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REVIEW

Gut microbiota in autism and mood disorders

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Stefano Fagiuoli, Giovanni Gasbarrini, Antonio Gasbarrini

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Antonio Gasbarrini, Catholic University, School of Medicine, 00168 Rome, Italy

Francesca Mangiola, Gianluca Ianiro, Francesco Franceschi, Antonio Gasbarrini, Department of Internal Medicine, Division of Internal Medicine, Gastroenterology and Liver Disease; "A. Gemelli" University Hospital, 00168 Rome, Italy

Stefano Fagiuoli, Gastroenterology and Transplant Hepatology, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

Giovanni Gasbarrini, "Ricerca in Medicina" ONLUS Foundation, 40121 Bologna, Italy

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Correspondence to: Antonio Gasbarrini, MD, Professor, Catholic University, School of Medicine, Largo F. Vito 1, 00168 Rome, Italy. agasbarrini@rm.unicatt.it
Telephone: +39-63-156018
Fax: +39-63-157249

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Abstract

The hypothesis of an important role of gut microbiota in the maintenance of physiological state into the gastrointestinal (GI) system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases. In the last few years, the importance of gut microbiota impairment in the etiopathogenesis of pathology such as autism, dementia and mood disorder, has been raised. The evidence of the inflammatory state alteration, highlighted in disorders such as schizophrenia, major depressive disorder and bipolar disorder, strongly recalls the microbiota alteration, highly suggesting an important role of the alteration of GI system also in neuropsychiatric disorders. Up to now, available evidences display that the impairment of gut microbiota plays a key role in the development of autism and mood disorders. The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results. A deeper assessment of the role of gut microbiota in the development of autism spectrum disorder (ASD), as well as the advancement of the therapeutic armamentarium for the modulation of gut microbiota is warranted for a better management of ASD and mood disorders.

Key words: Gut microbiota; Mood disorders; Autism; Depression; Gut microbiota modulation; Fecal microbiota transplantation

Core tip: Up to now, available evidences display that the impairment of gut microbiota plays a key role in the development of autism and mood disorders.

The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results, that suggest the microbiota modulation as a therapeutic approach for autism and mood disorders.

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INTRODUCTION

The gut microbiota, composed of thousands of different microbial species and more than 15000 kinds of bacteria for a weight equal to 1 kg, represents the first protection system of the gastrointestinal (GI) apparatus. The presence of the microbiota varies within the gastrointestinal tract, from few microorganisms in the stomach and small intestine, up to a concentration of approximately 1.012 bacteria in the colon, mostly represented by the *Firmicutes* and *Bacteriodetes phyla*[1,2]. Within the species that compose the microbiota, it's also possible to recognize the kingdom of *Archaea* and *eukaryotes*, and many viruses and *bacteriophages*[3,4]. Finally, there were several families of fungi, whose physiological role in the gastrointestinal system is still unclear.

The functions performed by the flora are manifold; in addition to the contribution to the establishment of the intestinal barrier, it promotes its maintenance, stimulating epithelial regeneration through the production of short chain fatty acids (SCFAs), leading to mucus production and exerting a trophic action on the mucous membrane[5].

The gut microbiota is involved in the maturation of the immune system: it stimulates innate immunity in the early years of life, leading to the maturation of the GALT, and acquired immunity, through stimulation of local and systemic immune responses[6]. Known, finally, is the role in the synthesis and metabolism of certain nutrients, hormones and vitamins, and clearance of drugs and toxic.

The human body, completely sterile at birth, is immediately in contact with a large amount of microbial communities, including the fecal, vaginal and skin microbiota of the mother. Subsequently, the composition of the flora undergoes changes, influenced by age, sex, state of immune maturation and by environmental factors.

The flora acquires its stability between 6 and 36 mo of life; in that period it's already possible to distinguish between a constant endogenous flora (core microbiota) and a still provisional one, highly sensitive to external stimuli[7,8].

In physiological conditions, the continuous stimulation of the immune system by the gut microbiota leads to a state of "low-grade physiological inflammation", which is a rapid and effective mechanism of defence against pathogens[9]. In addition, the flora exerts its protective role competitively, metabolizing those nutrients needed for pathogens survival, and producing molecules that inhibit the growth of such microbes[10].

Sonnenburg *et al*[11] has shown that the introduction of a compound of *Bacteroides thetaiotamicron* and *Eubacterium rectale* is able to induce the production of particular mucosal glycans, which may be metabolized exclusively by these bacterial species and not by pathogens, thus preventing their proliferation.

The hypothesis of an important role of gut microbiota in the maintenance of physiological state into the GI system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases.

