

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 vagus 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-acyl ethanolamine (NAE) family whose main members are N-arachidonylethanolamine (AEA), palmitoylethanolamide (PEA) and oleoylethanolamide (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, produced 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} bacterial cells 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) communication, 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 strengthened 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] identifying endocannabinoids, N-acyl ethanolamines (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, palmitoylethanolamide (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 and Carl 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].

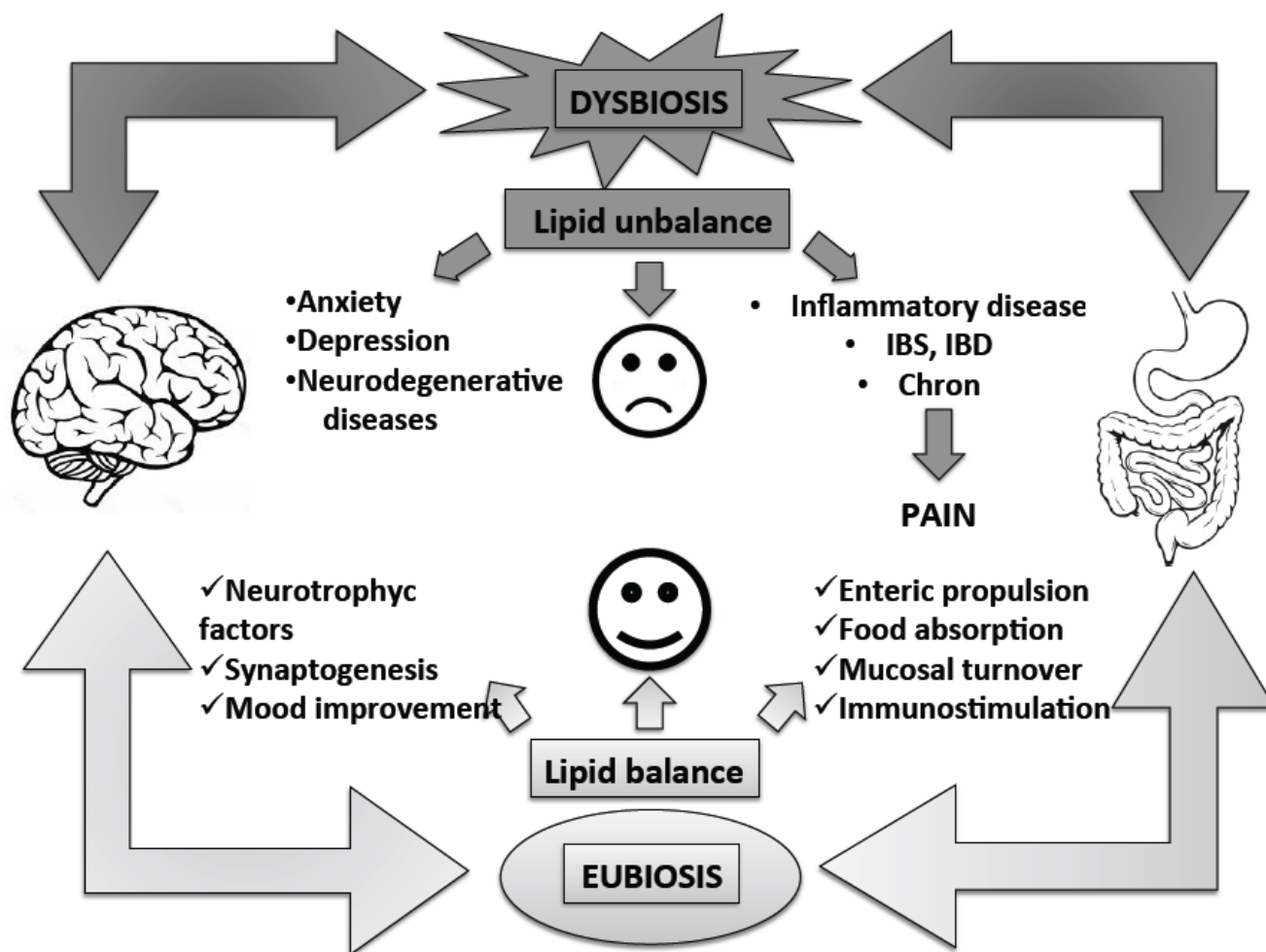


Fig. (1).

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, dysregulation of serotonin in the human gut has been implicated in an assorted 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-arachidonylethanolamine (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 in-

testine [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 CB₁ and CB₂. 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, CB₁ is mostly abundant in different brain areas, as well as in peripheral nerve terminals, while CB₂ 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), CB₁ 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 CB₁-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 CB₁ 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” endocannabinoids, 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 *Mycobacte-*

rium tuberculosis [76, 77], greatly impacting disease severity. The role of PPARs in gut inflammation has been recognized. Indeed, PPAR γ agonists are used to treat type-2 diabetes and are known to reduce colitis in mice [78]. Moreover, PPAR γ heterozygous mice exhibit an increased susceptibility to experimentally induced colitis [79], indicating that PPAR γ 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, PPAR γ is reduced in colonic epithelial cells from ulcerative colitis (UC) patients, suggesting PPAR γ 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 coworkers [89] showed that the administration of butyrate to patients with UC suppressed mucosal inflammation and decreased NF- κ B 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- κ B 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 PPAR γ [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 CB₁ but not CB₂. 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 CB₁ and/or CB₂ 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-HT_{3R}-mediated duodenal AEA release and downstream CB₁ 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 inhibition 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, literature show both a general gut microbiota and specific strains alteration in the ASD. The first study in 1988, exhibited 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 CB₁ 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 CB₁ 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-1 β [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 inflammatory 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, CB₁ agonists at lower doses are anxiolytic, while at higher doses are anxiogenic agents [191-193] and similar bimodal responses were found using CB₁ antagonists [194]. Human study revealed high level of CB₁ in post-mortem analysis of brain from patients with major depression [195] and the use of CB₁ antagonists has been associated with an antidepressant-like activity in several animal models of depression [196]. By contrast, enhancing the AEA-CB₁-receptor signaling pathway by both CB₁ 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 CB₁ [197-200]. Moreover, studies on CB₁ 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 impor-

tance 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 antimicrobial 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 typically 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-*a* 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 microbiota-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 protective 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 TGF β 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 dis-

orders 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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REFERENCES

- Schloissnig S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A, Waller A, Mende DR, Kultima JR, Martin J, Kota K, Sunyaev SR, Weinstock GM, Bork P. Genomic variation landscape of the human gut microbiome. *Nature*, **2013**, 493(7430):45-50.
- Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature*, **2007**, 449(7164):804-10.
- Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS biology*, **2007**, 5:e177.
- Koren O, Knights D, Gonzalez A, Waldron L, Segata N, Knight R, Huttenhower C, Ley RE. A guide to enterotypes across the human body: meta-analysis of microbial community structures in human microbiome datasets. *PLoS computational biology*, **2013**, 9:e1002863.
- O'Hara AM, Shanahan F. The gut flora as a forgotten organ. *EMBO reports*, **2006**, 7:688-693.
- Sommer F, Bäckhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol.*, **2013**, 11(4):227-38.
- Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nat Rev Micro*, **2012**, 10:735-742.
- Montiel-Castro AJ, González-Cervantes RM, Bravo-Ruiseco G, Pacheco-López G. The microbiota-gut-brain axis: neurobehavioral correlates, health and sociality. *Front Integr Neurosci.*, **2013**, 7:70.
- Berntson GG, Sarter M, Cacioppo JT. Ascending visceral regulation of corticallffective information processing. *Eur J Neurosci.*, **2003**, 18(8):2103-9.
- Li J, Butcher J, Mack D, Stintzi A. Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease. *Inflamm Bowel Dis.*, **2014**, 21(1):139-153.
- Lee KN, Lee OY. Intestinal microbiota in pathophysiology and management of irritable bowel syndrome. *World J Gastroenterol.* **2014**, 20(27):8886-8897.
- Czirr E, Wyss-Coray T. The immunology of neurodegeneration. *J Clin Invest.*, **2012**, 122(4):1156-63.
- Lampron A, Pimentel-Coelho PM, Rivest S. Migration of bone marrow-derived cells into the central nervous system in models of neurodegeneration. *J Comp Neurol.*, **2013**, 521(17):3863-76.
- Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling. *Cell Metab.*, **2015**, 22(4):658-68.
- Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, Geboes K, Chamailard M, Ouwehand A, Leyer G, Carcano D, Colombel JF, Ardid D, Desreumaux P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat Med.*, **2007**, 13(1):35-7.
- Alhouayek M, Botteman P, Subramanian KV, Lambert DM, Makriyannis A, Cani PD, Muccioli GG. N-Acylethanolamine-hydrolyzing acid amidase inhibition increases colon N-palmitoylethanolamine levels and counteracts murine colitis. *FASEB J.*, **2015**, 29(2):650-61.
- Kannampalli P, Shaker R, Sengupta JN. Colonic butyrate-algesic or analgesic? *Neurogastroenterol Motil.*, **2011**, 23(11):975-9.
- Cannon WB. Organization for physiological homeostasis. *Physiol Rev.* **1929**, 9:399-431.
- Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci.*, **2013**, 36:305-312.
- Naseribafrouei A, Hestad K, Avershina E, et al. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motil.*, **2014**, 26:1155-62.
- Mangiola F, Ianiro G, Franceschi F, Fagioli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. *World J Gastroenterol.*, **2016**, 22(1):361-8.
- Rhee SH, Pothoulakis C, Mayer EA. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nature reviews. Gastroenterology & hepatology*, **2009**, 6:306-314.
- Hughes DT, Sperandio V. Inter-kingdom signalling: communication between bacteria and their hosts. *Nat. Rev. Microbiol.*, **2008**, 6:111-120.
- Kunze WA, Mao YK, Wang B, Huizinga JD, Ma X, Forsythe P, Bienenstock J. Lactobacillus reuteri enhances excitability of colonic AH neurons by inhibiting calcium-dependent potassium channel opening. *Journal of cellular and molecular medicine*, **2009**, 13:2261-2270.
- Mao YK, Kasper DL, Wang B, Forsythe P, Bienenstock J, Kunze WA. Bacteroides fragilis polysaccharide A is necessary and sufficient for acute activation of intestinal sensory neurons. *Nature communications*, **2013**, 4:1465.
- Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *The Journal of physiology*, **2004**, 558:263-275.

