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Review

Microbiome – the Missing Link in the Gut-Brain Axis. The Focus on Gastrointestinal and Mental Health.

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Abstract:

The central nervous system (CNS) and the human gastrointestinal (GI) tract communicate through the gut-brain axis (GBA). Such communication is bi-directional and involves neuronal, endocrine and immunological mechanisms. The scientific data are mounting that gut microbiota is a source of a number of neuroactive and immunocompetent substances, which shape the structure and function of brain regions involved in control of emotions, physical activity and cognition. Most of GI maladies are associated with altered transmission within the GBA and influenced both by genetic and environmental factors. Current treatment protocols widely advocated for the treatment of GI disorders may positively or adversely affect the composition of intestinal microbiota with diverse impact on therapeutic outcome. The alterations of gut microbiota have been associated with mood and depressive disorders. and mental health is frequently altered in the course of many GI and non-GI ailments. Deregulation of the GBA may constitute a grip point for the development of diagnostic tools and personalized microbiota-based therapy. For example next generation sequencing (NGS) offers detailed analysis of microbiome footprints in patients with mental and GI disorders. Psychobiotics are new class of beneficial bacteria, with documented efficacy in the treatment of gut-brain axis disorders.

Keywords: gut brain axis, microbiota, functional gastrointestinal disorders

1. Introduction

Intestinal and gut microbiota represent one of the richest ecosystems in nature. Professor Rob Knight of the University of California, San Diego [1] reported that more than half of all cells in the human body were microorganisms, mainly bacteria, but also funghi and viruses. Until recently, the general belief was that intestinal microbes were mainly involved in the processes related to digestion.

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With the advent of new molecular techniques and bioinformatics, in-depth investigations have unraveled the intestinal microbiota as an active organ responsible for a number of physiological processes [2,3]. The topic of global microbial diversity is so crucial and important to human health and wellbeing, that scientists from Rutgers University-New Brunswick in recent issue of *Science* called for the creation of a global microbiota vault to protect long-term health of humanity [4].

The role of gut microbiome on human health is very diverse and implicated in the pathophysiology of various diseases. Its role in metabolism and obesity development has been clearly documented. Recently gut microbes have been implicated in the pathogenesis of cancer and more importantly microbial contribution has been described as of importance in cancer treatment. The pathogenesis and natural history of other frequent non-communicable diseases (NCuD) of gastrointestinal (GI) tract – e.g. non-alcoholic steatohepatitis (NASH), functional gastrointestinal disorders (FGIDs) and extraintestinal sites - e.g. cardiovascular disease (CVD) have been linked to GI microbes. Of importance, the alterations of gut microbiota have been associated with neurodegenerative diseases as well as mood disorders and depression. In fact mental health is frequently altered and associated with in many GI maladies.

2. Paradigm changer – Rome IV criteria and FGIDs

For years, FGIDs were viewed as purely functional disorders with no scientifically recognized mechanisms of action. According to the Rome IV criteria, the phenotype of FGIDs results from altered transmission of nerve and biochemical signals within the gut-brain-microbiota axis with mechanisms controlled by both genetic and environmental factors [5]. In fact, at least few studies conducted in patients suffering from functional dyspepsia (FD) and irritable bowel syndrome (IBS) found alterations in small bowel microbiota. Zhong et al. [6] showed that *Actinomyces, Atopobium, Leptotrichia, Prevotella* and *Veilonella* counts differed between FD and control patients. The finding was preceded by an observation that in FD patients gut barrier integrity is impaired and expressed as lowered transepithelial resistance, diminished expression of proteins of tight junctions, and finally elevated levels of mast cells, eosinophils and interstitial lymphocytes [7]. Significant reduction in the diversity of small bowel microbiota and the number of species was reported by Giamarellos-Bourboulis [8] and the elevated proportion of dilated junctions and intercellular distance between enetrocytes in their apical part by Martinez et al .[9]. The latter also found that the more tryptase

