tissue induces an obese phenotype in normal-diet-fed mice, characterized by glu-

cose intolerance, adipose tissue inflammation, altered lipid metabolism and affects gut microbiota composition. It has been demonstrated that chronic administration of a potent CB_1 agonist, HU-210, leads to severe metabolic disorders, such as glucose intolerance, muscle macrophage infiltration and lipid content [64].

However, the effect of the endocannabinoid system on gut-barrier function might be due to other mechanisms during intestinal inflammation [65]. Everard and co-workers [66] showed that administration of *Akkermansia muciniphila* in high-fat diet fed mice increased the intestinal levels of 2-AG, improved gut-barrier function and decreased endotoxaemia. Although the mechanisms involved are unknown, the increased level of 2-AG by a selective inhibitor of monoacylglycerol lipase can protect mice from colitis and reduce endotoxaemia and systemic inflammation [67]. Moreover, the deletion of the intestinal epithelial Myeloid differentiation primary response gene (MYD)88, which is involved in the signaling of most Toll-like receptors, partially protects against obesity, diabetes, inflammation and disruption of the gut barrier, increasing the anti-inflammatory endocannabinoids (2-AG and AEA) [68].

In addition to these "sheer" endocannabionoids, other related NAEs, such as *N*-palmitoylethanolamine and *N*-oleoylethanolamine (OEA), have also shown to modulate gut microbiota. Specifically, PEA has a prominent role in acute and chronic inflammation, as well as in pain [69]. Moreover, it has been suggested that these compounds have a role in the regulation of energy homeostasis, through PPAR-α mediated mechanism. Reduction of PEA levels was found in genetic obese mice, possibly linked to increased N-acylethanolamine acid amidase (NAAA) activity, the enzyme responsible for the metabolism of PEA that regulates its levels in the colon. In two murine models of IBD, NAAA inhibition increases PEA levels and reduces inflammation in colon [70, 71]. Apart from the well known role of PEA on behavior, inflammation and pain [72], it has been demonstrated that peripheral administration of PEA in ovariectomized obese rats increases the expression of leptin receptor in the hypothalamus and this effect is related to the reversal of leptin resistance and the suppression of food intake and fat accumulation [73]. OEA is considered a fat sensor, as it mediates the response of the gut to the consumption of high-fat meals [74], and regulates thermogenic processes through PPAR-α [75]. PPARs have been shown to be regulated by a number of bacterial pathogens, including *Helicobacter pylori* and *Mycobacterium tuberculosis* [76, 77], greatly impacting disease severity.The role of PPARs in gut inflammation has been recognized. Indeed, PPARγ agonists are used to treat type-2 diabetes and are known to reduce colitis in mice [78]. Moreover, PPARγ heterozygous mice exhibit an increased susceptibility to experimentally induced colitis [79], indicating that PPARγ are involved in maintaining gut homeostasis. PPARs activation has been shown to improve the severity of inflammatory bowel disease in rodent DSS, trinitrobenzene sulphonic acid, and ischemic colitis model [80]. Finally, PPARγ is reduced in colonic epithelial cells from ulcerative colitis (UC) patients, suggesting PPARγ role in the gut [81].

Butyrate, a SCFA, can reduce, as PEA or OEA, inflammation and glucose tolerance too in a model of steatosis induced by high fat diet in rats [82]. SCFAs, the final products of fermentation of dietary fiber in the colon, are compounds with an aliphatic tail of less than six carbon atoms. Among different SCFAs, butyrate is known to modulate numerous processes, from the main energy source for colonocytes [83], to signal metabolite affecting epithelial cell proliferation, to apoptosis and differentiation [84]. All these intestinal effects are ascribed to butyrate [85], indicating its possible therapeutic indications in many GI disorders and in IBD, where butyrate reveals anti-inflammatory properties [86]. Based on all its characteristics, butyrate can be considered a post-biotic given that is a nonviable bacterial metabolic product obtained from microorganisms that have biologic activity in the host. The importance of butyrate supplementation in UC has been proven by the impaired butyrate metabolism in intestinal inflamed mucosa [87]. This deficiency results from the reduction of butyrate uptake by the inflamed mucosa due to down regulation of the monocarboxylate transporter (MCT)-1 expressed on the apical membrane of intestinal epithelium [88]. Luhers and coworkes [89] showed that the administration of butyrate to patients with UC suppressed mucosal inflammation and decreased NF-κB activation in lamina propria macrophages. Moreover, in IBS, supplemental therapy with butyrate can reduce the frequency of selected clinical symptoms, without a significant effect on the reduction symptoms severity [90]. The effects exerted by butyrate are multiple and involve several distinct mechanisms of action. It is an anti-inflammatory agent, primarily inhibiting NF-κB activation [91], moreover it has a well-known epigenetic mechanism through inhibition of histone deacetylase (HDAC) [92], and also acts as signal molecules on Free Fatty Acid Receptor 2 (FFAR2, GPR43) and FFAR3 (GPR41) [93]. Recently, it has been demon-

strated that the effect of butyrate is related to PPARs involved in the control of inflammatory enzymes expression and pain [94]. In fact repeated oral butyrate-based compound administrations increase pain threshold in mice both in acute and chronic pain models, and these effects are PPARs mediated. In agreement with these data, many studies have shown that the anti-inflammatory activity of butyrate could be related to the up-regulation of PPARγ [95].