- [27] Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nature reviews Immunology*, **2009**, 9:313-323.
- [28] Corthésy B. Multi-faceted functions of secretory IgA at mucosal surfaces. *Front Immunol.*, **2013**, 4:185.
- [29] Cahenzli J, Balmer ML, McCoy KD. Microbial-immune cross-talk and regulation of the immune system. *Immunology*, **2013**, 138(1):12-22.
- [30] Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science*, **2012**, 336(6086):1268-73.
- [31] Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, Deng Y, Blennerhassett P, Macri J, McCoy KD, Verdu EF, Collins SM. The intestinal microbiota affects central levels of brain-derived neurotrophic factor and behavior in mice. *Gastroenterology*, **2011**, 141(2):599-609, 609.e1-3.
- [32] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse *via* the vagus nerve. *Proc Natl Acad Sci U S A*, **2011**, 108(38):16050-5.
- [33] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci.*, **2012**, 13(10):701-12.
- [34] Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, Deng Y, Blennerhassett PA, Fahnestock M, Moine D, Berger B, Huizinga JD, Kunze W, McLean PG, Bergonzelli GE, Collins SM, Verdu EF. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol Motil.*, **2011**, 23(12):1132-9.
- [35] Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Després S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*, **2011**, 477(7362):90-4.
- [36] Vicario M, Alonso C, Guilarte M, Serra J, Martínez C, González-Castro AM, Lobo B, Antolín M, Andreu AL, García-Arumí E, *et al.* Chronic psychosocial stress induces reversible mitochondrial damage and corticotropin-releasing factor receptor type-1 upregulation in the rat intestine and IBS-like gut dysfunction. *Psychoneuroendocrinology*, **2012**, 37:65-77.
- [37] Ewaschuk JB, Diaz H, Meddings L, Diederichs B, Dmytrash A, Backer J, Looijer-van Langen M, Madsen KL. Secreted bioactive factors from *Bifidobacterium infantis* enhance epithelial cell barrier function. *Am J Physiol Gastrointest Liver Physiol.*, **2008**, 295:G1025-34.
- [38] O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, O'Sullivan GC, Kiely B, Collins JK, Shanahan F, *et al.* Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*, **2005**, 128:541-51.
- [39] Ait-Belgnaoui A, Durand H, Cartier C, Chaumaz G, Eutamene H, Ferrier L, Houdeau E, Fioramonti J, Bueno L, Theodorou V. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology*, **2012**, 37(11):1885-95.
- [40] O'Mahony SM, Felice VD, Nally K, Savignac HM, Claesson MJ, Scully P, Woznicki J, Hyland NP, Shanahan F, Quigley EM, Marchesi JR, O'Toole PW, Dinan TG, Cryan JF. Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats. *Neuroscience*, **2014**, 277:885-901.
- [41] Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun.*, **2011**, 25(3):397-407.
- [42] De Palma G, Collins SM, Bercik P, Verdu EF. The microbiota-gut-brain axis in gastrointestinal disorders: stressed bugs, stressed brain or both? *J Physiol.*, **2014**, 592(14):2989-97.
- [43] Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome *via* β -adrenergic induction of myelopoiesis. *Proc Natl Acad Sci U S A.*, **2013**, 110(41):16574-9.
- [44] Bailey MT, Dowd SE, Parry NM, Galley JD, Schauer DB, Lyte M. Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by *Citrobacter rodentium*. *Infect Immun.*, **2010**, 78:1509-1519.
- [45] Campos-Rodríguez R, Godínez-Victoria M, Abarca-Rojano E, Pacheco-Yépez J, Reyna-Garfias H, Barbosa-Cabrera RE, Drago-Serrano ME. Stress modulates intestinal secretory immunoglobulin A. *Front Integr Neurosci.*, **2013**, 7:86.
- [46] Rostène W, Kitabgi P, Parsadaniantz SM. Chemokines: a new class of neuromodulator? *Nat Rev Neurosci.*, **2007**, 8(11):895-903.
- [47] Banks WA, Kastin AJ, Broadwell RD. Passage of cytokines across the blood-brain barrier. *Neuroimmunomodulation*. **1995**, 2(4):241-8.
- [48] Kelley KW, Bluthé RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. *Brain Behav Immun.*, **2003**, 17(Suppl 1):S112-8.
- [49] Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, **1992**, 258(5090):1946-9.
- [50] Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR, *et al.* Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol.*, **1995**, 50(1):83-90.
- [51] Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol.*, **2007**, 152(7):1092-101.
- [52] Ross RA. Anandamide and vanilloid TRPV1 receptors. *Br J Pharmacol.*, **2003**, 140(5):790-801.
- [53] Pertwee RG, Howlett AC, Abood ME, Alexander SP, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, Mechoulam R, Ross RA. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev.*, **2010**, 62(4):588-631.
- [54] Izzo AA, Piscitelli F, Capasso R, Aviello G, Romano B, Borrelli F, Petrosino S, Di Marzo V. Peripheral endocannabinoid dysregulation in obesity: relation to intestinal motility and energy processing induced by food deprivation and re-feeding. *Br J Pharmacol.*, **2009**, 158(2):451-61.
- [55] DiPatrizio NV, Piomelli D. Intestinal lipid-derived signals that sense dietary fat. *J Clin Invest.*, **2015** Mar 2;125(3):891-8.
- [56] Troy-Fioramonti S, Demizieux L, Gresti J, Muller T, Vergès B, Degraze P. Acute activation of cannabinoid receptors by anandamide reduces gastrointestinal motility and improves postprandial glycemia in mice. *Diabetes*, **2015**, 64(3):808-18.