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mRNA expression, the more bowel movements and higher number in Bristol stool scale. Importantly, the degranulation of mast cells were found to positively affect the firing of visceral-nociceptive sensory neurons in IBS [10]. According to the new ROME IV criteria, the following factors stand behind the pathogenesis of FGIDs: i) motility disturbance, ii) visceral hypersensitivity, iii) altered mucosal and immune function, iv) altered gut microbiota, and v) altered central nervous system (CNS). All of them are also associated with the concept of microbiota-gut-brain axis. Psychiatric symptomatology occurs in at least 36.5% of FGIDs patients [11] as well as patients with obesity and metabolic disorders [12]. Recently Wilder-smith et al. [13] identified both GI and CNS symptom profiles secondary to sugar provocation tests, as various components of food play a role in FGIDs symptoms origin.

3. The emerging role of microbiota-gut-brain axis

Studies in animal models have proven that microbiota play an essential role in shaping the structure and function of the CNS [14]. Researchers using sophisticated strategies for manipulating the microbiome observed the consequences of these changes one the brain and behavior. For example, it has been proven that the thickness of the myelin sheath, the length of dendrites and the density of dendritic spines are controlled by microbiota [15,16]. A recent study by Lu et al. [17], conducted in humanized germ-free mice demonstrated that slow-growing mice presented skewed neuron and oligodendrocytes development, as well as evident signs of neuroinflammation. It was elegantly shown that social competences and repetitive behaviors are at least partly a reflection of the composition of intestinal bacteria, as well [18]. These dependencies result directly from the existence of a physical and functional connection between the human digestive tract and its CNS. This concept, called the gut-brain axis (GBA) - with the participation of neural and biochemical mechanisms can therefore be a stepping stone for new therapies for mental diseases.

The CNS utilizes neural and endocrine pathways to cooperate with the gut. The sympathetic part of the autonomic nervous system and the hypothalamus-pituitary-adrenal axis (HPA) co-modulate the secretion, motility and blood flow to affect intestinal permeability and may influence the biology of various GI disorders [19]. Gut neural signals are passed through the enteric nervous system (ENS) and vagus nerve [20]. Biochemical information is carried out by cytokines, chemokines, neurotransmitters and microvesicles [21] as well as direct by-products of gut microbiota metabolic

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activity, i.e. short chain fatty acids (SCFAs). Completing the circle, once entering the circulation, these molecules influence HPA and GBA axis [22]. Indeed, elevated stress response may impair psychosomatic well-being [23]. A pioneering study by Sudo et al. [24] demonstrated that gut microbiota is essential to proper stress hormones release and the restoration of intestinal ecosystem may reverse abnormal stress response. More recently *in vivo* experiment demonstrated that stress mediators and their receptors expression is lowered in pathogen-free animals [25].

4. How the gut/brain talks to the brain/gut

Intestinal microbiota as an integral part of the intestinal barrier controls the transport of antigens through the pericellular route to the *lamina propria* where the gut associated lymphoid tissue (GALT) is located [26]. The proper composition of intestinal microbiota is therefore an exponent of the proper intestinal barrier permeability which guarantees undisturbed flow of molecules through the pericellular route to blood vessels. Gut microbes permanently train GALT to create immunity against commensal bacteria and food antigens but also to provide defense against pathogenic microorganisms [27]. During dysbiosis, as a result of GALT activation, effector cells and inflammatory mediators disrupt gut barrier integrity and result in elevated intestinal permeability [28]. The interaction of the intestinal barrier elements thus provides a physiologically selective ability to absorb and secrete specific substances, while inhibiting the translocation of microorganisms and the penetration of toxins and other harmful antigens [29,30]. The effects of increased intestinal permeability may manifest locally – in the GI tract - as well as extra-intestinally. For example, the concentration of zonulin - a protein that activates the intracellular signaling pathway leading to TJ [31] modulation and a marker of intestinal permeability increases in people with inflammatory and autoimmune diseases [32]. Of importance, gut barrier in structure and function resembles blood brain barrier (BBB) [33]. Both barriers are composed of epithelial and endothelial cells laced with lymphatic vessels, macrophages and cellular tight junctions. It has already been proven that both IBS and pseudomembranous colitis [34,35] are consequences of microbiota and intestinal barrier dysfunctions, and these entities are frequently coexisting with depression [36,37].