GUT MICROBIOTA AND PSYCHIATRIC DISORDERS: A FOCUS ON AUTISM SPECTRUM DISORDER AND MOOD DISORDERS

Recent data show the strong correlation between dysbiosis and conditions such as obesity, allergies, autoimmune disorders, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and psychiatric disorders[12-16].

Due to these new evidences about the fundamental role of gut microbiota in the alteration of immune, neural, and endocrine pathways, the so-called "gut-brain axis" is acquiring new significance, even if the communication routes are not still defined[16-18].

At the beginning of the past century, first hypotheses aroused about the correlation between these two systems; probably the most practice evidence can be found in a work of an army surgeon, who noted the correlation between a patient's gut function and his mood, monitoring gastric secretions through a fistula in his stomach[13].

In the last few years, much research has been done in this direction, underlying the importance of dysbiosis in the etiopathogenesis of pathology such as autism, dementia and mood disorder. The evidence of the inflammatory state alteration, highlighted in disorders such as schizophrenia, major depressive disorder and bipolar disorder[19-23], strongly recalls the microbiota alteration and highly suggests an important role of the alteration of GI system also in neuropsychiatric disorders.

In particular, the dysbiosis and the consequent alteration of intestinal permeability lead respectively to the production and spread into the bloodstream of a potent pro-inflammatory endotoxine, namely

lipopolysaccharide (LPS). This small molecule has an important influence in the modulation of the central nervous system (CNS), increasing the activity of areas deputed to the emotionalism control such as amygdala[24]. It also lead to production of inflammatory cytokines that alter the physiological brain activity, modulating the neuropeptides synthesis[25].

Rhee *et al*[26] highlighted the importance of bidirectional connections between gut and brain that occurs in both healthy and diseased states focusing attention on enterochromaffin cells. The signals generated by the stimulation of these pathways due to intraluminal gut stimuli, running on nervous system, strongly modulate the brain activity, including pain perception, immune-response modulation, emotional control and many other homeostatic functions.

However, this influence is not unidirectional, but is a continuous communication: the CNS is able to change the composition of microbiota and to alter the equilibrium in the gut permeability, modulating motility and secretion through the activation of the hypothalamus pituitary-adrenal (HPA) axis, autonomic and neuroendocrine system with an immediate impact on gut microbiota[26,27]. In this regard O'Mahony *et al*[28], showed that early maternal separation in rats increased corticosterone systemic level, resulting in the alteration of immune response and fecal microbiota. Among several actors of this axis, important molecules have been studied such as vasoactive intestinal peptide (VIP) serotonin, melatonin, gamma-aminobutyric acid (GABA), catecholamines, histamine and acetylcholine[29-32], even if interaction way and acting routes of these molecules is not fully established.

Autism spectrum disorder (ASD) is a range of developmental neuro-behavioral disorders characterized by restricted and repetitive behaviour, impaired social interaction and communication; among these, autism represents the primary type of ASD[12,16].

The possible role of gut microorganism in the pathogenesis of such disorders has been widely deepened by several studies in animal models using different approaches: comparison of gut microbiota composition between affected samples an controls; observation of behaviour changes after administration of gut microbiota modulators in affected subjects rather than virulence factors in controls.

It has been demonstrated that a large amount of species under the *Clostridium* genus (10 times more) characterised the qualitative composition of fecal samples of autistic children[33-35]. Then, the composition of microbiota has been characterized, showing an imbalance of *Bacteroidetes* and *Firmicutes phyla,* with an increased presence of *Bacteroidetes* and other gut commensal such as *Bifidobacterium*, *Lactobacillus*, *Sutterella*, *Prevotella, Ruminococcus genera* and *Alcaligenaceae* family[36-40].

In the 1998, Bolte[41] observed that a significant percentage of individuals with autism had a history of extensive antibiotic use that significantly disrupt protective intestinal microbiota. On this basis, he outlined the possibility of a subacute, chronic tetanus infection of the intestinal tract that underlies the pathogenesis of symptoms in autism observed in some individuals.

Sandler *et al*[42] speculated that the alteration of autochthonous gut flora microbiota leads to the colonization by bacteria able to produce neurotoxins, contributing, at least in part, to their autistic symptomatology. On this basis, they treated a small group of children affected by regressive-onset autism with poor oral absorption-antibiotic. At the end of treatment, short-term improvement was noted using multiple pre- and post-therapy evaluations.

It has been also studied the consequences of gut barrier alteration contribute to ASD. A study carried on by Emanuele *et al*[43] showed that LPS serum levels were significantly higher in autistic patients compared to heath individuals and correlated with socialization scores in an inverse and independent manner. These evidences support a role of microbiota and, generally, of an alteration of the gut barrier in its integrity, in the genesis of ASD.