- [57] Cota D, Marsicano G, Tschöp M, Grübler Y, Flachskamm C, Schubert M, Auer D, Yassouridis A, Thöne-Reineke C, Ortman S, Tomassoni F, Cervino C, Nisoli E, Linthorst AC, Pasquali R, Lutz B, Stalla GK, Pagotto U. The endocannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *J Clin Invest.*, **2003**, 112(3):423-31.
- [58] Hoareau L, Buyse M, Festy F, Ravanan P, Gonthier MP, Matias I, Petrosino S, Tallet F, d'Hellencourt CL, Cesari M, Di Marzo V, Roche R. Anti-inflammatory effect of palmitoylethanolamide on human adipocytes. *Obesity (Silver Spring)*, **2009**, 17(3):431-8.
- [59] Lam YY, Ha CW, Campbell CR, Mitchell AJ, Dinudom A, Oscarsson J, Cook DI, Hunt NH, Caterson ID, Holmes AJ, Storlien LH. Increased gut permeability and microbiota change associate with mesenteric fat inflammation and metabolic dysfunction in diet-induced obese mice. *PLoS One*, **2012**, 7(3):e34233.
- [60] Muccioli GG, Naslain D, Bäckhed F, Reigstad CS, Lambert DM, Delzenne NM, Cani PD. The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol.*, **2010**, 6:392.
- [61] Zhu C, Solorzano C, Sahar S, Realini N, Fung E, Sassone-Corsi P, Piomelli D. Proinflammatory stimuli control N-acylphosphatidylethanolamine-specific phospholipase D expression in macrophages. *Mol Pharmacol.*, **2011**, 79(4):786-92.
- [62] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, **2007**, 56(7):1761-72.
- [63] Silvestri C, Di Marzo V. The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. *Cell Metab.*, **2013**, 17(4):475-90.
- [64] Geurts L, Muccioli GG, Delzenne NM, Cani PD. Chronic endocannabinoid system stimulation induces muscle macrophage and lipid accumulation in type 2 diabetic mice independently of metabolic endotoxaemia. *PLoS One*, **2013**, 8(2):e55963.
- [65] Alhouayek M, Botteman P, Subramanian KV, Lambert DM, Makriyannis A, Cani PD, Muccioli GG. N-Acylethanolamine-hydrolyzing acid amidase inhibition increases colon N-palmitoylethanolamine levels and counteracts murine colitis. *FASEB J.*, **2015**, 29(2):650-61.
- [66] Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, de Vos WM, Cani PD. Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*, **2013**, 110(22):9066-71.
- [67] Alhouayek M, Lambert DM, Delzenne NM, Cani PD, Muccioli GG. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. *FASEB J.*, **2011**, 25(8):2711-21.
- [68] Everard A, Geurts L, Caesar R, Van Hul M, Matamoros S, Duparc T, Denis RG, Cochez P, Pierard F, Castel J, Bindels LB, Plovier H, Robine S, Muccioli GG, Renauld JC, Dumoutier L, Delzenne NM, Luquet S, Bäckhed F, Cani PD. Intestinal epithelial MyD88 is a sensor switching host metabolism towards obesity according to nutritional status. *Nat Commun.*, **2014** Dec 5;5:5648.
- [69] Lo Verme J, Fu J, Astarita G, La Rana G, Russo R, Calignano A, Piomelli D. The nuclear receptor peroxisome proliferator-activated receptor- α mediates the anti-inflammatory actions of palmitoylethanolamide. *Mol Pharmacol.*, **2005**, 67(1):15-9.
- [70] Borrelli F, Romano B, Petrosino S, Pagano E, Capasso R, Coppola D, Battista G, Orlando P, Di Marzo V, Izzo AA. Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. *Br J Pharmacol.*, **2015**, 172(1):142-58.
- [71] Esposito G, Capoccia E, Turco F, Palumbo I, Lu J, Steardo A, Cuomo R, Sarnelli G, Steardo L. Palmitoylethanolamide improves colon inflammation through an enteric glia/toll like receptor 4-dependent PPAR- α activation. *Gut*, **2014**, 63(8):1300-12.
- [72] Mattace Raso G, Russo R, Calignano A, Meli R. Palmitoylethanolamide in CNS health and disease. *Pharmacol Res.*, **2014**, 86:32-41.
- [73] Mattace Raso G, Santoro A, Russo R, Simeoli R, Paciello O, Di Carlo C, Diano S, Calignano A, Meli R. Palmitoylethanolamide prevents metabolic alterations and restores leptin sensitivity in ovariectomized rats. *Endocrinology*, **2014**, 155(4):1291-301.
- [74] Piomelli D. A fatty gut feeling. *Trends Endocrinol Metab.*, **2013**, 24(7):332-41.
- [75] Igarashi M, Di Patrizio NV, Narayanaswami V, Piomelli D. Feeding-induced oleoylethanolamide mobilization is disrupted in the gut of diet-induced obese rodents. *Biochim Biophys Acta.*, **2015**, 1851(9):1218-26.
- [76] Konturek PC, Kania J, Kukharsky V, Raitel M, Ocker M, Rembiesz K, Hahn EG, Konturek SJ. Implication of peroxisome proliferator-activated receptor gamma and proinflammatory cytokines in gastric carcinogenesis: link to Helicobacter pylori-infection. *J Pharmacol Sci.*, **2004**, 96(2):134-43.
- [77] Rajaram MV, Brooks MN, Morris JD, Torrelles JB, Azad AK, Schlesinger LS. Mycobacterium tuberculosis activates human macrophage peroxisome proliferator-activated receptor gamma linking mannose receptor recognition to regulation of immune responses. *J Immunol.*, **2010**, 185(2):929-42.
- [78] Saubermann LJ, Nakajima A, Wada K, Zhao S, Terauchi Y, Kadowaki T, Aburatani H, Matsushashi N, Nagai R, Blumberg RS. Peroxisome proliferator-activated receptor gamma agonist ligands stimulate a Th2 cytokine response and prevent acute colitis. *Inflamm Bowel Dis.*, **2002**, 8(5):330-9.
- [79] Desreumaux P, Dubuquoy L, Nutten S, Peuchmaur M, Englaro W, Schoonjans K, Derijard B, Desvergne B, Wahli W, Chambon P, Leibowitz MD, Colomel JF, Auwerx J. Attenuation of colon inflammation through activators of the retinoid X receptor (RXR)/peroxisome proliferator-activated receptor gamma (PPARgamma) heterodimer. A basis for new therapeutic strategies. *J Exp Med.*, **2001**, 193(7):827-38.
- [80] Adachi M, Kurotani R, Morimura K, Shah Y, Sanford M, Madison BB, Gumucio DL, Marin HE, Peters JM, Young HA, Gonzalez FJ. Peroxisome proliferator activated receptor gamma in colonic epithelial cells protects against experimental inflammatory bowel disease. *Gut.*, **2006**, 55(8):1104-13.
- [81] Dubuquoy L, Dharancy S, Nutten S, Pettersson S, Auwerx J, Desreumaux P. Role of peroxisome proliferator-activated receptor gamma and retinoid X receptor heterodimer in hepatogastroenterological diseases. *Lancet*, **2002**, 360(9343):1410-8.
- [82] Mattace Raso G, Simeoli R, Russo R, Iacono A, Santoro A, Paciello O, Ferrante MC, Canani RB, Calignano A, Meli R. Effects of sodium butyrate and its synthetic amide derivative on liver inflammation and glucose tolerance in an animal model of steatosis induced by high fat diet. *PLoS One*, **2013**, 8(7):e68626.