5. Microbiota- gut-brain axis and susceptibility to neuropsychiatric disease and response to therapy

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The structure of intestinal microbiota is strongly influenced by diet and environmental stressors, predominantly drugs. Lately it was proved that these factors dominate over the impact of one's genotype to affect the gut flora composition [38]. Consequently, it has been recognized that it may be the optimal marker of susceptibility to express certain clinical phenotypes and thus the response to pharmacotherapy [39]. Indeed, since the concept of bidirectional signalling between the gut and the brain started to evolve, scientists all over the world have made attempts to discover microbial fingerprints in neurology and psychiatry. Emerging research suggested that gut-brain axis dysfunction may be involved in the aetiology of depression and anxiety, schizophrenia, addiction, as well as neurodevelopmental and neurodegenerative diseases and age-related cognitive decline [40–44]. Major microbiota-related alterations in particular neuropsychiatric conditions are summarized in table 1. Importantly, uninterrupted stress regulation is pivotal to mental health and altered stress response has been implicated in the origin of psychiatric diseases [42]. Moreover, numerous studies conducted in animals and humans have demonstrated that both acute and chronic stress interferes with intestinal barrier integrity and induce adverse alterations in intestinal microbiota composition. This has been confirmed in models of early-life [45] and prenatal stress models[46]. As concluded by Yarandi et al. [47] water and ion in the gut might be reduced and elevated respectively under stressful conditions which impairs the physical protection of the gut barrier against both pathogenic microorganisma and nociceptive molecules. Also HPA activation, in particular corticotropin-releasing factor (CRF) showed a causative role in gut integrity disruption [48]. Elevated intestinal permeability was also found to stress-induced hypersensitivity of the rectum in tested animals analysed by means of partial restraint stress [49].

6. Drug-microbiome interactions – still neglected problem in clinical medicine

Aside microbiota alterations playing at least partly the role in aetiology of neuropsychiatric diseases, of paradox the treatment of these conditions may adversely affect the composition of intestinal microbiota. In fact, multiple drugs were found to be involved in dysbiosis origin [50–52]. Certain pharmaceuticals utilized in neurology and psychiatry, predominantly antidepressants and antypsychotics, were historically characterized for being antibacterial agents. Evidence gathered mostly from animal studies but also in humans proves that second-generation antipsychotics, mainly

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161 olanzapine and risperidone, change the composition of intestinal bacteria towards bacterial species
162 promoting obesity. As demonstrated by a few authors, the administration of these psychotropic
163 drugs may increase *Firmicutes/Bacteroidetes* ratio [53–57], previously found to be a microbiota profile
164 of the obese [58]. Skewed intestinal microbiota following the psychotropic pharmacotherapy in
165 humans expressed as elevated phylogenetic diversity evaluated by means of PcoA of unweighted
166 UniFrac distances [59] and reduced Simpson diversity in females [60] have been reported. Chronic
167 use of risperidone in children elevated the levels of *Clostridium*, *Lactobacillus*, *Ralstonia*, and
168 *Eubacterium* but only in patients with significant gain in BMI [59]. Flowers et al. conducted gut
169 microbiota analyses in adult patients diagnosed with bipolar disorder and proved that psychotropic
170 treatment increased concentration of family *Lachnospiraceae* in the whole cohort of patients treated
171 with SGAs and a group of obese subjects. Also, lowered counts of *Akkermansia genera* was noticed in
172 the whole cohort of patients receiving treatment[60]. Yuan et al., aside lower level of *Clostridium*
173 *coccoides* and *Lactobacillus* spp. and elevated number of *Escherichia coli* in adult schizophrenia patients,
174 all since 6 week of risperidone treatment, demonstrated that these variations may have induced body
175 weight gain, increase in fasting plasma glucose, HOMA-IR and LDL cholesterol concentration[61] .
176 As far as metabolic disturbances are concerned, studies by Bahr et al. [59] and Flowers et al. [60]
177 microbiota alteration during psychotropic treatment may correlate with weight gain.
178
179 Table 1. Microbiota alteration in various psychiatric conditions
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The disease	Microbiota-related fingerprint	Reference
Depression	↑ *Bacteroidetes, Proteobacteria, Actinobacteria, Enterobacteriaceae, Alistipes* ↓*Faecalibacterium, Bifidobacterium, Lactobacillus*; serotonin, noradrenalin	[62,63]
Schizophrenia	↑*Corinobacteriaceae, Prevotella, Succinivibrio, Collinsella, Megasphaera, Klebsiella, Methanobrevibacter, Clostridium* ↓ *Blautia, Coprococcus, Roseburia,*	[64,65]
Bipolar disorder	↑ *Bacteroides, Actinobacteria, Coriobacteria* ↓ *Faecalibacterium, Roseburia, Alistipes,*	[66,67]
Parkinson's disease	↑ *Bacteroides, Roseburia*	[68]