Nevertheless, the existence of a gastrointestinal dysbiosis as an actor in the ASD etiopathogenesis remains a controversial topic. In this regard, the study carried on by Gondalia *et al*[44] didn't showed clinically meaningful differences in the gut microbiota characterization between children affected by autism and their neurotypical siblings.

Depression is a major form of mood disorder characterized by depressed mood and/or recurrent thoughts of death and/or loss of interest or pleasure in life activities present over a period of at least 2 wk, accompanied by at least five additional symptoms that cause clinically significant impairment in social, work, or other important areas of functioning[13]. It results from neuro-psychiatric disturbance, immunological deregulation, genetic factors and environmental influences; nevertheless, a correlation with gut microbiota is emerging[45-47]; Through humoral route, microbiota can also influence CNS neurotransmission: it has been demonstrated that in GF mice anxiety-like behavior is reduced and modulated after restoration of the intestinal microbiota[48-50]. In particular, administration of *Lactobacillus* sp, *Bifidobacteria* sp, *L. helvetucys*, *B. longum*, *L. rhamnosus* and *Lactobacillus farciminis* in murine sample lay to an improvement of depression and anxiety symptoms[51].

In particular, an alteration of intestinal permeability, causing high level of LPS into the bloodstream, lead to the activation of inflammatory and immune response; these processes have been hypothesized as causative factors in psychiatric disorders such as depression[52,53]. Moreover, as support to this hypothesis, it has been demonstrated that the administration of LPS in healthy subject is associated to increase of pro-inflammatory cytokines and plasma norepinephrine, whit higher

Table 1 Alterations of gut microbiota found in autism and mood disorders

Disease	Microbiota alterations
Autism	Imbalance of *Bacteroidetes/Firmicutes* ratio Increase of *Bacteroidetes* phylum, *Bifidobacterium*, *Lactobacillus*, *Sutterella*, *Prevotella*, *Ruminococcus* genera, *Alcaligenaceae* family
Depression	Increase of *Alistipes* Negative correlation between *Faecalibacterium* abundance and severity of disease

depression rates[54].

Among clinical studies conducted, gut microbiota has been characterized, showing an overexpression of *Alistipes* in patients affected by depression disorder[47]. The overexpression of this bacterium, a genus in the phylum of *Bacteroidetes,* has been demonstrated in other disorders, such as chronic fatigue syndrome and in IBS[55,56]. This evidence lead to speculate about a gut microbiota alteration as common mechanism of action in the genesis of these disorders. Moreover, *Alistipes* has been linked to depression mood by generation of inflammatory molecules able to spread into the bloodstream in condition of altered intestinal permeability[47,51,57]. Another study, carried on by Jiang *et al*[58], confirmed the overexpression of *Alistipes* in psychiatric disorder and observed a negative correlation between expression of *Faecalibacterium* and the severity of depressive manifestations. An overview of main alterations of gut microbiota in autism and depression is available in Table 1.

POTENTIAL FOR THERAPEUTICS

Antibiotics

Antibiotics are the oldest drugs used in the management of diseases of the gastrointestinal tract. Their use, especially for infectious diseases, can achieve an alteration of the composition of the gut microbiota that can lead to significant side effects, not the least of antibiotic-associated diarrhoea due to *Clostridium difficile*[59]. Despite this, the antibiotic therapy is currently encouraged in the management of disorders such as IBS, IBD and SIBO in which the modulation of the intestinal flora leading to a net clinical improvement.

Currently, researches are being made in order to clarify the modulation of gut microbiota in the management of psychiatric disorder. It has been demonstrated that reduction of luminal LPS concentration due to antibiotic therapy lead to attenuation of HPA axis stress response and to increase of hypothalamic pro-inflammatory cytokines expression[60].

Desbonnet *et al*[61] have reproduced the effect of microbiota depletion on murine specimens: they administered them a combination of antibiotics and then assessed the effects from weaning onwards on adult cognitive, social and emotional behaviours and markers of gut-brain axis dysfunction in mice. They demonstrated that the reduction and diversity of the gut microbiota influences adult behaviours and key neuromodulators of the gut-brain axis: it reduced anxiety, induced cognitive deficits, altered the brain hormone expression and altered dynamics of the tryptophan metabolic pathway.

In support of these findings, some studies have successfully tested minocycline, second-generation tetracycline, as a treatment for depression, on the basis of its neuroprotective activities and regulation of pro-inflammatory agents[62,63].

In an other study, 11 children affected by ASD have been treated with vancomycin: after the planned 8 wk of treatment, communication and behaviour tests improvement has been observed[42].

