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Insight into role of microbiota-gut-brain peptides as a target for biotechnology innovations

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1. ABSTRACT

It has long been understood that some microorganisms may modify their hosts behavior in various systems. Nevertheless, it has only been in recent years that gut microbiota have opened new perspectives to appreciate their potential for affect complex neurological function in mammals. Efforts have demonstrated the ability of these gut-microbiota to impact neurological outcomes, suggested a prominent role for the gut microbiota in the gut-brain interactions, indicating that alterations in bidirectional microbiota-brain-gut may be involved in a number of brain disorders. Further, the identification of bioactive microbial signals, including their immune mediators, gut hormones and/or peptides, during health and disease situations, can serve as a tool for discovering novel activities that influence behavior and neurological function in hosts. Current review aims to provide an overview and shed some light on fundamental characteristics of the gut microbiota in modulating neurological disorders and consequently to draw up alternative strategies for using the gut microbiota or their active molecules as a therapeutic target for future diagnoses.

2. INTRODUCTION

To date, the exciting realization that gut microbiota play a pivotal role in nervous system activity through the creation of bioactive metabolites has increased the understanding of bidirectional brain-gut interactions (1). Given the considerable amount of 10^{14} microorganisms that reside in the adult gastrointestinal tract, growing evidences suggest that dysregulation in bidirectional microbiota-gut-brain communication is now rightly seen as a major interaction involved in the risk factors in pathogenesis, development of metabolic dysfunction and several brain disorders, including autism spectrum disorders (ASDs) (2), anxiety and depression (3). Assuming that gut microbiota represent an extensive reservoir of bioactive signaling molecules, including gut peptides, short-chain fatty acids and cytokines, which are responsible for providing the host with inaccessible metabolic capabilities a large and growing variety of studies are extrapolating the findings for human inflammatory processes, pain, brain function and behavior (4). Using this information, it is possible to design a wide variety of unique compounds that may be explored for the creation of novel bioinspired molecules with various biotechnological applications. Undoubtedly, the bioactive signaling molecules from gut microbiota seems to be important for medical devices. As an alternative, it is likely that the identification of gut peptides in several diseases could allow us to develop a commercial drug to treat mental illnesses and perhaps even correct them in the brain, leading to treatment by personalized medicine.

3. BIDIRECTIONAL INTERACTIONS OF THE GUT MICROBIOTA AND BRAIN FUNCTION

3.1. Gut-brain axis: Threshold between health and disease

Until recently it was thought that the gut is a long structure with the prime purpose of digestion, intake, absorption and excretion (5). Although these functions are essential to life, the gut seems to be much more complex than that. Indeed, gut is the only organ that exhibits an intrinsic nervous system with an ability to mediate reflexes in the complete absence of brain input (6). After a long period without progress in the field of brain research, the enteric nervous system in humans has received special attention since it contains around 500 million neurons outside the central nervous system,

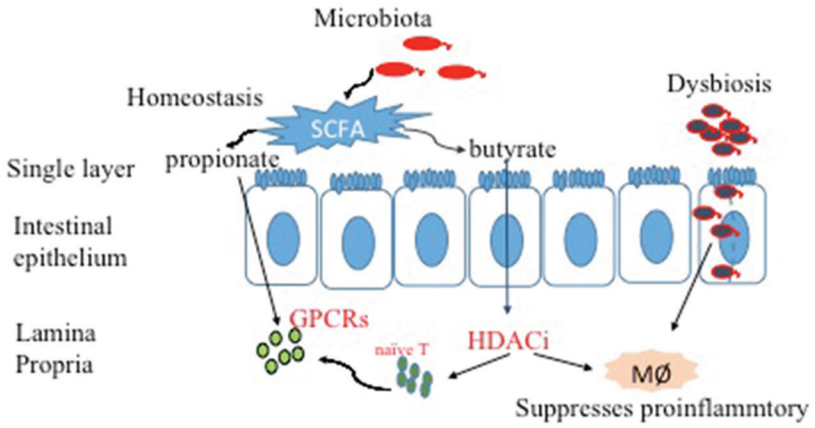

Figure 1. Schematic illustrating of know microbial metabolites has important roles in the development of intestinal immunity and control of the intestinal mucosa in states of health and disease. Legend: (SCFA) short-chain fatty acids; (GPCRs) GPCRs protein–coupled receptors, (HDACi) inhibitors histone deacetylase, (MØ) macrophages.