- [83] Fleming SE, Fitch MD, DeVries S, Liu ML, Kight C. Nutrient utilization bycells isolated from rat jejunum, cecum and colon. *J Nutr.*, **1991**, 121(6):869-78.
- [84] Boren J, Lee WN, Bassilian S, Centelles JJ, Lim S, Ahmed S, Boros LG, Cascante M. The stable isotope-based dynamic metabolic profile of butyrate-induced HT29 cell differentiation. *J Biol Chem.*, **2003**, 278(31):28395-402.
- [85] Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J Gastroenterol.*, **2011**, 17(12):1519-28.
- [86] Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. *Aliment Pharmacol Ther.*, **1998**, 12(6):499-507.
- [87] De Preter V, Arijis I, Windey K, Vanhove W, Vermeire S, Schuit F, Rutgeerts P, Verbeke K. Impaired butyrate oxidation in ulcerative colitis is due to decreased butyrate uptake and a defect in the oxidation pathway. *Inflamm Bowel Dis.*, **2012**, 18(6):1127-36.
- [88] Thibault R, De Coppet P, Daly K, Bourreille A, Cuff M, Bonnet C, Mosnier JF, Galmiche JP, Shirazi-Beechey S, Se-gain JP. Down-regulation of the monocarboxylate transporter 1 is involved in butyrate deficiency during intestinal inflammation. *Gastroenterology*, **2007**, 133(6):1916-27.
- [89] Lührs H, Gerke T, Müller JG, Melcher R, Schaubert J, Boxberge F, Scheppach W, Menzel T. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. *Scand J Gastroenterol.*, **2002**, 37(4):458-66.
- [90] Banasiewicz T, Krokowicz Ł, Stojcev Z, Kaczmarek BF, Kaczmarek E, Maik J, Marciniak R, Krokowicz P, Walkowiak J, Drews M. Microencapsulated sodium butyrate reduces the frequency of abdominal pain in patients with irritable bowel syndrome. *Colorectal Dis.*, **2013**, 15(2):204-9.
- [91] Vinolo MA, Rodrigues HG, Hatanaka E, Sato FT, Sampaio SC, Curi R. Suppressive effect of short-chain fatty acids on production of proinflammatory mediators by neutrophils. *J Nutr Biochem.*, **2011**, 22(9):849-55.
- [92] Berni Canani R, Di Costanzo M, Leone L. The epigenetic effects of butyrate: potential therapeutic implications for clinical practice. *Clin Epigenetics*, **2012**, 4(1):4.
- [93] Nøhr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, Husted AS, Sichlau RM, Grunddal KV, Poulsen SS, Han S, Jones RM, Offermanns S, Schwartz TW. GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes. *Endocrinology*, **2013**, 154(10):3552-64.
- [94] Russo R, De Caro C, Avagliano C, Cristiano C, La Rana G, Mattace Raso G, Berni Canani R, Meli R, Calignano A. Sodium butyrate and its synthetic amide derivative modulate nociceptive behaviors in mice. *Pharmacol Res.*, **2016**, 103:279-91.
- [95] Dubuquoy L, Rousseaux C, Thuru X, Peyrin-Biroulet L, Romano O, Chavatte P, Chamailard M, Desreumaux P. PPARgamma as a new therapeutic target in inflammatory bowel diseases. *Gut*, **2006**, 55(9):1341-9.
- [96] Eckmann, L. Animal models of inflammatory bowel disease: Lessons from enteric infections. *Ann. N. Y. Acad. Sci.*, **2006**, 1072, 28-38.
- [97] Yan, F.; Wang, L.; Shi, Y.; Cao, H.; Liu, L.; Washington, M.K.; Chaturvedi, R.; Israel, D.A.; Cao, H.; Wang, B.; et al. Berberine promotes recovery of colitis and inhibits inflammatory responses in colonic macrophages and epithelial cells in DSS-treated mice. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **2012**, 302, G504-G514.
- [98] Baumgart, D.C.; Sandborn, W.J. Crohn's disease. *Lancet*, **2012**, 380, 1590-1605.
- [99] Ordas, I.; Eckmann, L.; Talamini, M.; Baumgart, D.C.; Sandborn, W.J. Ulcerative colitis. *Lancet*, **2012**, 380, 1606-1619.
- [100] Di Sabatino A, Battista N, Biancheri P, Rapino C, Rovedatti L, Astarita G, Vanoli A, Dainese E, Guerci M, Piomelli D, Pender SL, MacDonald TT, Maccarrone M, Corazza GR. The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease. *Mucosal Immunol.*, **2011**, 4(5):574-83.
- [101] Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Geary R, Glas J, Van Gossom A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhardt AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annesse V, Hakonarson H, Daly MJ, Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat. Genet.*, **2010**, 42, 1118-25.
- [102] Cosnes, J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*, **2011**, 140, 1785-1794.
- [103] Chassaing, B., Darfeuille-Michaud, A. The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. *Gastroenterology*, **2011**, 140, 1720-1728.
- [104] MacDonald, T.T. New cytokine targets in inflammatory bowel disease. *Gastroenterol Hepatol*, **2011**, 7, 474-476.
- [105] Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. *Pharmacol Res.*, **2009**, 60(2):85-92.
- [106] Alhouayek M, Muccioli GG. The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. *Trends Mol Med.*, **2012**, 18(10):615-25.
- [107] Sałaga M, Mokrowiecka A, Zakrzewski PK, Cygankiewicz A, Leishman E, Sobczak M, Zatorski H, Małeczka-Panas E, Kordek R, Storr M, Krajewska WM, Bradshaw HB, Fichna J. Experimental colitis in mice is attenuated by changes in the levels of endocannabinoid metabolites induced by selective inhibition of fatty acid amide hydrolase (FAAH). *J Crohns Colitis*, **2014**, 8(9):998-1009.
- [108] Storr MA, Keenan CM, Emmerdinger D, Zhang H, Yüce B, Sibaev A, Massa F, Buckley NE, Lutz B, Göke B, Brand S, Patel KD, Sharkey KA. Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. *J Mol Med (Berl)*, **2008**, 86(8):925-36.
- [109] Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther.*, **2010**, 126:21-38.
- [110] Esposito G, Capoccia E, Turco F, Palumbo I, Lu J, Steardo A, Cuomo R, Sarnelli G, Steardo L. Palmitoylethanolamide improves colon inflammation through an enteric glia/toll