4. DYSBIOSIS (IBD AND IBS) AND LIPIDS

The GI tract is the most complex organ of the human body. The intestinal mucosa, which is continuously exposed to a variety of commensal microbiota and food antigens, maintains intestinal homeostasis and integrates both acquired and innate immune systems. An alteration of this homeostasis can lead to abnormal immune response to the enteric microbiota, causing chronic inflammation. IBD are characterized by prolonged inflammation of all or part of the GI tract, which in turn led to a malfunction of GI organs along with abdominal pain, persistent diarrhea, cramping, weight loss, rectal bleeding, fatigue with consequent compromised quality of life [96, 97]. The two types of IBD are Crohn's Disease (CD) and UC. In details, CD affects the GI tract from mouth to anus and is characterized by abdominal pain, fever, weight loss and clinical signs of bowel obstruction or diarrhea [98]. Instead, UC damages solely colon, extending proximally through the entire colon and rectum [99]. In 2011, Di Sabatino and coworkers [100] showed that the content of the major endocannabinoid AEA is reduced in IBD inflamed mucosa as a consequence of both defective synthesis and increased degradation. In this study, the authors detected AEA, 2-AG, and PEA levels in gut mucosa of IBD patients, and they found that AEA levels, but not 2-AG and PEA ones, are significantly reduced in inflamed compared to uninflamed areas. Moreover, they found a higher expression of CB_1 but not CB_2. However, even today no clear causes have been found about IBD; pathology development and course may be affected by the complex interactions between genetic factors [101], breast feeding, diet, smoking, drugs *etc.* [102], and microbial factors [103], sustaining inflammation, changes of mucosal barrier, and defects in the immune system [104]. Intestinal inflammation in animal models related to the expression of genes to IBD susceptibility suggests that IBD may be caused by a dysregulated GI immune response towards microbiota.

It has been reported that some immune processes are modulated by the endocannabinoid system. Indeed, cannabinoids reduce the MHC class II expression on the surface of dendritic cells and inhibit peripheral T-cell activation in response to LPS and anti-CD3 antibodies [105]. Many *in vivo* studies on various animal models of IBD demonstrated that the administration of CB_1 and/or CB_2 agonists improved colitis [106]. Moreover, several evidences indicate that FAAH plays an important protective and restorative role in the early stages of inflammation [107]. As shown by Storr and coworkers [108] FAAH mRNA expression was altered following TNBS injection in mice. Thus, the inhibition of FAAH alleviates colitis symptoms by raising the levels of endogenous cannabinoids [109]. Furthermore, there are evidence supporting the role of PEA as an anti-inflammatory compound, capable of alleviate inflammation in murine models of IBD. In a matter of fact, PEA reduces the macroscopic parameters of murine colitis, namely the colon weight/length ratio and the weight of the cecal content [110]. Furthermore, PEA significantly reduces proinflammatory cytokine production and immune cell infiltration. Recently, it has been shown that NAAA inhibitors were able to prolong PEA half life, as a potential therapeutic strategy in the IBD [16].

Recent studies have suggested that diet has an important role in the etiology of IBD. In particular, population who eat several starch kinds (the main precursors of SCFA) has low incidence to develop GI ailments, such as IBD and IBS. Therapeutic use of butyrate has been suggested in the treatment of chronic IBD. Indeed, butyrate is an effective remedy to histological healing of experimental colitis induced in rats by trinitrobenzenesulphonic acid [111]. Moreover, UC exhibits an altered metabolism of SCFA in epithelial cells of the colon [112] leading to low intra-luminal concentrations of these fatty acids, contributing to mucosal damage [113]. In some studies, butyrate administered locally in patients with UC, has shown positive effects, accelerating the clinical, endoscopic and histological healing process, when administered along with anti-inflammatory drugs, such as mesalazine [114,115]. Finally, quantitative and qualitative changes in the composition of the enteric microbiota have been observed in the IBD, through a decrease in the diversity and an increase in the concentration of bacterial species [116, 117]. It was observed that in CD, the dysbiosis is characterized by the loss of intestinal bacteria from the *Firmicutes phylum*, including *Faecalibacterium prausnitzii*, which are the most important butyrate producing

bacterium in cluster IV of the *Clostridium leptum phylogenetic* group in the gut [118].