and so it might be likened to a second brain (7). Otherwise, there is still lots of learn about the largest and most functionally complex organ: the brain. Recently, research established that the brain is directly connected to the immune system (8). Recently it was found a network of lymph vessels, however, surrounds that central nervous system little is known about the mechanisms, which regulate the entry and exit of immune cells of the central nervous system. It is known that T cells are transported into and out of the meninges that cover the dural sinuses. The system expresses all the molecular features of lymphatic endothelial cells is capable of performing both fluid and immune cells from the cerebrospinal fluid, and are connected to the nodes (9). Besides this discovery revolutionizing our assumptions about neuroimmunology, this knowledge has a profound implication for a variety of neurological disorders, shedding new light on novel therapies for multiple sclerosis, psychiatric disturbances and Alzheimer's disease.

It is well established that brain development occurs in prenatal life and continues after birth. During life, many factors, including but not limited to gender, diet, genetics and lifestyle, may induce brain development. Furthermore, the brain-gut axis is generated during embryogenesis. Intensive research efforts to understand the bidirectional brain-gut interactions have confirmed that communication along this axis plays a vital role in the regulation of many important functions in health and pathological conditions (10). Generally, in health, it is responsible for the regulation of digestive processes and especially in the immune system. On the other hand, in pathological conditions, it can cause altered brain-gut interactions and consequently can exert a great risk of metabolic syndromes, neuro-developmental dysfunctions and cardiovascular disease in later life (11). The uses of molecular-based approach studies have elucidated host-microbe interactions in detail, it has long been believed that during their close co-evolutionary history it is estimated that there are more than 1,000 bacterial and archaeal species in the human gastrointestinal tract (12). In total, the core microbiota is dominated by 90% of Bacteroidetes and Firmicutes phylum (13, 14). Although several studies emphasize that the entire composition of the gut microbiota may widely varies widely in humans (13). In this context, the microorganisms seem to be essential for host health, including food processing, digestion of complex indigestible polysaccharides, synthesis of vitamins, and inhibition of pathogens.

Different group of the microorganism colonized the gut including archaea, protozoa, fungi, viruses and bacteria (14). In order, the commensal and pathogenic gut microbiota are separated in the gastrointestinal tract by three distinct compartments. Briefly: (I) intestinal epithelium is made up of a number of cell types with functions that range from cytokine secretion, IgA secretion, production of anti-microbial peptides and mucus production, (II) single layer of intestinal epithelial cells from the innate and adaptive immune cells, and (III) lamina propria in these sites naïve T cells are induced to become regulatory T cells or pro-inflammatory effector cells via specialized dendritic cells (15) (Figure 1). Due to the diverse functions and complicated nature of these intestinal compartments the regulation and maintenance of homeostasis is important to prevent dysregulated immune responses and development of inflammatory disease (16). As we can see, the host depends on its gut microbiota for a number of vital functions and thus the intestinal microbiota may contribute to health (17). For this reason, commensal bacteria are necessary for digestion mainly short-chain fatty acids as well as acetate, butyrate, and propionate. It is important to note that the SCFAs in the lumen of the colon, are readily absorbed

and constitute 6%-9% of our daily energy requirement in humans. Other function the of SCFA is the recognition by G protein–coupled receptors (GPCRs), GPCR-independent mechanisms have been shown to account for the anti-inflammatory effects of SCFA. Growing evidence suggests that the SCFA inhibitory activity of histone deacetylase (HDAC), what are responsible for the removal of the acetyl group from histones, could result in the ability to influence expression of genes encoded by DNA linked to the histone molecule (18).