Thus, it's possible to speculate that antibiotic treatment, through modulation of gut micriobiota, should be able to influences symptoms and expression of psychiatric disorders.

Probiotics

Probiotics are defined as live micro- organisms, preferentially of human origin, that upon ingestion in specific and sufficient numbers confer non-specific health benefits to the host[64].

Currently widely used in gastrointestinal system disorders, they exert their therapeutic effect by interacting on various levels in the reconstitution of the gastrointestinal barrier. In addition to a direct effect in the composition of Gut Microbiota, they are able to modulate the GI barrier through the increase of mucin production by globet cells, strengthening the tight junctions and thus the apical intercellular adhesion[65-68].

Probiotics are also involved in the modulation of the immune and inflammatory response by promoting the production of regulatory T cells. They may also regulate the Th1 response, by inhibition the production by the dendritic cells of pro-inflammatory cytokines such as IL-12, TNF-α and INF-α, or increase the expression of anti-inflammatory mediators such as IL-10 and β-TFGF[67].

Some studies tested probiotics as symptoms' modulator in disorders such as anxiety and depression. For example, Bravo *et al*[69] demonstrated that chronic administration of *L. rhamnosus* modulates GABA expression in CNS in rat, leading to a reduction in the hippocampus, amygdala, and locus coeruleus and to an increase in cortical regions. Furthermore, it reduces levels of corticosterone induced by stress and depression- and anxiety-related symptoms. In particular, these events didn't appear in vagotomised mice, indicating a fundamental role of vagal sings, and generally of neuronal transmission, in the gut-brain axis.

Similarly, combination of *L. helveticus* and *B. longum* appears to have an anxiolytic-like activity in

rats and, in addition to a diet formulation containing high levels of polyunsaturated fatty acids (PUFAs) n-3, to reduce post-MI depression[70,71].

Despite these impressive results, few clinical trials have been conducted with poor results. A double-blind, randomized clinical trial demonstrated that the daily administration of mixture of probiotics containing *L. helveticus* and *B. longum* for a month reduce psychological distress in healthy controls[70].

Rao *et al*[72] showed that the daily administration of *Lactobacillus casei* for two months improves anxiety related symptoms in subject affected by chronic fatigue syndrome[58].

However, the daily assumption of *L. casei* enriched milk didn't show significant effects in term of mood in healthy individuals while seemed to have potentially negative effects on recall memory[73].

Finally, Hsiao *et al*[74] showed that the oral administration of *Bacteroides fragilis*, improved some mood symptoms- such as anxiety, stereotypical behaviour and sensorimotor gating-in a maternal immune activation (MIA) animal model that is known to display features of ASD.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) represents the injection of filtrate stools from a healthy donor to a patient for the healing of a specific disease. Despite it had been sporadically used in ancient times, its first application in contemporary medicine in English literature, dates back 1958, when Ben Eiseman infused fecal material in four patients with pseudomembranous colitis[75]. After this pioneering experience, several attempts were reported over time for the treatment of *C. difficile* infection. To date, several systematic reviews and meta-analyses[76-78], as well as three randomized controlled trials[79-81], outlined the undoubted efficacy of FMT for the treatment of recurrent *C. difficile* infection. Some proof-of-concept randomized controlled trials investigated the efficacy of FMT in metabolic syndrome[82] and IBD, respectively[83,84]. In particular, it has been reported that FMT improved sexual function in patients with Crohn's diseases: this finding might get stronger the connection between of gut microbiota and depression/mood[85]. At present, despite the theoretical background for the application of FMT to autism is sound, to date it was experienced only in two autistic children, in whom it showed an amelioration of specific symptoms[86].

CONCLUSION

In the last few years, the importance of gut microbiota in the maintenance of physiological state into the GI system is supported by several studies that have shown a qualitative and quantitative alteration of the intestinal flora in a number of gastrointestinal and extra-gastrointestinal diseases. The application of gut microbiota modulators, such as probiotics, antibiotics, up to FMT, has been widely experimented as therapeutic instrument for GI diseases with exciting results.

Up to now, available evidences display that the impairment of gut microbiota plays a key role also in the development of autism and mood disorders, but the mechanism through which it does is not fully clear. The application of therapeutic modulators of gut microbiota to autism and mood disorders has been experienced only in experimental settings to date, with few but promising results.

A deeper assessment of the role of intestinal flora in the genesis and development of mood disorders and ASD is currently required; the knowledge advancement of the modulation of the intestinal flora not only about possible modalities but also about the timing in which this should be done, would lead to a new and safe therapeutic weapon in the management of ASD and mood disorders.

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