IBS is characterized by the presence of abdominal pain with one or a combination of the following symptoms: comorbid changes in stool appearance and altered frequency of stooling and/or relief of pain upon defecation [119]. Factors such as younger age, prolonged fever, anxiety, depression, and history of childhood physical and psychological abuse are often associated with the development of this pathology after acute infectious gastroenteritis [120]. Although IBS is a highly common functional bowel disorder of unknown origin and with an intricate pathophysiology, it is commonly described as a disorder of the brain-gut axis, including central, spinal cord, peripheral elements, including the ENS and the immune system [121, 122]. It was noticed that psychological stress is a predominant factor on GI symptoms and exacerbation, likely because of the significant psychiatric co-morbidities, including both anxiety and depression [123]. IBS symptoms have been previously linked with visceral hypersensitivity and aberrant serotonin (5-HT) signaling. Feng and coworker [124] showed a possible correlation between 5-HT and the endocannabinoid system, in particular duodenal biopsies from IBS patients exhibited increased 5-HT and decreased AEA levels, most likely related to abdominal pain severity. They demonstrated that the analgesic effect induced by acute intraduodenally injection of 5-HT involves vagal 5-HT3R-mediated duodenal AEA release and downstream CB_1 activation [21, 125]. Visceral pain is a common debilitating symptom of many disorders, such as GI (colic, colitis) but also urogenital (interstitial cystitis, endometriosis) and thoracic (non-cardiac chest pain, angina) ailments. Taken together it is clear that IBS has a complex etiology and thus a multifaceted pathophysiology. Moreover, low levels of NAEs in IBS patients may be involved in hyperalgesia and in abdominal pain, and cause alterations in the bowel motility, that could be improved by direct or indirect CB or PPARs agonists [126]. Indeed, in IBS patients, a decrease in PEA was observed in comparison to healthy subjects, and this reduction was associated with abdominal pain [127]. FAAH inhibitors have been suggested for their analgesic action in IBS patients, where visceral pain is one of the major symptoms [128, 129]. Since FAAH inhibitors act site-specifically in the GI tract, they could be active both after systemic and topical (enemas) administration.

Butyrate represents a potential new compound for IBS therapy. In fact, butyrate plays an important role due to inhibitation of the signal of proinflammatory cytokines, restoration of the microbial composition, and also reduction of visceral pain. Banasiewicz and coworkers [130] performed a double-blind, randomized, placebo-controlled study on patients with IBS, who received microcapsulated butyric acid or placebo as an adjunct to standard therapy. Four weeks later, the patients showed a significant decrease in the frequency of abdominal pain during defecation.

Recently, the role of sodium butyrate in pain behaviour and its derivative has been addressed, the N-(1-carbamoyl-2-phenyl-ethyl) butyramide (FBA), identifying different and converging genomic and non-genomic mechanisms of action, which cooperate in nociception control [94]. In this study, a significant effect of both butyrate-based compounds was shown on inflammatory visceral pain and on neuropathic pain.

5. GUT-BRAIN AXIS, CNS DISEASE AND LIPIDS

Gut microbiota imbalance is known to influence the CNS functions and viceversa emotional and physiological stress can influence gut microbiota through gut-brain axis.

Therefore, it is a key factor understanding how gut microbes could exert beneficial and therapeutic effect on neurocognitive behaviors. Lately, a large body of literature reports that several CNS disorders are related to gut dysbiosis, accordingly with gut-brain axis hypothesis.

5.1. Autism Spectrum Disorders

Autism spectrum disorder (ASD) is a range of neurodevelopmental disorders characterized by repetitive and stereotyped behaviours and dysfunction in communication and social interactions skills [131, 132].

In recent years, many studies indicate that active neuroinflammatory process in different brain regions is relatively common in children with an ASD. It has been revealed that they present GI problems and altered GI flora underlying the pathological role of gut microbiota in this disease [133]. Many children with ASD are also more likely to have IBS, so the effective reduction of GI symptoms, as diarrhea and bloating, is a positive result considering the severity of autism. In details, litterature show both a general gut microbiota and specific strains alteration in the ASD. The first study in 1988, exhibitted that *Clostridium tetani can* induce autism. However, during the recent years, several studies report numerous species under the Clostrid-

ium genus present in faecal samples of autistic children [134]. In addition, other phyla as Bacteroidetes and Firmicutes are implicated in autism [135]. Other human gut microbiome studies, based on cultures from stool samples, show that *Bifidobacterium, Prevotella, Sutterella, Lactobacillus, Ruminococcus genera and Alcaligenaceae* family are also linked with autism [136, 137].

Nonetheless, special diets or dietary supplementations may alter microbiota composition. Emerging data have indicated that polyunsaturated fatty acids (PUFA) levels in the plasma of children with ASD are significantly low, in particular docosahexaenoic acid (DHA) [138], and patients treated with dietary supplementations rich in omega-3 fatty acids and linoleic acid, substantially improve their behavioral symptoms [139]. Indeed, dietary omega-3 contributes to decrease inflammation and alter endocannabinoid system related gene expression, reducing AEA, 2-AG and all the acylethanolamides, with the exception for PEA [140]. These studies suggest beneficial effects in psychiatric illness and their link with endocannabinoids [141]. In particular, Schultz and co-workers [142] have published the first study relating endocannabinoid system and autism. Several studies describe that an abnormal endocannabinoid signaling might contribute to ASD symptoms and in particular, to normal social behavior.

Even though the direct activation of CB_1 receptors produces social deficit in rats [143], their suppression can impair social interaction in a context-dependent manner [144]. In addition, human studies have found that marijuana may enhance sociability [145] and a polymorphism in the CB_1 gene modulates social gaze [146].