More recently, dietary HDAC inhibitors have been shown to have a similar regulatory effect as pharmacological HDAC inhibitors without the possible side-effects (19) (Figure 1). There is therefore a significant and growing interest in the use of these as anti-inflammatory and chemo-preventive compounds. HDAC inhibitors in turn regulate the activity of HDACs, and have been widely used as therapeutics in psychiatry and neurology, in which some disorders associated with aberrant HDAC function (Alzheimer's disease) (20). HDAC inhibitors have also been shown to reduce colonic inflammation (21) inhibit cell proliferation, and stimulate apoptosis (22).

Functional studies using well-established germ free animals models together with "omics" technologies and new computacional tools suggests that the human microbiome plays a critical role in the development and maturation of key systems on maintenance of host health. In order to overcome those obstacles, wide efforts have been focused on the impact of probiotic agents, germ-free animals' models and pathogenic infections (23). Not only in the basic physiological processes or in the immune defense but there is a growing research field showed that the gut microbiome influence brain development and functions (24, 25). For this reason, researchers have become increasingly interested in the huge genetic diversity found in the human microbiome and most specifically in the microbial communities present in gut environment, because they are responsible for influence numerous aspects of metabolism, producing metabolic precursors to hormones and neurotransmitters or directly producing the active metabolites themselves. In fact, the human microbiome has been considered a reservoir of crucial metabolic capabilities (26).

The elucidation of the gut microbiota has generated a huge number of reports clearly demonstrating the complex bidirectional signaling between microbiota-gut-brain axis. Although, several experiments about the large-scale dynamics of the microbiome utilized distinct molecular tools, most of these technics were performed on rodents and humans from stool samples, where preliminary analysis have been proposed to better understand the evolution of healthy and disease interactions (23, 27-29). Additionally, the relationship between microbial gut and neurological conditions including the neurodegenerative disorder like autism spectrum disorders (ASDs), depression and schizophrenia has been observed (23, 27-29). Since the relations between the microbial gut and neurological conditions have been based only on preliminary observations there are a doubt in relation if the microbial community that inhabit the host gut are cause or consequences of health and disease states. In this context, one of the first analysis was previously been reported in 1833, where Beaumont and colleagues demonstrated that the gastric secretions could be associated with gut functions (30), after that, the bidirectional communication between the brain and the gut has been the focus of special attention in the scientific community. It seems that gut can influence brain function as well as the brain signals may influence the host gut activities (25). In this regard, there are diverse mechanisms of communication between the gastrointestinal tract (GI) and the central nervous system (CNS) including neural messages carried by vagus nerve, immune activity carried by cytokines and endocrine messages carried by gut hormones or by growth factors among others (31) (Figure 2). Although the particular mechanisms are unclear yet, the proposed mechanisms including signaling molecules based on cytokines, neurotransmitters, hormones or neuropeptides, that governing communication in both neural and/or humoral routes (32) (Figure 2).

The gut-brain axis interaction is responsible by link between emotional and cognitive axes of the brain with peripheral intestinal actions. This complex communication is combining to allow brain to influence the activities of intestinal functional effector cells and consequently the gut microbiota under this influence can be altered, being itself modulated by brain-gut interactions. This means that there are both direct and/or indirect pathways bidirectional interactions mediating the relationship between the GI and CNS. For example under stress, the brain could secretes corticosterone, adrenaline and noradrenaline that regulate the gut functions through the hypothalamus–pituitary–adrenal (HPA) axis, and thus contributing to homeostasis (33). It has previously been reported that mice with gut microbiota privation showed high concentration of hypothalamus stress hormone and conversely a reduced levels of brain-derived neurotrophic factor (34). Remarkably, this scenario can be changed by re-colonization with a specific bacterial species including *Bifidobacterium infantis* in adulthood, suggesting that active molecules from microbiota could play a role in brain development mediating neurological functions.