- like receptor 4-dependent PPAR- α activation. *Gut*, **2014**, 63(8):1300-12.
- [111] Butzner JD, Parmar R, Bell CJ, Dalal V. Butyrate enema therapy stimulates mucosal repair in experimental colitis in the rat. *Gut*, **1996**, 38(4):568-573.
- [112] Roediger WE. The colonic epithelium in ulcerative colitis: an energy-deficiency disease? *Lancet*, **1980**, 2(8197):712-715.
- [113] Chapman MA, Grahn MF, Boyle MA, Hutton M, Rogers J, Williams NS. Butyrate oxidation is impaired in the colonic mucosa of sufferers of quiescent ulcerative colitis. *Gut*, **1994**, 35(1):73-76.
- [114] Vernia P, Cittadini M, Caprilli R, Torsoli A. Topical treatment of refractory distal ulcerative colitis with 5-ASA and sodium butyrate. *Dig Dis Sci.*, **1995**, 40(2):305-307.
- [115] Vernia P, Monteleone G, Grandinetti G, Villotti G, Di Giulio E, Frieri G, Marcheggiano A, Pallone F, Caprilli R, Torsoli A. Combined oral sodium butyrate and mesalazine treatment compared to oral mesalazine alone in ulcerative colitis: randomized, double-blind, placebo-controlled pilot study. *Dig Dis Sci.*, **2000**, 45(5):976-981.
- [116] Guarner F. What is the role of the enteric commensal flora in IBD? *Inflamm Bowel Dis.*, **2008**, 14Suppl 2:S83-S84.
- [117] Chassaing B, Darfeuille-Michaud A. The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. *Gastroenterology*, **2011**, 140:1720-1728.
- [118] Barcenilla A, Pryde SE, Martin JC, Duncan SH, Stewart CS, Henderson C, Flint HJ. Phylogenetic relationships of butyrate-producing bacteria from the human gut. *Appl Environ Microbiol.*, **2000**, 66:1654-1661.
- [119] Lee BJ, Bak YT. Irritable bowel syndrome, gut microbiota and probiotics. *J Neurogastroenterol Motil.*, **2011**, 17(3):252-66.
- [120] Wouters MM, Van Wanrooy S, Nguyen A, Dooley J, Aguilera-Lizarraga J, Van Brabant W, Garcia-Perez JE, Van Oudenhove L, Van Ranst M, Verhaegen J, Liston A, Boeckxstaens G. Psychological comorbidity increases the risk for postinfectious IBS partly by enhanced susceptibility to develop infectious gastroenteritis. *Gut*, **2016**, 65(8):1279-88.
- [121] Camilleri M. Physiological underpinnings of irritable bowel syndrome: neurohormonal mechanisms. *J Physiol.*, **2014**, 592(14):2967-80.
- [122] Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol.*, **2010**, 7(3):163-73.
- [123] Muscatello MR, Bruno A, Scimeca G, Pandolfo G, Zoccali RA. Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome. *World J Gastroenterol.*, **2014**, 20(24):7570-86.
- [124] Feng CC, Yan XJ, Chen X, Wang EM, Liu Q, Zhang LY, Chen J, Fang JY, Chen SL. Vagal anandamide signaling via cannabinoid receptor 1 contributes to luminal 5-HT modulation of visceral nociception in rats. *Pain*, **2014**, 155(8):1591-1604
- [125] Klooker TK, Liefeld KE, Van Den Wijngaard RM, Boeckxstaens GE. The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. *Neurogastroenterol Motil.*, **2011**, 23(1):30-5, e2.
- [126] Fichna J, Wood JT, Papanastasiou M, Vadel SK, Oprocha P, Sałaga M, Sobczak M, Mokrowiecka A, Cygankiewicz AI, Zakrzewski PK, Malecka-Panas E, Krajewska WM, Kościelniak P, Makriyannis A, Storr MA. Endocannabinoid and cannabinoid-like fatty acid amide levels correlate with pain-related symptoms in patients with IBS-D and IBS-C: a pilot study. *PLoS One*, **2013**, 8(12):e85073.
- [127] Fichna J, Sałaga M, Stuart J, Saur D, Sobczak M, Zatorski H, Timmermans JP, Bradshaw HB, Ahn K, Storr MA. Selective inhibition of FAAH produces anti-diarrheal and anti-nociceptive effect mediated by endocannabinoids and cannabinoid-like fatty acid amides. *Neurogastroenterol Motil.*, **2014**, 26(4):470-81.
- [128] Sakin YS, Dogrul A, Ilkaya F, Seyrek M, Ulas UH, Gulsen M, Bagci S. The effect of FAAH, MAGL, and Dual FAAH/MAGL inhibition on inflammatory and colorectal distension-induced visceral pain models in Rodents. *Neurogastroenterol Motil.*, **2015**, 27(7):936-44.
- [129] Finegold SM. State of the art; microbiology in health and disease. Intestinal bacterial flora in autism. *Anaerobe*, **2011**, 17(6):367-368.
- [130] Banasiewicz T, Kaczmarek E, Maik J, et al. Quality of life and the clinical symptoms at the patients with irritable bowel syndrome treated complementary with protected sodium butyrate. *Gastroenterol Prakt.*, **2011**, 5:45-53.
- [131] Kern JK, Geier DA, Sykes LK, Geier MR. Relevance of Neuroinflammation and Encephalitis in Autism. *Front Cell Neurosci.*, **2016**, 19:9:519.
- [132] Horvath K, Papadimitriou JC, Rabsztyrn A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr.*, **1999**, 135(5):559-563.
- [133] Buie T, Campbell DB, Fuchs GJ, III, et al. Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics.*, **2010**, 125(Suppl 1):S1-S18.
- [134] Bolte ER. Autism and Clostridium tetani. *Med Hypotheses*, **1998**, 51(2):133-44.
- [135] Williams BL, Hornig M, Buie T, Bauman ML, Cho Paik M, Wick I, Bennett A, Jabado O, Hirschberg DL, Lipkin WI. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. *PloS one*, **2011**, 6:e24585.
- [136] Kang DW, Park JG, Ilhan ZE, Wallstrom G, Labaer J, Adams JB, Krajmalnik-Brown R. Reduced incidence of prevotella and other fermenters in intestinal microflora of autistic children. *PloS one*, **2013**, 8:e68322.
- [137] Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Increased abundance of Sutterella spp. and Ruminococcus torques in feces of children with autism spectrum disorder. *Molecular autism*, **2013**, 4:42.
- [138] Brigandi SA, Shao H, Qian SY, Shen Y, Wu BL, Kang JX. Autistic children exhibit decreased levels of essential Fatty acids in red blood cells. *Int J Mol Sci.*, **2015**, 16(5):10061-76.
- [139] Siguel EN, Lerman RH. Prevalence of essential fatty acid deficiency in patients with chronic gastrointestinal disorders. *Metabolism*, **1996**, 45(1):12-23.
- [140] Kim J, Carlson ME, Kuchel GA, Newman JW, Watkins BA. Dietary DHA reduces downstream endocannabinoid and inflammatory gene expression and epididymal fat mass while improving aspects of glucose use in muscle in C57BL/6J mice. *Int J Obes (Lond.)*, **2016**, 40(1):129-37.
- [141] Mostafa GA, Al-Ayadhi LY. Reduced levels of plasma polyunsaturated fatty acids and serum carnitine in autistic children: relation to gastrointestinal manifestations. *Behav Brain Funct.*, **2015**, 11:4.
- [142] Schultz ST. Can autism be triggered by acetaminophen activation of the endocannabinoid system? *Acta Neurobiol Exp (Wars)*, **2010**, 70:227-231.
- [143] V. Trezza, L.J. Vanderschuren. Bidirectional cannabinoid modulation of social behavior in adolescent rats. *Psychopharmacology*, **2008**, 197 pp. 217-227
- [144] Haller J, Varga B, Ledent C, Barna I, Freund TF. Context-dependent effects of CB1 cannabinoid gene disruption on

- anxiety-like and social behaviour in mice. *Eur J Neurosci.*, **2004**, 19(7):1906-12.
- [145] CT Tart. Marijuana intoxication: common experiences. *Nature*, **1970**, 226:701-704.
- [146] B Chakrabarti, S Baron-Cohen. Variation in the human cannabinoid receptor CNR1 gene modulates gaze duration for happy faces. *Mol Autism.*, **2011**, 2:10.
- [147] Cassano T, Gaetani S, Macheda T, Laconca L, Romano A, Morgese MG, Cimmino CS, Chiarotti F, Bambico FR, Gobbi G, Cuomo V, Piomelli D. Evaluation of the emotional phenotype and serotonergic neurotransmission of fatty acid amide hydrolase-deficient mice. *Psychopharmacology (Berl)*, **2011**, 214(2):465-76.
- [148] D'Agostino G, Cristiano C, Lyons DJ, Citraro R, Russo E, Avagliano C, Russo R, Raso GM, Meli R, De Sarro G, Heisler LK, Calignano A. Peroxisome proliferator-activated receptor alpha plays a crucial role in behavioral repetition and cognitive flexibility in mice. *Mol Metab.*, **2015**, 4(7):528-36.
- [149] Kerr DM, Downey L, Conboy M, Finn DP, Roche M. Alterations in the endocannabinoid system in the rat valproic acid model of autism. *Behav Brain Res.*, **2013**, 249:124-32.
- [150] Macfabe DF. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders. *Microb Ecol Health Dis.*, **2012**, 23:10.3402/mehd.v23i0.19260.
- [151] MacFabe DF, Cain DP, Rodriguez-Capote K, Franklin AE, Hoffman JE, Boon F, Taylor AR, Kavaliers M, Ossenkopp KP. Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders. *Behav Brain Res.*, **2007**, 176(1):149-69.
- [152] Pons R, Andru AL, Checcarelli N, Vila MR, Engelstad K, Sue SM, *et al.* Mitochondrial DNA abnormalities and autistic spectrum disorders. *J Pediatr.*, **2004**, 144:81-5.
- [153] Kim KC, Kim P, Go HS, Choi CS, Park JH, Kim HJ, Jeon SJ, Dela Pena IC, Han SH, Cheong JH, Ryu JH, Shin CY. Male-specific alteration in excitatory post-synaptic development and social interaction in pre-natal valproic acid exposure model of autism spectrum disorder. *J Neurochem.*, **2013**, 124:832-843.
- [154] Kratsman N, Getselter D, Elliott E. Sodium butyrate attenuates social behaviour deficits and modifies the transcription of inhibitory/excitatory genes in the frontal cortex of an autism model. *Neuropharmacology*, **2016**, 102:136-45.
- [155] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. *Biol Psychiatry*, **2010**, 67(5):446-57.
- [156] Jokela M, Hamer M, Singh-Manoux A, Batty GD, Kivimäki M. Association of metabolically healthy obesity with depressive symptoms: pooled analysis of eight studies. *Mol Psychiatry*, **2014**, 19(8):910-4.
- [157] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. *Nat Rev Neurosci.*, **2006**, 7(2):137-51.
- [158] Fond G, Loundou A, Hamdani N, Boukouaci W, Dargel A, Oliveira J, Roger M, Tamouza R, Leboyer M, Boyer L. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*, **2014**, 264:651-660.
- [159] Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology*, **2012**, 37:1369-1378.
- [160] Neufeld KA, Kang N, Bienenstock J, Foster JA. Effects of intestinal microbiota on anxiety-like behavior. *Commun Integr Biol.*, **2011**, 4:492-494.
- [161] Barden N. Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. *J Psychiatry Neurosci.*, **2004**, 29(3):185-93.
- [162] Garcia-Ródenas CL, Bergonzelli GE, Nutten S, Schumann A, Cherbut C, Turini M, Ornstein K, Rochat F, Corthésy-Theulaz I. Nutritional approach to restore impaired intestinal barrier function and growth after neonatal stress in rats. *J Pediatr Gastroenterol Nutr.*, **2006**, 43(1):16-24.
- [163] Gareau MG, Jury J, MacQueen G, Sherman PM, Perdue MH. Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. *Gut*, **2007**, 56(11):1522-8.
- [164] Diaz Heijtz R, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, Hibberd ML, Forssberg H, Pettersson S. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A*, **2011**, 108(7):3047-52.
- [165] Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil*, **2011**, 23:255-264.
- [166] Phillips JGP. The treatment of melancholia by the lactic acid bacillus. *Br J Psychiatry*, **1910**, 56:422-431.
- [167] Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. *Neuroscience*, **2010**, 170(4):1179-88.
- [168] Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse *via* the vagus nerve. *Proc Natl Acad Sci U S A*, **2011**, 108(38):16050-5.
- [169] Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdj A, *et al.* Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. *Br J Nutr.*, **2011**, 105:755-764.
- [170] Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun.*, **2011**, 25(3):397-407.
- [171] Lopresti AL, Maker GL, Hood SD, Drummond PD. A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. *Prog Neuropsychopharmacol Biol Psychiatry*, **2014**, 48:102-11.
- [172] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*, **2006**, 444:1022-3.
- [173] Jeffery IB, O'Toole PW, Öhman L, Claesson MJ, Deane J, Quigley EM, Simrén M. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*, **2012**, 61(7):997-1006.
- [174] Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, Wilson R, Rudi K. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motil.*, **2014**, 26(8):1155-62.
- [175] Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, Wang W, Tang W, Tan Z, Shi J, Li L, Ruan B. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun.*, **2015**, 48:186-94.
- [176] Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut mi-

- crobiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A.*, **2008**, 105(43):16731-6.
- [177] Maes M, Kubera M, Leunis JC, Berk M, Geffard M, Bosmans E. In depression, bacterial translocation may drive inflammatory responses, oxidative and nitrosative stress (O&NS), and autoimmune responses directed against O&NS-damaged neopeptides. *Acta Psychiatr Scand.*, **2013**, 127(5):344-54.
- [178] Löwe B, Andresen V, Fraedrich K, Gappmayer K, Wegscheider K, Treszl A, Riegel B, Rose M, Lohse AW, Broicher W. Psychological outcome, fatigue, and quality of life after infection with shiga toxin-producing *Escherichia coli* O104. *Clin Gastroenterol Hepatol.*, **2014**, 12(11):1848-55.
- [179] Goehler LE, Park SM, Opitz N, Lyte M, Gaykema RP. *Campylobacter jejuni* infection increases anxiety-like behavior in the holeboard: possible anatomical substrates for viscerosensory modulation of exploratory behavior. *Brain Behav Immun.*, **2008**, 22(3):354-66.
- [180] Lyte M, Li W, Opitz N, Gaykema RP, Goehler LE. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia *Citrobacter rodentium*. *Physiol Behav.*, **2006**, 30;89(3):350-7.
- [181] Davey KJ, Cotter PD, O'Sullivan O, Crispie F, Dinan TG, Cryan JF, O'Mahony SM. Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. *Transl Psychiatry*, **2013**, 3:e309.
- [182] Vince AJ, McNeil NI, Wager JD, Wrong OM. The effect of lactulose, pectin, arabinogalactan and cellulose on the production of organic acids and metabolism of ammonia by intestinal bacteria in a faecal incubation system. *Br J Nutr.*, **1990**, 63(1):17-26.
- [183] Sun J, Wang F, Hong G, Pang M, Xu H, Li H, Tian F, Fang R, Yao Y, Liu J. Antidepressant-like effects of sodium butyrate and its possible mechanisms of action in mice exposed to chronic unpredictable mild stress. *Neurosci Lett.*, **2016**, 618:159-66.
- [184] Valvassori SS, Varela RB, Arent CO, Dal-Pont GC, Bobsin TS, Budni J, Reus GZ, Quevedo J. Sodium butyrate functions as an antidepressant and improves cognition with enhanced neurotrophic expression in models of maternal deprivation and chronic mild stress. *Curr Neurovasc Res.*, **2014**, 11(4):359-66.
- [185] Mamalakis G, Tornaritis M, Kafatos A. Depression and adipose essential polyunsaturated fatty acids. *PLEFA*, **2002**, 67(5):311-318.
- [186] Carrie I, Clement M, de Javel D, Frances H, Bourre JM. Phospholipid supplementation reverses behavioral and biochemical alterations induced by n-3 polyunsaturated fatty acid deficiency in mice. *J Lipid Res.*, **2000**, 41(3):473-480.
- [187] Ross BM. Omega-3 polyunsaturated fatty acids and anxiety disorders. *Prostaglandins Leukot Essent Fatty Acids*, **2009**, 81(5-6):309-12.
- [188] Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr.*, **2009**, 28(5):525-542.
- [189] Skouroliakou M, Konstantinou D, Koutri K, Kakavelaki C, Stathopoulou M, Antoniadi M, Xemelidis N, Kona V, Markantonis S. A double-blind, randomized clinical trial of the effect of omega-3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr.*, **2010**, 64(9):940-7.
- [190] Watkins BA, Kim J. The endocannabinoid system: directing eating behavior and macronutrient metabolism. *Front Psychol.*, **2015**, 5:1506.
- [191] Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr.*, **2006**, 83(6 Suppl):1505S-1519S.
- [192] Viveros MP, Marco EM, File SE. Endocannabinoid system and stress and anxiety responses. *Pharmacol Biochem Behav.*, **2005**, 81(2):331-42.
- [193] Scherma M, Medalie J, Fratta W, Vadivel SK, Makriyannis A, Piomelli D, Mikics E, Haller J, Yasar S, Tanda G, Goldberg SR. The endogenous cannabinoid anandamide has effects on motivation and anxiety that are revealed by fatty acid amide hydrolase (FAAH) inhibition. *Neuropharmacology*, **2008**, 54(1):129-40.
- [194] Lafenêtre P, Chaouloff F, Marsicano G. The endocannabinoid system in the processing of anxiety and fear and how CB1 receptors may modulate fear extinction. *Pharmacol Res.*, **2007**, 56(5):367-81.
- [195] Mato S, Rodriguez-Puertas R, González-Maeso J, Meana J, Sallés J & Pazos A. Receptores centrales para cannabinoides en cerebro humano postmortem: estudio radiométrico en la depresión mayor. 1a Reunión nacional sobre investigación en cannabinoides Madrid 2000.
- [196] Witkin JM, Tzavara ET, Davis RJ, Li X, Nomikos GG. A therapeutic role for cannabinoid CB1 receptor antagonists in major depressive disorders. *Trends Pharmacol Sci.*, **2005**, 26(12):609-17.
- [197] Pistis M, Ferraro L, Pira L, Flore G, Tanganelli S, Gessa GL, Devoto P. Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. *Brain Res.*, **2002**, 948(1-2):155-8.
- [198] Hill MN, Gorzalka BB. Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test. *Eur Neuropsychopharmacol.*, **2005**, 15(6):593-9.
- [199] Kathuria S, Gaetani S, Fegley D, Valiño F, Duranti A, Tonini A, Mor M, Tarzia G, La Rana G, Calignano A, Giustino A, Tattoli M, Palmery M, Cuomo V, Piomelli D. Modulation of anxiety through blockade of anandamide hydrolysis. *Nat Med.*, **2003**, 9(1):76-81.
- [200] Patel S, Hillard CJ. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. *J Pharmacol Exp Ther.*, **2006**, 318(1):304-11.
- [201] Aso E, Ozaita A, Valdizán EM, Ledent C, Pazos A, Maldonado R, Valverde O. BDNF impairment in the hippocampus is related to enhanced despair behavior in CB1 knockout mice. *J Neurochem.*, **2008**, 105(2):565-72.
- [202] Crupi R, Impellizzeri D, Bruschetta G, Cordaro M, Paterniti I, Siracusa R, Cuzzocrea S, Esposito E. Co-Ultramicronized Palmitoylethanolamide/Luteolin Promotes Neuronal Regeneration after Spinal Cord Injury. *Front Pharmacol.*, **2016**, 7:47.
- [203] Braak H., de Vos R. A., Bohl J., & Del Tredici K. Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett.*, **2006**, 396, 67-72.
- [204] Holmqvist S., Chutna O., Bousset L., Aldrin-Kirk P., Li W., Bjorklund T., Wang Z. Y., Roybon L., Melki R., & Li J. Y. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. *Acta Neuropathol.*, **2014**, 128, 805-820.
- [205] Devos D., Lebouvier T., Lardeux B., Biraud M., Rouaud T., Pouclet H., Coron E., Bruleydes Varannes S., Naveilhan P., Nguyen J. M., Neunlist M., & Derkinderen P.