In contrast, enhancing the endogenous level of AEA, through the inhibition of its deactivating enzyme, FAAH, or FAAH loss of function in mice increases social interactions in two distinct ASD-related models, BTBR T+tf/J (BTBR) and *fmr1*$^{-/-}$ mice [147]. Furthermore, substrates of FAAH as NAEs (AEA, OEA and PEA) are increased after sociability tests, suggesting a behavioral deficit due to reduced AEA tone in critical brain areas. Interestingly, the down-regulation of GPR55 and PPAR gene expression supports a role for these receptors in autism [148]. Moreover, rats subjected to the exposure of valproic acid, which is considered another murine model of autism, showed abnormalities in sociability and nociception tests and alterations in distinct elements of endocannabinoid system [149].

SCFAs are linked to autism, being the object of studies in autistic children [150]. Discordant data shows an increase or decrease in the SCFA in faecal samples, as the result of poor absorption based on the increased gut permeability or excessive fermentation. Interestingly, due to increased gut permeability or abnormal microbiota, the elevated level of SCFAs in the circulatory system, may actually be negative in autistic children. In particular, between them, propionic acid, injected both peripherally and centrally in rodents, induces repetitive behaviors and object preference [151], and also alters basic mitochondrial functions [152]. In agreement with these studies, prenatal or early postnatal exposure to valproate, an anti-epileptic and mood-stabilizing drug and histone deacetylase inhibitor, like butyrate, increases the risk of autism which was recently used to induce a mouse model of ASD [153]. On the other hand, chronic treatment with sodium butyrate at postnatal period, improved social behavior in a mouse model of autism [154]. All together, these studies point out that the time of exposure is crucial to reveal the effects of treatments on autism-like behavior.

5.2. Mood Disorders

Among the mental illnesses, depression and anxiety are the result of a multi-factorial disease caused by behavioral disturbance and immunological, metabolic and neurotransmitter dysregulation, common in people of all ages [155-157]. They are also frequent conditions in obesity, IBS patients and people with GI disturbances, indicating a key role of the gut microbiota and the gut-brain axis in these disorders [158-160]. Literature shows three lines of evidence by which the gut microbiota is correlated to depression, namely through inflammation, the HPA axis or neurotransmitter signaling pathways [161]. Moreover, early postnatal life represents an important stage for both the stress response system and the colonization by gut microbiota, which can influence the development of brain plasticity. Studies that use rats show that neonatal stress caused by maternal separation leads to long-term changes in the diversity and composition of gut microbiota [162], which may contribute to alterations in stress-related behavior persisting throughout life. In support of this, the use of probiotics during the early stress period has been shown to normalize basal corticosterone levels, which are elevated after maternal separation [163]. In this case, the use of GF mouse model is a useful tool to study this brain-gut axis. GF mice showed exaggerated HPA stress response and motor activity and less anxiety-like behavior compared to specific pathogen-free mice [164]. The modulation of gut microbiota is able to

reverse this HPA stress response in the GF mice due to the use of *Bifidobacterium infantis* [165]. Since 1910, different data from animal studies have provided the evidence of this relationship and the important effects of the use of probiotics on both GI and psychiatric symptoms [166]. Indeed, species under *Lactobacillus* and *Bifidobacterium* genus have showed antidepressant effects in different animal models [167, 168] and healthy volunteers have low score in anxiety tests and low urinary free cortisol levels [169].

On the other hand, mental illnesses and stress-related alterations may also affect the microbiota profile [170]. High levels of inflammation markers, like IL-6, TNF-α, and IL-1β [171], have been found in patients with depression; thus alteration in gut microbiota may be linked to depressive symptoms through the inflammatory response. Indeed, in both human and animal studies, obesity and depression have been associated with low levels of *Bacteroidetes* [172] and significant overgrowth of *Acidaminococcaceae* family [173]. Across human studies, an increase in *Oscillibacter* and *Alistipes* has been reported in depressed subjects with abdominal pain in IBS patients with inflammation [174]. Moreover, a decrease in fecal *Faecalibacterium,* known to have anti-inflammatory activity [176], has been observed in depression [175]. Evidences from previous studies suggest a role of different inflammogenic enteric pathogenic gram-negative bacteria of the *Enterobacteriaceae* family [177]. Although their presence in normal gut flora results in the increased permeability of the gut wall in depressed patients, which may induce their translocation into the systemic circulation, leading to behavioral and psychological changes in both animals and humans [178].

In contrast, mice infection with *Campylobacter jejuni* or *Citrobacter rodentium* increases anxiety-like behaviour, accompanied by an increase in the neuronal activation marker c-Fos in the CNS [179, 180], whereas *Trichuris muris* displays the same effect through immunological and metabolic mechanisms [32].

According to the previous animal studies [181], clinical trials revealed a profound lower expression of various species of the *Lachnospiraceae* and *Ruminococcaceae* families, within the *phylum Firmicutes*, in stool samples from patients with depression. The *Lachnospiraceae* family has also a role in the breakdown of carbohydrates into SCFAs. Consequently, low level of these bacteria leads to a reduction of SCFAs, which in turn results in intestinal barrier dysfunction [182].