For this reason, studies based on functional analysis, mainly that the used germ-free (GF) animals, seems to be essential to determine the microbial role in shaping mood and behavior in the host (35). Moreover, high evidence of GI problems occurrence in people suffering mental disorders have been also observed (20). Although the direction of causality among

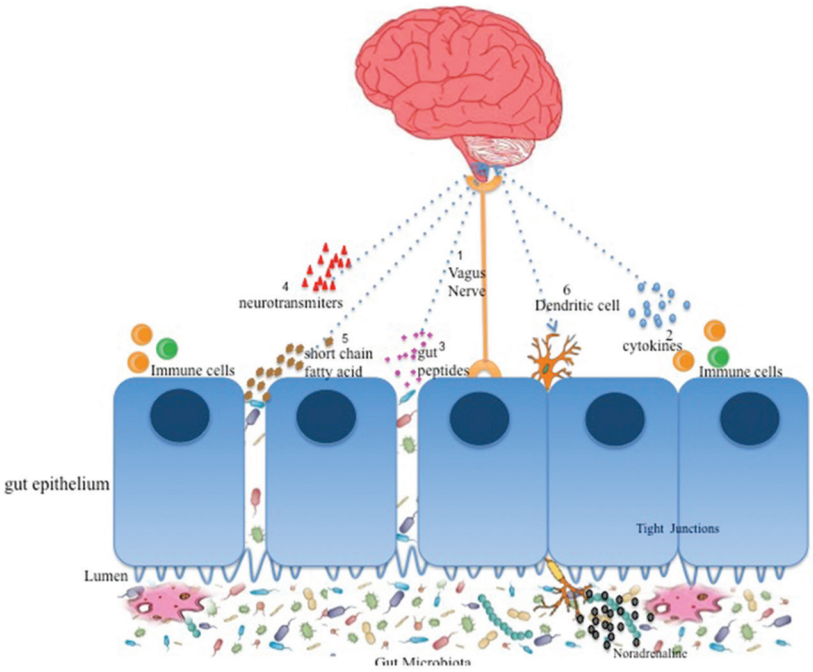

Figure 2. Schematic illustrating of know signaling pathways which gut microbiota can influence the brain functions. Although these communications remain still unclear multiple mechanisms including (1): Neurotransmission or other molecules derived from gut microbes along the vagus nerve. (2): The cytokine release by immune cells in the gut lumen. (3): The vagus nerve may be influenced by gut peptides released by gut microbiota. (4): Neurotransmitters produced as microbiota metabolites. (5): Short-chain fatty acids are taken up by the epithelial cells by diffusion normalizing gut permeability and (6) The transfer of molecules from the lumen to the gut tissue occurs via active transport by dendritic cells.

interconnected pathophysiological factors is still unclear, it is important to identify systemic microbiota changes and specific microorganism that can be targeted for diagnosis as well as for treatment (36). Probably there is an association temporal between neurodevelopmental in relation to the age beginning of mental disorders and degree of microbiota diversity during life. The microbiota dynamically changes throughout lifespan, establishing its symbiotic rapport with the host during infancy, adolescence and aging. The body becomes vulnerable to external stressors, which may result in mental disorders. Initial changes in intestinal microbiota during life can affect neurodevelopment and potentially lead to adverse outcomes of later mental health in life (32). Under these conditions, in case of children with Autism Spectral Disorders (ASD), the *Prevotella* genera are highly enriched in the fecal microbiota of different populations (37). Data set about of the autistic fecal samples was characterized by distinct and less diverse gut microbial compositions (36). Moreover, in such studies, it was observed that the gut microbiota of children with ASD in US differ even more than children living in other parts of the world, especially when compared to developing countries (37). In that case, autism patients seemed to be characterized by higher abundance of *Clostridium* (38), *Bacteroidetes* (39), *Desulfovibrio* (40), *Sutterella* spp. (41), *Roseburia* sp., *Roseburia inulinivorans*, *Caloramator*, *Sarcina*, *Alistipes* and *Akkermansia* (42), and by lower levels of *Firmicutes* (39), *Verrucomicrobia* (42), *Bifidobacterium* (42) and *Prevotella* (37).