	↓ *Blautia, Coprococcus, Dorea, Oscillospira, Akkermansia*	
Autism Spectrum Disorder	↑: *Streptococcus, Clostridiales, Comamonadaceae, Akkermansia, Rhosococcus, Oscillospira, Desulvibrio, Burkholderia, Collinsella, Corynebacterium, Dorea, and Lactobacillus;* acetic and propionic acid, p-cresol, Glutamate*;* ↓ *Firmicutes, Faecalibacterium, Ruminococcus, Proteobacteria, Fuscobacteria, Verrumicrobia, Bifidobacterium, Neisseria, Alistipes, Bilophila, Dialister, Parabacteroides,* and *Veillonella;* butyric acid	[69–72]
Attention-Deficit Hyperactivity Disorder	↑*Actinobacteria (Bifidobacterium* genus*)* ↓ *Firmicutes (Clostridiales* order*)*	[73]
Alzheimer's disease	↑*Blautia, Phascolarctobacterium, Gemella, E.coli, Shigella, Ps. aueruginosa* ↓*Ruminococcaceae, Turicibacteraceae, Peptostreptococcaceae, Clostridiaceae, Mogibacteriaceae,* and the genera *SMB53 (*family, *Clostridiaceae) Dialister, Clostridium, Turicibacter,* and cc115 (family *Erysipelotrichaceae)*	[74,75]
Multiple sclerosis	↑*Akkermansia muciniphila, Acinetobacter calcoaceticus* ↓*Parabacteroides distasonis*	[76]

Among antidepressants, the first drug introduced into clinical entities – isoproniasid - *via* producing isonicotinoyl radicals may interrupt normal cell cycle and inhibit the growth of bacterial cells **[77,78]**. Tricyclic antidepressants were found to possess antiplasmid activity and inhibit the growth of *E. coli*, *Yersinia enterocolitica* **[79]** and *Giardia lamblia* **[80]** by means of decreasing the activity of DNA gyrase **[81]**. Tricyclic antidepressants are active relative to Plasmodium falciparum **[82]** and *Leishmani*a spp.**[83]**. Selective serotonin re-uptake inhibitors may inhibit the growth of *Staphylococcus*, *Enterococcus* **[84–86]**, *Citrobacter* spp, *P. aeruginosa*, *K. pneumoniae*, *M. morganii*, *Clostridium perfringens* and *Clostridium difficile* **[84,87]**. Efflux pump inhibition may be involved in these properties **[88]** . Ketamine may control the growth of *Staphylococcus aureus, Staphylococcus epidermidis, Entecoccus faecalis, Streptococcus pyogenes* i *P. aeruginosa* oraz *Candida albicans* **[87,89]**.