- Colonic inflammation in Parkinson's disease. *Neurobiol Dis.*, **2013**, 50, 42-48.
- [206] Reijerkerk A, Kooij G, van der Pol SM, Khazen S, Dijkstra CD, de Vries HE. Diapedesis of monocytes is associated with MMP-mediated occludin disappearance in brain endothelial cells. *FASEB J*. **2006**, 20:2550-2.
- [207] Verslegers M, Lemmens K, Van Hove I, Moons L. Matrix metalloproteinase-2 and -9 as promising benefactors in development, plasticity and repair of the nervous system. *Prog Neurobiol.* **2013**, 105:69-78.
- [208] Svedin P, Hagberg H, Sävman K, Zhu C, Mallard C. Matrix metalloproteinase-9 gene knock-out protects the immature brain after cerebral hypoxia-ischemia. *J Neurosci.* **2007**, 27:1511-8.
- [209] Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, Mutlu E., Shannon KM, Colonic bacterial composition in Parkinson's disease, *Mov. Disord.*, **2015**, 30:1351-1360.
- [210] Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Bürmann J, Faßbender K, Schwierz A, Schäfer KH. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Parkinsonism Relat Disord.*, **2016**, pii: S1353-8020(16)30323-6.
- [211] Quigley EM. Microflora modulation of motility. *J Neurogastroenterol Motil.*, **2011**, 17(2):140-7
- [212] Cassani E, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, Barichella M. Use of probiotics for the treatment of constipation in Parkinson's disease patients. *Minerva Gastroenterol Dietol.*, **2011**, 57(2):117-21.
- [213] Heetun ZS, Quigley EM. Gastroparesis and Parkinson's disease: a systematic review. *Parkinsonism Relat Disord.*, **2012**, 18(5):433-40.
- [214] Hyland NP, Quigley EM, Brint E. Microbiota-host interactions in irritable bowel syndrome: epithelial barrier, immune regulation and brain-gut interactions. *World J Gastroenterol.*, **2014**, 20(27):8859-66.
- [215] Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic. *Microbes Infect.*, **1999**, 1(2):125-9.
- [216] Brenes M, Medina E, Romero C, De Castro A. Antimicrobial activity of olive oil. *Agro Food Industry Hi-Tech*, **2007**, 18, 6-8.
- [217] Lebouvier T, Neunlist M, Bruley des Varannes S, et al. Colonic biopsies to assess the neuropathology of Parkinson's disease, its relationship with symptoms. *PLoS One*, **2010**, 5:e12728.
- [218] Pouclet H, Lebouvier T, Coron E, et al. A comparison between rectal and colonic biopsies to detect Lewy pathology in Parkinson's disease. *Neurobiol Dis.*, **2012**, 45:305-9.
- [219] Singh RK, Rai D, Yadav D, Bhargava A, Balzarini J, De Clercq E. Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid. *Eur J Med Chem.*, **2010**, 45, 1078-1086.
- [220] Lai SW, Liao KF, Lin CL, Sung FC. Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan. *Eur J Epidemiol.*, **2014**, 29(1):57-62.
- [221] Marques SCF, Oliveira CR, Pereira CMF, Outeiro TF. Epigenetics in neurodegeneration: A new layer of complexity. *Prog Neuropsychopharmacol Biol Psychiatry*, **2011**, 35(2):348-55.
- [222] Abel T, Zukin RS. Epigenetic targets of HDAC inhibition in neurodegenerative and psychiatric disorders *Curr Opin Pharmacol*, **2008**, 8(1):57-64.
- [223] Konsoula Z, Barile FA. Epigenetic histone acetylation and deacetylation mechanisms in experimental models of neurodegenerative disorders. *J Pharmacol Toxicol Methods*, **2012**, 66(3):215-20
- [224] St Laurent R, O'Brien LM, Ahmad ST. Sodium butyrate improves locomotor impairment and early mortality in a rotenone-induced Drosophila model of Parkinson's disease. *Neuroscience*, **2013**, 246:382-90.
- [225] Rao JS, Ertley RN, Lee HJ, DeMar Jr JC, Arnold JT, Rapoport SI, Bazinet RP. N-3 polyunsaturated fatty acid deprivation in rats decreases frontal cortex BDNF via a p38 MAPK-dependent mechanism. *Mol Psychiatry*, **2007**, 12:36-46.
- [226] Bousquet M, Gibrat C, Saint-Pierre M, Julien C, Calon F, Cicchetti F. Modulation of brain-derived neurotrophic factor as a potential neuroprotective mechanism of action of omega-3 fatty acids in a parkinsonian animal model. *Prog Neuropsychopharmacol Biol Psychiatry*, **2009**, 33:1401-8.
- [227] Mahmoudi S, Samadi P, Gilbert F, Ouattara B, Morissette M, Gregoire L, Rouillard C, Di Paolo T, Lévesque D. Nur77 mRNA levels and L-Dopa-induced dyskinesias in MPTP monkeys treated with docosahexaenoic acid. *Neurobiol Dis.*, **2009**, 36:213-22.
- [228] More SV, Choi DK. Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. *Mol Neurodegener.*, **2015**, 10:17.
- [229] Esposito E, Impellizzeri D, Mazzone E, Paterniti I, Cuzzocrea S. Neuroprotective activities of palmitoylethanolamide in an animal model of Parkinson's disease. *PLoS One*, **2012**, 7(8):e41880.
- [230] Avagliano C, Russo R, De Caro C, Cristiano C, La Rana G, Piegari G, Paciello O, Citraro R, Russo E, De Sarro G, Meli R, Mattace Raso G, Calignano A. Palmitoylethanolamide protects mice against 6-OHDA-induced neurotoxicity and endoplasmic reticulum stress: *In vivo* and *in vitro* evidence. *Pharmacol Res.*, **2016**, 113(Pt A):276-289.
- [231] Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *J Alzheimers Dis.*, **2010**, 22, 483-492.
- [232] Aziz, Q., Doré, J., Emmanuel, A., Guarner, F., Quigley, E. M. Gut microbiota and gastrointestinal health: current concepts and future directions. *Neurogastroenterol. Motil.*, **2013**, 25, 4-15.
- [233] Hornig, M. The role of microbes and autoimmunity in the pathogenesis of neuropsychiatric illness. *Curr. Opin. Rheumatol.*, **2013**, 25, 488-795.
- [234] Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. *Asian Pac J Trop Biomed.*, **2011**, 1(2):154-60.
- [235] Mitew, S., Kirkcaldie, M. T., Dickson, T. C., and Vickers, J. C. Altered synapses and gliotransmission in Alzheimer's disease and AD model mice. *Neurobiol. Aging*, **2013**, 34, 2341-2351.
- [236] Paula-Lima, A. C., Brito-Moreira, J., and Ferreira, S. T. Deregulation of excitatory neurotransmission underlying synapse failure in Alzheimer's disease. *J. Neurochem.*, **2013**, 126, 191-202.
- [237] Carlino, D., De Vanna, M., and Tongiorgi, E. Is altered BDNF biosynthesis a general feature in patients with cognitive dysfunction? *Neuroscientist*, **2013**, 19, 345-353.
- [238] Lakhan, S. E., Caro, M., and Hadzimehalis, N. NMDA receptor activity in neuropsychiatric disorders. *Front. Psychiatry*, **2013**, 4, 52-55.
- [239] Brenner, S. R. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson's-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. *Med. Hypotheses*, **2013**, 80, 103-108.