It has long been believed that the higher diversity of gut bacteria is associated to a better microbial integrity and the ability to protect the human intestine from environmental stresses (36). Furthermore, the prebiotic utilization showed an increase of beneficial commensal bacteria and also decreased production of cortisol hormones, hormones related to stress in healthy patients. It is important to note that prebiotics administered in healthy individuals resulted in lower cortisol levels on waking and improved emotional state before the stress process. Interesting data demonstrate that depression could be associated with a chronic low-grade inflammatory response (43).

Studies in healthy subjects provide clear evidence between microbiota and emotional processes since leads to a decrease at cortisol hormones production. Furthermore, metagenome analyses were performed to determine the differences between the microbiota of healthy and depressed groups. The fecal samples from 55 volunteers from mental health clinic of the Innlandet Hospital in Norway were compared, where 37 depressed and 18 non-depressed samples (44). In this study a strong correlation between the intestinal microbiota and depression was found,

and bacteria from Lachnospiraceae family *Oscillibacter* and *Alistipes* genera were prevalent in depressed patients (29). The *Oscillibacter* type strain has valeric acid as its main metabolic end product, an analog of neurotransmitter gamma-aminobutyric acid (GABA) (45). The families Acidaminococcaceae, Enterobacteriaceae, Fusobacteriaceae, Porphyromonadaceae, and Rikenellaceae were significantly higher in the depressed samples. Conversely, the genera relatively more abundant, in the depressed samples were *Alistipes, Blautia, Clostridium, Lachnospiracea incertae sedis, Megamonas, Parabacteroides, Parasutterella, Phascolarctobacterium, Oscillibacter* and *Roseburia* (43). In contrast, the Enterobacteriaceae includes inflammogenic enteric pathogens such as *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri* and *Klebsielle pneumonia* (46), all of these Gram-negative bacteria are observed in normal gut microbiota.

However, increased permeability of the gut wall in depressed patients may allow invasive Gram-negative bacteria to translocate into mesenteric lymph nodes or the systemic circulation (44). Harmful substances produced by bacteria may compromise the intestine epithelial barrier integrity, allowing the entry of bacterial products or proteins with neuroactive properties into the circulation. Such mechanism could explain how microbiota modifications may lead to neuropsychiatric disease (47). A recent analysis marker of intestinal inflammation and bacterial translocation schizophrenia collectively indicates that structural damage to the GI barrier was present in patients with schizophrenia. High concentrations of phenylalanine metabolite have been found in the urine of individuals with autism and schizophrenia, which is likely due to multiple species of anaerobic bacteria in the *Clostridium* genus, it was proposed that the gut bacteria produced these metabolites (48). Nevertheless, the role of the microbiota in regulating brain development, immune function, and metabolism but the composition of the microbiota in individuals with schizophrenia has yet to be investigated (49).

Across the evolution, the gut microbiota has established important purposes including protective functions against pathogens, supplying essential nutrients, metabolizing compound with inaccessible nutrients such as complex polysaccharides, aiding in the fermentation of non-digestible dietary fiber (50). Meanwhile promoting the metabolism of peptides that consequently results in the recovery of metabolic energy for the host from gut anaerobic microbial community (51). Detailed studies of origins and establishment of the host-microbe interactions in the neonatal intestine has demonstrated that microbial composition could affect by vaginally or cesarean delivery, by food intake (breastfeeding or baby formula), aging, and illness or early exposure to antibiotics (52-54). Meanwhile, Aagaard and collaborators have evidenced that this colonization begins before delivery (43). This speculation of early placental microbiome colonization suggests that bacterial genetic diversity present in human placenta is more similar with the human oral microbiome than others tissues, including skin, vaginal or gut environments (55). It is important to note that the gut microbiota–host interactions are an emergent science area and intense research has resulted in the significant advances in our comprehending under their role in the human homeostasis. This knowledge has greatly facilitated the study of the human microbiome providing valuable information for clinical application leading to personalize medicine beginning at or even before birth.