Among SCFAs, butyrate displays antidepressant profile in animal models of depression and chronic mild stress [183, 184]. Previous studies indicate an association between omega-3 and omega-6 dietary supplementation in people affected by different kind of depressed mood, major depression, or post-partum depression [185]. Considering that anxiety disorders are common comorbid of major depression, the diet supplementation may be an effective treatment of anxiety as well [186, 187]. As for depression disorder treatment, the possible mechanism is associated with reduced oxidative stress [188] and pro-inflammatory cytokines [189].

Consistent with the signaling role of endocannabinoid/NAE in the regulation of appetite and metabolism, inflammation, pain and mood disorders, it is interesting to determine the beneficial effects of this system on anxiety, as well as on the depressive disorders [190]. Despite the clear role of the endocannabinoid system in mood disorders, different studies have reported a bimodal action in anxiety as in the depressive disorders. Indeed, CB_1 agonists at lower doses are anxiolytic, while at higher doses are anxiogenic agents [191-193] and similar bimodal responses were found using CB_1 antagonists [194]. Human study revealed high level of CB_1 in post-mortem analysis of brain from patients with major depression [195] and the use of CB_1 antagonists has been associated with an antidepressant-like activity in several animal models of depression [196]. By contrast, enhancing the AEA-CB_1-receptor signaling pathway by both CB_1 agonists and inhibitors of FAAH, has evidenced an antidepressant-like and dose-dependent anxiolytic effects in both rats and mice, without anxiogenic effects at high dose as happens for CB_1 [197-200]. Moreover, studies on CB_1 knockout mice have evidenced an increase in the depressive behavior [201]. In particular, taken together, we can assume that the dose and the duration of treatment and brain region of interest are important contributing factors to determine these contrasting results. In addition, plasma levels of NAE molecules are particularly low in woman with depression. Among NAEs, the antidepressant-like activity of PEA was recently investigated in combination with luteolin in a mouse model of anxiety/depressive-like behavior [202]. Instead, exposure to stress contributes to the increase in inflammatory markers and the NAE catabolism, resulting in the down-regulation of PEA and OEA levels. However, AEA levels do not decline in a similar way to PEA and OEA, although they share the same catabolic pathway. The aforementioned studies about the correlation be-

tween gut microbiota and mood disorders could represent an important start point for future directions.

5.3. Neurodegenerative Diseases: Parkinson's disease (PD), Alzheimer's Disease(AD) and Multiple Sclerosis (MS).

5.3.1. Parkinson's Disease (PD)

Lewy bodies, a physiopathological characteristic of PD, are constituted by aggregated proteins -mainly alpha synuclein and ubiquitin- also found in the ENS in *post mortem* cases of early PD. This pathology is characterized by a GI dysregulation that usually appears several years before its typical symptoms. Braak and coworkers [203] have hypothesized that this pathology "begins" in the gut, and then spreads to the CNS *via* vagus nerve and spinal cord. In fact, it has been demonstrated that alpha synuclein injected in the gut wall migrated to the brain *via* vagus nerve at a rate estimated to be 5-10mm/day in rats [204]. It has been also observed that colonic biopsies of PD patients have a low-grade inflammation, with an increased expression of pro-inflammatory cytokines compared to the control subjects [205]. To date, the mechanisms involved in these effects are not clear at all. However, it has been suggested that matrix metalloproteinase-9, a major component of the basement membrane, may contribute to the pathogenesis of PD regulating blood-brain barrier permeability through the release of cytokines and free radicals and by cleaving vascular basal lamina and/or tight junctions between cells within the neurovascular unit [206, 207]. This process may contribute to enhanced permeability and inflammation in autoimmune encephalitis, hypoxic brain injury, and other inflammatory diseases of the CNS [208].

It was noted that bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia* were significantly lower in PD patients compared to controls [209]. Moreover, proteobacteria of the genus *Ralstonia* were significantly more abundant in mucosa of PD than in controls, which potentially tips the microbial balance within the colon to a more inflammatory phenotype. Fecal microbiota collected from 72 PD subjects and age-matched controls showed higher counts of *Enterobacteriaceae* and reduced *Prevotellaceae*. *Prevotella* is known to metabolize complex carbohydrates, providing SCFAs as well as thiamine and folate, that promote a healthy intestinal environment. Decreased *Prevotella* numbers are likely to result in reduced production of these important micronutrients. However, the study did not evaluate whether or not the patients had a history of GI disturbances or significant inflammation. The importance of SCFA is highlighted by the same reports that show association between PD and the abundance of certain gut microbiota and show a reduction in fecal SCFA concentrations [210, 211]. Nevertheless, changes in the gut microbiome could have a direct effect on the CNS *via* the gut-brain axis with a chronic mild systemic inflammation, possibly driving the pathogenesis: in fact, microbiota can influence the development of normal motor patterns and thus alteration in its composition, especially if sustained it may potentially lead to sensory-motor dysfunction [212]. PD patients show both dysmotility and alterations in the microbiota composition, but which one comes first is not clear yet. The dysmotility has been proposed to result from several factors including diet [213], autonomic dysfunction, direct involvement of the ENS, or as a side-effect of certain anti-Parkinsonian medications [214]. An imbalance in the intestinal microbiota can lead to increased permeability, as well as systemic and intestinal inflammation, due to the translocation of bacterial products and of bacteria themselves [215]. Several studies evidence the possibility of GI symptoms even prior to the development of motor ones of PD [216-218]. Moreover, recently, it has been showed that IBS patients have higher hazard of PD compared to population who are IBS free [219, 220].