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7. Modulation of microbiota-gut-brain axis as promising tool to manage gastrointestinal and an mental health.

Mood disorders and depression are associated also frequently with other GI conditions such as liver disease, inflammatory bowel disease (IBD), food intolerance, enteropathies (e.g. celiac disease) as well as cancer. All these conditions have been linked to the alterations of microbiota-gut-brain axis. Therefore modulation of microbiota-gut-brain pathways opens up new avenues to the management of chronic diseases [90–96].

The new treatment avenues could be addressed through the modulation of microbiota-gut-brain axis by means of prebiotic and probiotic administration. The World Gastroenterology Organisation (WGO) recently issued a Global Guideline on Prebiotics and Probiotics use by health care professionals [97]. Among probiotics, those are recommended in the management of disorders of gut-brain interaction, commonly known as FGIDs: *Lactobacillus plantarum* 299V, *Bifidobacterium infantis* 35624; *Bifidobacterium animalis* DN-173 010, and *Saccharomyces boullardi* CNCM I-745.

7.1. Psychobiotics – new kids on the block

Psychobiotics are new class of probiotics, which, when ingested, confer mental health benefits through interactions with microbiota-gut-brain axis [98]. This term should also include prebiotics, which favourably influence the growth of beneficial gut bacteria [99]. As mentioned above, psychobiotics and neurobiotics, capable of GBA and HPA modulation could be advocated in the management of patients endangered with iatrogenic complications associated with pharmacotherapy and polypharmacy. The use of these new probiotic compounds could be of great use in the daily management of stress and depression in FGIDs patients but also with other gastrointestinal and extraintestinal complaints associated with mental or mood alterations [100,101]. The data supporting their use are already strong and new studies shall create even more evidence to medical societies as well as govermental agencies to help them evaluate the microbiota-gut-brain axis therapeutics in the management of stress in contemporary medicine [102,103]. Table 2 includes examples of psychobiotic strains and their clinical applications [97,104,105]. As a few probiotic strains were found to be effective to counteract mood disorders and FGIDs, there is still limited data in individuals with ASD,

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223 Parkinson's and Alzheimer's diseases. There is an urgent need for a great investment in clinical trials
224 in these entities [106–110].
225
226 Table 2. Probiotics strains with documented efficacy in gut-brain axis disorders [97,104,105]

Condition	Strain
Anxiety and depression	*Lactobacillus fermentum* NS8 and NS9, *Lactobacillus casei* Shirota, *Lactobacillus gasseri* OLL2809, *Lactobacillus rhamnosus* JB-1, *Lactobacillus helveticus* Rosell -52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactococcus lactis* W19 and W58, *Bifidobacterium longum* Rosell-175, *Bifidobacterium longum* NCC3001, *Bifidobacterium longum* 1714, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52
Stress	*Lactobacillus casei* Shirota, *Lactobacillus helveticus* Rosell -52, *Lactobacillus plantarum* PS128, *Bifidobacterium longum* Rosell-175, *Lactobacillus gasseri* CP230*
FGIDs	*Lactobacillus plantarum 299v* (DSM 9843), *Escherichia coli* DSM17252, *Bifidobacterium animalis* DN-173 , *Saccharomyces boulardii* CNCM I-745 *Bifidobacterium infantis* 35624, *Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175, *Enterococcus faecium* NCIMB 30176

227 *para-psychobiotic-heat inactivated strain
228
229 8. Conclusions
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231 Recently a new United Nation's (UN) Commission on global mental health and sustainable
232 development has been published [111]. This Commission is in line with other UN General Assembly
233 and High-Level Meeting report and expand the issues of mental health from those with mental
234 disorders to whole populations. Accordingly the good mental health is viewed as a fundamental to
235 individual's well-being and overall health. Also the efforts are taken on the need of systemic and
236 global changes in order to align mental health across all medical specialties [112]. The data already
237 emerge that the microbiome-gut-brain axis function draws the potential to create personalized,
238 microbiota-based therapies in all disorders of brain and gut interaction.
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