3.2. Microbiota-gut-brain: Implication for gut hormones

Given the considerable amount of 10^{14} microorganisms that reside in the adult gastrointestinal tract (56), growing evidence suggests that when the balance between host and microbial communities are disrupted, gut microbial imbalances may have several effects in different behaviors including emotional and/or social behavior. Nevertheless, a wide variety of prevalent disorder such as inflammatory bowel disease, diabetes, anxiety mood disorder, multiple sclerosis, autism-spectrum disorders, and even obesity are gradually being linked to gut microbiota–host metabolic interactions (57). The communication of gut microbiota and brain may occur by a number of signaling molecules (Figure 2). These molecules have been identified as metabolites and neurotransmitter. They are released into the gut lumen and consequently can result in alterations in gastrointestinal secretion and motility. Among metabolites that are produced by gut microbiota are included SCFAs, GABA, tryptophan, serotonin, cytokines and catecholamines (58).

Current efforts have been made to elucidate the implication of gut hormones in the microbiota-gut-brain interactions. Although these implications awaits to be analyzed, it is important to note that the endocrine cells localized in the gut mucosa are closely with the gut microbiota, these direct contacts underscore an important role of the gut microbiota in the releasing multiple signals that may directly influenced the brain functions (4) including immune mediators, circulating cytokines and gut hormones.

Additionally, there is another category of signaling molecules that includes a huge variety of peptides. Since the 70's decade the presence of peptides in GI and brain has been detected, suggesting the first hypothesis that species of gut microbiota could be capable of producing small molecules such as possible bioactive neuropeptides (59). The neuropeptides are valuable mediators that play a pivotal role in the activity of the gastrointestinal microbiota and consequently in the bidirectional gut-brain communication. In relation the

Table 1. Candidate hormones involved in the gut-brain axis

Candidates hormones	Type	Purpose	Reference
Acetate	SCFAs	Energy source	(85)
Propionate	SCFAs	Signaling molecules	(69)
Butyrate	SCFAs	Host metabolism; histone acetylation	(86)
Serotonin	Neurotransmitters	Mood, emotion, cognition	(24)
Dopamine	Neurotransmitters	Reward (CNS)	(87)
Noradrenaline	Neurotransmitters	Motility/secretion (ENS)	(24)
GABA	Neurotransmitters	Inhibitory transmitter in the brain receptor	(88)
Tryptophan	Precursors to neuroactive	Precursor to serotonina (5-HT)	(79)
Cortisol	HPA hormones	Stress response	(67)
Peptide-1 PYY	Gut peptides	GI motility/secretion	(66)
Glucagon like peptide-1	Gut peptides	Reduce food intake	(66)
Cholecystokinin (CCK)	Gut peptides	Satiety peptides	(89)
Substance P	Gut peptides	Stimulation of bowel motility	(68)
Neuropeptide Y (NPY)	Gut peptides	Inhibition of gastric emptying	(66)
Somatostatin	Gut peptides	Represses the release of growth hormones and all known GI hormones	(89)
Ghrelin	Gut peptides	Regulation of food intake, energy homeostasis, gastric emptying, and acid secretion	(89)
Neurotensin	Gut peptides	Potentiation of insulin secretion, and trophic effects on the pancreas and gut mucosa	(89)

bidirectional communication between the gut and the brain, current efforts based on members of the neuropeptide Y (NPY), family of biologically active peptides, NPY, peptide YY (PYY) and pancreatic polypeptide (PP) has enabled great progress our knowledge about the operation of the gut–brain axis in health and disease.

Biologically active peptides could be produced by central and peripheral neurons alongside with endocrine cells in the GI. The neuropeptides, due activation of the vagus nerve (Figure 2) have been intimately associated to wide range of roles in health and disease, indicating at multiple levels of the gut brain axis interactions. By definition the neuropeptides share transduction mechanisms with gut hormones such as peptide-1 PYY, glucagon like peptide-1, cholecystokinin (CCK), substance P, neuropeptide Y (NPY), somatostatin and corticotropin (Table 1). It has long been understood that gut microbiota are able to produce more than 20 different gut hormones involved in the gut-brain axis (60).