Finally, on this basis, butyrate represents an important tool not only for its role in the gut inflammation (IBS and IBD), but also for its therapeutic potential through histone remodelling, as an inhibitor of HDAC. Epigenetics, the process by which gene activity is altered without altering genetic information, has long attracted interest in neurodegenerative disease, due to the multifactorial origins of this pathology. Epigenetic factors are thought to contribute to neuronal cell death in PD [221], and it is suggested that alteration in epigenetic regulation could hold therapeutic promise against neurodegeneration [222, 223]. In particular, butyrate has been shown to improve rotenone-induced models of PD by preventing the death of dopaminergic neurons [224]. Moreover, it has recently been shown that BDNF expression decreases in n-3 PUFA deficient rats and the upregulation of BDNF and its receptor has been recognized as a potential mechanism of action of n-3 PUFA [225, 226]. DHA supplementation in a non-human primate (MPTP) model reduces levodopa-induced dyskinesia, suggesting an innovative and safe approach to improve the quality of life of PD patients [227].

Increasing evidence suggests a prominent modulatory function of the cannabinoid signaling system in the

basal ganglia. As the cannabinoid signaling system undergoes a biphasic pattern of change during the progression of PD, it explains the motor inhibition typically observed in patients with PD. Cannabinoid agonists such as WIN-55,212-2 have been experimentally demonstrated as neuroprotective agents in PD, with respect to their ability to suppress excitotoxicity, glial activation, and oxidative injury that cause degeneration of dopaminergic neurons. Additional benefits provided by cannabinoid related compounds, including OEA, have been reported to possess efficacy against bradykinesia and levodopa-induced dyskinesia in PD. Despite promising preclinical studies on PD, the use of cannabinoids has not been studied extensively at the clinical level [228]. However, a vast body of literature documents the beneficial effects of exogenously administered PEA in the experimental models of PD [229, 230].

5.3.2. Alzheimer's Disease (AD)

The mediterranean diet particularly rich in fibers, anti-oxidants, and natural antimicrobic agents appears to be able to support the growth of a beneficial microbiota and able to prevent the development of putrefactive bacteria characterized by free radicals and toxic metabolites production [231,232]. The great abundance of flavonoids and radical scavengers correlate with protective aspects of the mediterranean diet and the beneficial effects in neurodegenerative diseases, such as AD [233, 234].

Considerable interest has been emerged in the understanding of the role of gut microbiota in the context of AD. Gram-positive facultative anaerobic or microaerophilic *Lactobacillus* and other *Bifidobacterium* species are copious in the GI tract. They are capable of metabolizing glutamate to produce gamma-amino butyric acid (GABA), the major inhibitory neurotransmitter in the CNS. Dysfunctions in GABA-signaling are also linked to defects in synaptogenesis, and cognitive impairment, including AD [235-237]. Another important example is constituted by BDNF, a neurotrophin that has pleiotropic effects on neuronal development, differentiation, synaptogenesis and the synaptic plasticity, underlying circuit formation and cognitive function. It has been found that BDNF exhibits in brains and serum in patients with schizophrenia, anxiety and AD [238]. In experimental infection models that lead to alterations in the microbiota populations, BDNF expression is reduced in the hippocampus and cortex of GF mice, and this reduction is associated with increased anxiety behavior and progressive cognitive dysfunction [16-239]. Finally, pre-clinical findings show neurobiological mechanisms in which omega-3 alteration may contribute to the modulation of BDNF in the hippocampus, the regulation of HPA axis, and in neuroinflammation; all conditions related to dysbiosis.

It has also been shown that there exists an interaction between microbiota and the N-methyl-D-aspartate glutamate receptor. This receptor regulates synaptic plasticity and cognition [240]. In the GI tract, there is a small number of *Cyanobacteria* that produce β-N-methylamino-L-alanine (BMAA), which is elevated, for example, in the brain of AD and PD patients. BMAA is an excitotoxin that activates metabotropic glutamate receptor 5 and induces depletion of glutathione. Thus, neurons and glial cells are unable to effectively control reactive oxygen species and reactive nitrogen species production in the brain. BMAA is also implicated in the aggregation of the amyloid peptide as seen in the AD, and in facilitating protein misfolding tipically seen in the PD [241]. Interestingly, BMAA, a neurotoxic amino acid normally not incorporated into protein, has been linked with intra-neuronal protein misfolding and neuroinflammation, that characterize PD, AD and prion disease [242, 243]. *Cyanobacteria* generate other neurotoxins, such as saxitoxin and anatoxin-α that may further contribute to neurological diseases, especially during aging when the intestinal epithelial barrier of the GI tract becomes more permeable [244]. Differences in exposure to pathogens and genetic vulnerability toward microbioma-mediated autoimmunity may be significant determinants of age-related neurological disease course and outcome [245, 246]. Finally, it is well known that a sustained inflammation, in gut, as much as in brain, would up-regulate the expression of already triplicated amyloid precursor protein gene and contribute earlier to brain amyloid accumulation.