- [240] He, F., and Balling, R. The role of regulatory T cells in neurodegenerative diseases. *WileyInterdiscip Rev. Syst. Biol. Med.*, **2013**, 5, 153-180.
- [241] Schwartz, K., and Boles, B. R. Microbial amyloid functions and interactions within the host. *Curr. Opin. Microbiol.*, **2013**, 16, 93-99.
- [242] Tran, L., and Greenwood-Van Meerveld, B. Age-associated remodeling of the intestinal epithelial barrier. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2013**, 68, 1045-1056.
- [243] Ball, M. J., Lukiw, W. J., Kammerman, E. M., and Hill, J. M. Intracerebral propagation of Alzheimer's disease: strengthening evidence of a herpes simplex virus etiology. *Alzheimers Dement.*, **2013**, 9, 169-175.
- [244] Douglas-Escobar, M., Elliott, E., and Neu, J. Effect of intestinal microbial ecology on the developing brain. *JAMA Pediatr.*, **2013**, 167, 374-379.
- [245] Ochoa-Reparaz J, Mielcarz DW, Begum-Haque S, Kasper LH. Gut, bugs, and brain: role of commensal bacteria in the control of central nervous system disease. *Annals of neurology*, **2011**, 69:240-247.
- [246] Berer K, Mues M, Koutrolos M, Rasbi ZA, Boziki M, Johner C, Wekerle H, Krishnamoorthy G. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature*, **2011**, 479:538-541.
- [247] Endocannabinoids and beta-amyloid-induced neurotoxicity *in vivo*: effect of pharmacological elevation of endocannabinoid levels. van der Stelt M, Mazzola C, Esposito G, Matias I, Petrosino S, De Filippis D, Micale V, Steardo L, Drago F, Iuvone T, Di Marzo V. *Cell Mol Life Sci.*, **2006**, 63(12):1410-24.
- [248] Fidaleo M, Fanelli F, Ceru MP, Moreno S. Neuroprotective properties of peroxisome proliferator-activated receptor alpha (PPAR α) and its lipid ligands. *Curr Med Chem.*, **2014**, 21:2803-2821
- [249] Zhang H, Gao Y, Qiao PF, Zhao FL, Yan Y. Fenofibrate reduces amyloidogenic processing of APP in APP/PS1 transgenic mice via PPAR- α /PI3-K pathway. *Int J Dev Neurosci.*, **2014**, 38:223-231.
- [250] D'Agostino G, Russo R, Avagliano C, Cristiano C, Meli R, Calignano A. Palmitoylethanolamide protects against the amyloid- β 25-35-induced learning and memory impairment in mice, an experimental model of Alzheimer disease. *Neuropsychopharmacology*. **2012**, 37(7):1784-92.
- [251] Root-Bernstein RS, Westall FC. Serotonin binding sites. II. Muramyl dipeptide binds to serotonin binding sites on myelin basic protein, LHRH, and MSH-ACTH 4-10. *Brain Res Bull.*, **1990**, 25(6):827-41.
- [252] Westall FC. Molecular mimicry revisited: Gut bacteria and multiple sclerosis. *J Clin Microbiol*, **2006**, 44, 2099-2104.
- [253] Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*, **2009**, 139(3):485-98.
- [254] Winer S, Paltser G, Chan Y, Tsui H, Engleman E, Winer D, Dosch HM. Obesity predisposes to Th17 bias. *Eur J Immunol.*, **2009**, 39(9):2629-35.
- [255] Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature*, **1998**, 394(6696):897-901.
- [256] La Cava A, Matarese G. The weight of leptin in immunity. *Nat Rev Immunol.*, **2004**, 4(5):371-379.
- [257] Frisullo G, Mirabella M, Angelucci F, Caggiula M, Morosetti R, Sancricca C, Patanella AK, Nociti V, Iorio R, Bianco A, Tomassini V, Pozzilli C, Tonali PA, Matarese G, Baccocchi AP. The effect of disease activity on leptin, leptin receptor and suppressor of cytokine signalling-3 expression in relapsing-remitting multiple sclerosis. *J Neuroimmunol.*, **2007**, 192(1-2):174-83.
- [258] Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, Langer-Gould A, Strober S, Cannella B, Allard J, Klonowski P, Austin A, Lad N, Kaminski N, Galli SJ, Oksenberg JR, Raine CS, Heller R, Steinman L. Genomicroarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat Med.*, **2002**, 8(5):500-8.
- [259] Miyake S, Kim S, Suda W, Oshima K, Nakamura M, Matsuoka T, Chihara N, Tomita A, Sato W, Kim SW, Morita H, Hattori M, Yamamura T. Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with a Striking Depletion of Species Belonging to Clostridia XIVa and IV Clusters. *PLoS One*, **2015**, 10(9):e0137429.
- [260] Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushima K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature*, **2013**, 500(7461):232-6.
- [261] Tao R., de Zoeten E.F., Ozkaynak E., Chen C., Wang L., Porrett P.M., Li B., Turka L.A., Olson E.N., Greene M.I., Wells A.D., Hancock W.W. Deacetylase inhibition promotes the generation and function of regulatory T cells. *Nat. Med.*, **2007**, 13:1299-1307.
- [262] Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, Liu H, Cross JR, Pfeffer K, Coffey PJ, Rudensky AY. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*, **2013**, 504(7480):451-5.
- [263] Haghikia A, Jörg S, Duscha A, Berg J, Manzel A, Waschbisch A, Hammer A, Lee DH, May C, Wilck N, Balogh A, Ostermann AI, Schebb NH, Akkad DA, Grohme DA, Kleinewietfeld M, Kempa S, Thöne J, Demir S, Müller DN, Gold R, Linker RA. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. *Immunity*, **2015**, 43(4):817-29.
- [264] Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*, **2013**, 504(7480):446-50.
- [265] Wang L, de Zoeten EF, Greene MI, Hancock WW. Immunomodulatory effects of deacetylase inhibitors: therapeutic targeting of FOXP3+ regulatory T cells. *Nat Rev Drug Discov.*, **2009**, 8(12):969-81.
- [266] Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut*, **1987**, 28(10):1221-1227.
- [267] Banati M, Csecei P, Koszegi E, Nielsen HH, Suto G, Bors L, Trauninger A, Csepány T, Rozsa C, Jakab G, Molnár T, Berthele A, Kalluri SR, Berki T, Illes Z. Antibody response against gastrointestinal antigens in demyelinating diseases of the central nervous system. *Eur J Neurol.*, **2013**, 20(11):1492-5.
- [268] Ezendam J, de Klerk A, Gremmer ER, van Loveren H. Effects of Bifidobacterium animalis administered during lactation on allergic and autoimmune responses in rodents. *Clinical and experimental immunology*, **2008**, 154:424-431.
- [269] Ezendam J, van Loveren H. Lactobacillus casei Shirota administered during lactation increases the duration of auto-

- immunity in rats and enhances lung inflammation in mice. *The British journal of nutrition*, **2008**, 99:83-90.
- [270] Maassen CB, Claassen E. Strain-dependent effects of probiotic lactobacilli on EAE autoimmunity. *Vaccine*, **2008**, 26:2056-2057.
- [271] Kobayashi T, Kato I, Nanno M, Shida K, Shibuya K, Matsuoka Y, Onoue M. Oral administration of probiotic bacteria, *Lactobacillus casei* and *Bifidobacterium breve*, does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis. *Immunopharmacology and immunotoxicology*, **2010**, 32:116-124.
- [272] Kobayashi T, Suzuki T, Kaji R, Serata M, Nagata T, Ando M, Iizuka R, Tsujibe S, Murakami J, Kiyoshima-Shibata J, Kato I, Nanno M, Shida K. Probiotic upregulation of peripheral IL-17 responses does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis mouse models. *Immunopharmacology and immunotoxicology*, **2012**, 34:423-433.
- [273] Kwon HK, Kim GC, Kim Y, Hwang W, Jash A, Sahoo A, Kim JE, Nam JH, Im SH. Amelioration of experimental autoimmune encephalomyelitis by probiotic mixture is mediated by a shift in the helper cell immune response. *Clinical immunology (Orlando, Fla)*, **2013**, 146:217-227.
- [274] Takata K, Kinoshita M, Okuno T, Moriya M, Kohda T, Honorat JA, Sugimoto T, Kumanogoh A, Kayama H, Takeda K, Sakoda S, Nakatsuji Y. The lactic acid bacterium *Pediococcus acidilactis* suppresses autoimmune encephalomyelitis by inducing IL-10-producing regulatory T cells. *PloS one*, **2011**, 6:e27644.
- [275] Rezende RM, Oliveira RP, Medeiros SR, Gomes-Santos AC, Alves AC, Loli FG, Guimaraes MA, Amaral SS, da Cunha AP, Weiner HL, Azevedo V, Miyoshi A, Faria AM. Hsp65-producing *Lactococcus lactis* prevents experimental autoimmune encephalomyelitis in mice by inducing CD4⁺LAP⁺ regulatory T cells. *Journal of autoimmunity*, **2013**, 40:45-57.
- [276] Piccio L, Stark JL, Cross AH. Chronic calorie restriction attenuates experimental autoimmune encephalomyelitis. *Journal of leukocyte biology*, **2008**, 84:940-948.
- [277] Kleinewietfeld M, Manzel A, Titze J, Kvakana H, Yosef N, Linker RA, Muller DN, Hafler DA. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*, **2013**, 496:518-522.
- [278] Baker D, Pryce G. The endocannabinoid system and multiple sclerosis. *Curr Pharm Des.*, **2008**, 14(23):2326-36. Review.

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