Intensive efforts to understand the effects of neurotransmitters and neuromodulators synthetized by gut microbiota have been done (24). Members of the genera *Escherichia* and *Streptococcus* are capable of synthesize 5-hydroxytryptamine (5-HT). Additionally, some *Bacillus* and *Saccharomyces* generate dopamine and/or noradrenaline and members of the genera *Lactobacillus* and *Bifidobacterium* produce GABA (61, 62) (Table 1). Although the accumulating evidence available about the manipulation of the intestinal microbiota is mostly restricted to peptide level changes, such results has been showed that the release of peptide by *Lactobacillus rhamnosus* GG shows a positive effect in gastrointestinal disorders in infancy (63). It was also described by (64) that treatment with *Lactobacillus rhamnosus* conferred significant reduction of anxiety and depression-related behavior, while *Lactobacillus paracasei* has been found to attenuate antibiotic-induced visceral hypersensitivity rodent animal models (65).

In this context, a particular neurotransmitter that consisting of 36 amino acids denominated of neuropeptide Y (NPY) has the potential in the interaction between gut microbiota and function of host brain. This particular interaction is constructed across Y receptors throughout several neuronal pathways where this neuropeptide's involvement in controlling energy homeostasis, inflammatory processes or stress resilience (66). The NPY is found the most prevalent neuropeptides within the brain, and given the considerable abundance the NPY exhibit antimicrobial effect against *Enterococcus faecalis* and *Lactobacillus acidophilus* (67).

Analysis using a combination of *Bifidobacterium lactis*, *Lactobacillus rhamnosus* GG and addition to altering gut microbiota, showed that alteration in the gut microbiota structure can alter the gut hormone release thought an increased of that plasma levels concentrations of NPY and PYY in adult rats (68). These functional implications of the NPY were possible to be inferred due the NPY exerts its biological actions via 5 NPY receptor types (a human pseudogene), along the gut–brain signaling pathways (66). Certainly, efforts are devoted to increase our understanding of how the brain can also influenced the function and composition of the gut microbiota. Detailed studies have indicated that bacteria have the capacity to generate many neurotransmitters and neuromodulators (26), inclusive it has previously been reported that host cells (61) can recognize some quorum-sensing molecules. Advances in this field have been showed that hosts are metabolically dependent of a myriad of neurochemicals produced by microorganisms, providing the concept basic for a massive microbiota-gut-brain axis signaling system.

Assuming that gut microbiota represent an extensive reservoir of signaling molecules, which are responsible for provide the host inaccessible metabolic capabilities, there are a vast number of hormones candidate (Table 1) that might mediate changes in gastrointestinal motility and secretion as well as host metabolism. Among the several molecules that may modulate host physiology and behavior the SCFAs such as acetate, butyrate, and propionate are the manly candidate hormones of the gut microbiota, due they are the major products of the bacterial fermentation of complex carbohydrates and proteins in the gut (69). Detailed study has been showed that in the myenteric ganglia and enteroendocrine cells there are different types of SCFA receptors (70). Additionally, as mentioned, the GABA receptors are the major inhibitory neurotransmitter in the brain and results of studies in which was observed alteration on neuroreceptor expression were correlated with altered emotional behaviors (64, 71). In this regard, one of the plausible mechanism of SCFAs transport to the brain is that them are carried from monocarboxylate transporters at the blood-brain barrier, which the SCFAs can cross these barriers and enter the CNS (72, 73). Once in the brain, for example, the acetate, has been observed to alters the concentrations of neurotransmitters and increases anorectic gut neuropeptide expression (peptide YY and glucagon-like peptide-1), probably modulating physiological modifications in the hypothalamus (74). Moreover, a dietary fermentable fiber can bring health benefits by increasing SCFAs circulating levels in the colon (50).