The endocannabinoids OEA and PEA have been implicated in the pathology of neurodegenerative diseases. In the particularly case of Alzheimer's disease, different studies showed their proctective role in neuroinflammation, oxidative stress and neurodegeneration [247, 248]. Recent *in vivo* evidence shows that fenofibrate reduces β-amyloid production in an Alzheimer's disease transgenic mouse model and also PEA exerts neuroprotective effect in an experimental model of AD induced by Ab25-35 [249, 250]. Future investigations are necessary to understand the possible involvement of these compounds and the gut brain axis on this disease.

5.3.4. Multiple Sclerosis (MS)

MS is a chronic demyelinating inflammatory disease of CNS. For reproducing human MS, the most widely and extensively studied animal model of autoimmunity is experimental autoimmune encephalomyelitis (EAE). EAE is induced after immunization with antigens including myelin basic protein, myelin oligodendrocyte glycoprotein (MOG) or proteolipid protein in the presence of bacterial adjuvant, which leads to myelin-reactive T cells responsible for the pathology features. Recent studies have begun to underline the correlation between microbiome and its relevant factors to MS pathogenesis, with a particular attention on EAE models [245]. Berer and coworkers [246] have demonstrated that commensal microbiota is essential for the development of spontaneous EAE in MOG TCR double-transgenic mice, which simulates opticospinal MS. GF RR mice were protected from EAE because of an attenuated T helper 17 cells and auto-reactive B cell responses [246]. EAE can also be induced by commensal microbiota, since GF B6 mice developed this pathology in a less severe manner, characterized by decreased interferon gamma and interleukin-17 responses. Antibiotic therapies could control EAE progression, modulating gut microbiota. Indeed, the hypothesis that gut microbiome is the potential site of molecular mimicry, is supported by the fact that with induction of EAE, both the adjuvant and immunogen need to be injected simultaneously [251]. However, it might be a microbial antigen that triggers an inflammatory response in the MS, and the only area of the human body with sufficient amounts of adjuvants in the form of bacterial cell walls is the gut [252].

It has already been demonstrated that there is a positive correlation between the body mass index and the risk of developing MS, especially at younger ages [253]. Obesity is characterized by an inadequate accumulation of white adipose tissue (WAT) that can lead to a state of systemic inflammation called "metaflammation". WAT is not only involved in energy storage, but also operates as an endocrine organ secreting pro-inflammatory cytokine, such as tumor necrosis factor (TNF)-α, IL-6 or leptin. The latter in particular, deeply influencing T cell responses in the EAE [254, 255], enhances phagocytosis and cytokine secretion in macrophages and promotes CD4+ T cell proliferation and survival [256]. Both monocytes and T cells are present in MS lesions and patient-derived cerebrospinal fluid, highly express leptin and leptin receptor [257, 258]. However, MS incidence is not necessarily accompanied by weight gain, so a direct effect of fatty acids on immunity was supposed. Finally, as reported above, PEA is able to increase the expression and signaling of leptin receptor in the hypothalamus and these effects might be related to the suppression of food intake and fat accumulation [73].

In MS patients, the levels of Clostridia clusters XIVa and IV were shown to be reduced [259], both formed by diverse bacterial species that are able to produce SCFAs, such as butyrate [260], that displays anti-inflammatory properties. This probably indicates that a reduction in these microbes in MS patients may be associated with disease [261]. Most studies have demonstrated that the effect of SCFA mechanism involves regulatory T cells (Tregs). In fact, the administration of butyrate to GF mice mimicked the effect of Clostridium colonization and increased Treg levels in colon lamina propria [262]. In the EAE model, SCFA increases Tregs, while suppresses T helper 17 cells differentiation [263], furthermore, butyrate as inhibitor of HDAC could regulate the differentiation of Tregs in the gut, producing an improvement of the disease. Indeed, as reported in several papers, butyrate maintains acetylation of genes important for Treg function [264, 265]. To date, the *in vivo* amelioration of EAE remains unfortunately unclear, even if synthetic small inhibitors of HDAC have already shown to decrease inflammation in animal models of arthritis, IBD, asthma, diabetes, cardiovascular diseases, and MS. Hence, SCFA as naturally occurring nutrients [266] or fermentation products may have a possible therapeutic use in autoimmune diseases, such as MS by triggering the production of anti-inflammatory Tregs. In fact, a higher percentage of MS patients exhibited antibody responses against GI antigens in contrast to healthy control, indicating a possible alteration in gut microbiome and immune status [267]. Ezendam and coworkers have observed that oral treatment with a single bacterium or bacteria mixture can modulate EAE; in particular, *Bifidobacterium animalis* reduced the duration of symptoms in a rat EAE model [268]. On the contrary, *Lactobacillus casei Shirota* exacerbated EAE symptoms in rats [269]. However, later studies indicated that Lactobacilli, did not enhance but rather suppressed EAE in rats [270]. This has been supported by other studies using probiotic mixtures of strains under the Lactobacillus genus. Indeed, *Lactobacilli*, alone or in combination with other strains of *Bifidobacterium* genus, alleviates EAE symptoms in mice regulating pro- and anti-inflammatory cytokine responses [271-273]. Probiotic treatment with *Bacteroides fragilis* and *Pediococcus acidilactici* (strain R037) also significantly reduced mice susceptibility to EAE [274]. Furthermore, engi-