Recently, evidence that the intraventricular administration of SCFAs (propionic acid) in the rodent model induces a variety of behavioral alterations of relevance to ASD was provided (67). Nevertheless, it is important to shed light, with further research, if the alterations in intestinal microbiota-derived SCFAs are reproduced at physiologically relevant concentrations in the brain of ASD individuals. In addition, the acetate, the dominant SCFAs, could be correlated with suppression of food intake being able to control the host appetite (75), as well as studies using well-established tests have demonstrated that acetate plays an important role in controlling inflammation and in combating pathogen invasion (76, 77). While the butyrate, which is metabolized in the gut epithelium, is characterized to exhibit an effect on histone acetylation, this important physiological function facilitates the access of DNA repair enzymes where was possible to observed an antidepressant effect in the rodent model brain (78). Thus impact in gut microbiota structure consequently alters the SCFA profile and its can be responsible by modifications in gut barrier integrity, inflammatory responses and energy metabolism. Collectively, the SCFAs play a pivotal role in the interaction between gut microbiota and the host (72, 73).

Beside the SCFAs, the gut microbiota yields some huge other gut hormones that are released into the bloodstream and act at distal site. Among them, tryptophan is recognized as a precursor to serotonin which in turn its a crucial neurotransmitter within both the enteric and central nervous systems (79). There is evidence through studies with GF animals' models that the peripheral availability of this specific amino acid in the host circulation is controlled by the gut microbiota (80). Although, it seems plausible, but not yet proved, that administration of the probiotic *Bifidobacterium infantis* normalized the plasma tryptophan concentrations in the host circulation when compared to colonized specific pathogen-free controls (81). This find is interesting because the availability of tryptophan in the circulation is critical for regulating host CNS 5-hydroxytryptamine, 5-HT synthesis. Because, the dysregulation of 5-HT is recently associated with irritable bowel syndrome (IBS) (82) and some cardiovascular disease (83) indicating that the serotonin biosynthesis from gut microbiota exerts impact in the gastrointestinal motility and hemostasis (84). Overall, studies indicate that vagus nerve appears to differentiate between non-pathogenic and potentially pathogenic bacteria, (33) and for this reason expansions in our understanding of the microbiota-gut-brain probably will come from analysis using well-established test of how distinct microbial stimuli activate the vagus and the nature of the signals transmitted to the brain. Due the growing evidence that the presence or absence of gut microbes influenced the brain, it is not surprising that scientists worldwide have turned their attention to this field. It is therefore interesting to contemplate that, the National Institute of Mental Health (NIMH), in September 2014, awarded four grants worth up to $1 million each to research on the gut microbiome's role in mental disorders.

4. PROSPECTS: OPPORTUNITIES TO TARGET THE GUT MICROBIOME

Knowledge about the influence of human intestinal microbiota in the genesis and/or maintenance of psychiatric disorders is still low, but it appears as one of the promising segments in area of gastro-biological psychiatry. Observed complex bidirectional signaling between microbiota-gut-brain axes, playing a key role in neuropsychiatric disorders genesis, where microbiota can affect the central nervous system through multiple pathways. Although the field is considered still recent, there is no doubt that microbiota-gut-brain connections provided us evidence to support the influence of gut bacteria on the neurological outcomes, suggested a prominent attractive therapeutic targets for nervous-system disorders as well as autism spectrum disorders (ASDs), anxiety, and depression. It seems plausible that the microbiota will take use of several information carriers from health and disease through measure of gut hormones, immune mediators or signaling molecules. It is important to note that neuropeptides are important transmitters in afferent, central and efferent pathways of the bidirectional gut-brain communication network. Given the considerable importance of this emerging field, it remains to be investigated if the bacterial gut itself expresses neuropetides receptors or instead the bacterial gut only release signaling molecules that are ligands at these receptors. Fortunately, modulation of gut microbiota studies including use of probiotics, antibiotics, germ-free animals and fecal microbiota transplants have provided valuable information for clinical application as well as offer unforeseen opportunities for drug development peptide. More importantly, maybe it seems plausible, the use of the gut microbiota as a therapeutic target to diagnose neurodevelopmental disorders, treat mental illnesses and perhaps even fix them in the brain leading the key to treatment to personalized medicine.

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