neered strains, such as Salmonella-CFA/I and Hsp65-producing *Lactococcus lactis* can prevent EAE in mice *via* Tregs-associated TGFβ and IL-13 signals [275].

Finally, Piccio and coworkers found that high-fat diet increased EAE severity in mice. In contrast, caloric restriction diet attenuated EAE symptoms, which was associated with hormonal, metabolic and cytokine changes rather than immune suppression [276]. It has also been illustrated that mice fed with a high-salt diet developed a more severe form of EAE, in line with the ability of sodium chloride to activate T helper 17 cells [277].Therefore, several evidences pointed out a central role of gut microbiome in linking diet with MS and EAE. However, endocannabinoids has some potential to relieve, pain, spasms and spasticity in the MS [278] showing as in AD and PD, a clear anti-inflammatory and neuroprotective potential, while until now no studies have considered a possible link with the microbiota-brain axis.

CONCLUSION

The concept of a gut-brain axis has been introduced to describe a recognized integrative physiology between the GI and the CNS, with particular emphasis on the key role of microbiota in this bidirectional system. The interaction between the host and its gut microbiome is a complex relationship whose manipulation could be essential in preventing or treating not only various gut diseases, like IBS, IBD, but also CNS disorders, such as mood alteration, AD, PD, and autism. As previously described, dysbiosis can contribute to the pathogenesis of IBD and IBS, commonly defined as gut-brain axis disorders, producing a state of malaise where pain is one of the main symptoms, but in more than one case, this state of chronic inflammation or immune activation can also contribute to neurological and neurodegenerative diseases. Several evidences suggest that many bioactive lipids (AEA, PEA, OEA, butyrate) are involved in many physiological processes directly linked with the maintenance of gut-barrier function, the regulation of inflammation and pain, and energy metabolism. In particular, it has been shown that dysregulation of the endocannabinoid system as well as PEA or OEA alteration, might play an important role in etiopathogenesis of intestinal disorders, including IBS and IBD. Recent evidence showed the possibility to decrease the symptoms of these pathologies through the manipulation of endocannabinoid or PPARs system, suggesting that these targets could represent a new therapeutic strategy for these conditions. Moreover, several evidences underline that mood disorders or neurodegenerative diseases or autism are characterized by changes in gut microbiota, but there is a lack of data about lipidomics, CNS disorders and microbiota . Finally, the modulation of gut microbiota or the supplementation with postbiotic molecules, restoring normal intestinal integrity, could be beneficial to peripheral and central disorders related to dysbiosis, representing a good strategy to prevent the development of diseases.

LIST OF ABBREVIATIONS

2-AG	=	2-arachidonoylglycerol
5-HT	=	Serotonin
AD	=	Alzheimer's Disease
AEA	=	Anandamide
ASD	=	Autism spectrum disorder
BDNF	=	Brain-derived neurotrophic factor
BMAA	=	β-N-methylamino-L-alanine
CB	=	Cannabinoid
CD	=	Crohn's Disease
CNS	=	Central nervous system
DHA	=	Docosahexaenoic acid
EAE	=	Experimental autoimmune encephalomyelitis
ENS	=	Enteric nervous system
FAAH	=	Fatty acid amide hydrolase
FFAR	=	Free Fatty Acid Receptor
GABA	=	Gamma-amino butyric acid
GF	=	Germ-free
GI	=	Gastrointestinal
GPR	=	G-protein-coupled receptor
HDAC	=	Histone deacetylase
HPA	=	Hypothalamic-pituitary-adrenal
IBD	=	Inflammatory Bowel Disease
IBS	=	Irritable Bowel Syndrome
LPS	=	Lipopolysaccharide
MCT	=	Monocarboxylate transporter
MOG	=	Myelin oligodendrocyte glycoprotein
MS	=	Multiple Sclerosis
MYD	=	Myeloid differentiation primary response gene

NAAA = N-acylethanolamine acid amidase

NAE = N-acylethanolamine

NAPE-PLD = N-acyl phosphatidylethanolamine-specific phospholipase D

OEA) = Oleoilethanolamide

PD = Parkinson's disease

PEA = Palmitoylethanolamide

PPAR = Peroxisome proliferator-activated receptors

PUFA = Polyunsaturated fatty acids

SCFA = Short chain acid

Tregs = Regulatory T cells

UC) = Ulcerative Colitis

WAT = White adipose tissue

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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