

The potentially important role of intestinal brain (gut microbiota) in neuropsychiatric health

Domina Petric^{1*}

¹Department of Clinical pharmacology and toxicology, University Hospital Center Split, Split 21 000, Croatia.

*Corresponding to: Domina Petric, Department of Clinical pharmacology and toxicology, University Hospital Center Split, Soltanska 1, Split 21 000, Croatia.
E-mail: domina.petric@gmail.com.

Introduction

Intestinal microbiota, consisting of trillions of bacteria, has important implications for health from the very beginning of human life. Neonatal gut is colonized by microbes immediately after birth. *Bifidobacterium* is an example of host-microbe co-evolution (symbiosis between bacteria and human) being genetically adapted to utilize specific glycans of human milk. Some studies have found a link between reduced diversity of intestinal microbiota or its aberrant composition on the one hand and the development of asthma, inflammatory bowel diseases and various metabolic disorders on the other hand [1]. Intestinal microbiota has also been studied in various motility disorders, as well as behavioral disorders, neurodegenerative diseases, cerebrovascular accidents and neuroimmune-mediated disorders, and using various animal models, immune-related, vagus nerve-associated and neuroactive compounds modulating pathways were identified along the gut-brain-axis (GBA). Some bacteria may produce and consume dopamine, norepinephrine, serotonin, and GABA (gamma-aminobutyric acid), meaning that manipulating gut microbiome may have significant implications on human neural system [2]. Here author summarizes available up-to-date evidence on potentially important implications of intestinal microbiota on neuropsychiatric health.

Intestinal microbiota and neuropsychiatric health

The bidirectional communication between intestinal microbiota (intestinal brain) and human brain (central nervous system, CNS) has been intensively studied [3]: afferent spinal and vagal sensory nerves carry out the visceral feedback from the intestines to the thoracic and upper lumbar spinal cord, as well as to the nucleus of the solitary tract, whilst preautonomous neural projections from cingulate and insular cortex, amygdala, bed nucleus of the stria terminalis and hypothalamus provide bidirectional control of the GBA [4]. Available evidence shows the association between intestinal microbiota and neural development, modulation of neurotransmission and behavior: *Candida*, *Escherichia*, *Enterococcus*, *Streptococcus* are serotonin producers [5]; *Bifidobacterium* and *Lactobacillus* generate GABA [5-7]; *Lactobacillus* is acetylcholine producer; *Bacillus* and *Serratia* produce dopamine; *Escherichia* and *Saccharomyces* can produce norepinephrine [8]. Although neurotransmitters produced in the intestine will hardly cross the blood-brain barrier (BBB), except for the GABA (because GABA transporters are present in the BBB), intestine-related neurotransmitters can act on the enteric nervous system and therefore, indirectly influence CNS [9, 10]. Some studies have shown that intestinal microbiota may play a role in anxiety and depression: there is a bidirectional communication between *intestinal brain* and CNS that influences stress reactivity [11] (stress may alter the healthy composition of intestinal microbiota and then the aberrant intestinal flora may enhance the stress experienced in the brain, resulting in anxiety and/or depression); several animal studies have shown a beneficial effect of *Lactobacillus* and *Bifidobacteria* on anxious-depressive behavioral patterns [12]. Results of a study showed that intestinal microbiome dysbiosis consisting of *Lactobacillus* depletion and augmentation of *Akkermansia* may contribute to the exacerbation of neuroinflammation [13]. Administration of antibiotics, especially broad-spectrum may cause intestinal dysbiosis,

which may be associated with psychiatric adverse effects, including anxiety and depression, as it has been shown in clinical reports [14], animal studies [15, 16] and clinical trials on penicillin and quinolones [17]. Results of a study showed that fluoxetine can attenuate stress-induced changes in the intestinal microbiota [18], which may be understood as an additional mechanism of action of this commonly prescribed antidepressant. Two meta-analyses showed a potentially mild therapeutic effect of probiotic treatment in patients that suffer from depressed mood [19, 20], with the note that multiple strains may be superior to a single strain of probiotic [20].

As available epidemiological data showed a significantly increased risk of developing schizophrenia after prenatal microbial infection [21], which may produce intestinal dysbiosis, and because it has been shown that patients suffering from schizophrenia have a higher incidence of intestinal barrier dysfunction and increased bacterial translocation [22], there is an increasing interest among scientist about the potential association of intestinal dysbiosis and psychosis, however available data still did not provide the answer whether dysbiosis can predispose someone to schizophrenia and what kind of alterations in the intestinal microbiota could precisely be associated with it. Nevertheless, there may be some clinical benefits of probiotics in alleviating both metabolic disturbances associated with anti-psychotic therapy and symptoms of schizophrenia [3], which may be inter-related, and therefore further research on this issue may be relevant.

Available evidence shows that gastrointestinal (GI) discomfort and GI-related symptoms are more prevalent in children suffering from autism spectrum disorder (ASD) when compared to healthy controls [23]. A correlation between the severity of GI symptoms and the severity of ASD-related symptoms, such as impairments in social interaction, deficits in verbal and non-verbal communication, and patterns of behavior with restricted, repetitive and stereotyped patterns, has been reported [24], as well as aggravation of neurobehavioral symptoms when GI ailments were present [23]. Although the link of ASD and intestinal dysbiosis is confirmed in preclinical studies [3], more clinical research is necessary before firm clinical recommendations regarding the use of prebiotics and probiotics (synbiotics) as an additional therapeutic option in ASD can be made.

The different patterns of intestinal flora has been observed in epilepsy. It has been reported that ketogenic diet resulted in a shift between *Proteobacteria* and *Bacteroidetes* towards the latter one, which was dominant in healthy individuals. This shift could be associated with the observed clinical improvement in infants suffering from drug-resistant epilepsy (DRE) [25]. In another study with children suffering from DRE, ketogenic diet was associated with significant clinical improvements as well as increased levels of *Bacteroidetes* [26], which may be inter-related.

There is some evidence implicating that bidirectional communication between *intestinal brain* and CNS may contribute to the pathogenesis of migraine [27], with gut dysbiosis-associated increased levels of proinflammatory cytokines being implicated in migraine pain initiation [28], however, there is no sufficient clinical evidence that could yield specific nutritional recommendations for migraine attacks at this point.

In Parkinson's disease (PD) it has been reported that the enrichment

of *Verrucomicrobiaceae*, *Bifidobacteriaceae*, *Ruminococcaceae*, *Christensenellaceae* and *Akkermansia*, and depletion of *Prevotellaceae*, *Faecalibacterium* and *Lachnospiraceae*, could be an important pathophysiological phenomenon [3]. Another important observation is that intestinal microbiota metabolizes levodopa (*Enterococcus faecalis* metabolizes levodopa to dopamine, *Eggerthella lenta* metabolizes dopamine to m-tyramine), which affects its bioavailability and efficacy [29], and therefore, further clinical research on personalized microbiota-based therapeutic options in PD may be of great value.

Conclusion

The well known expression, *I have a feeling in a gut*, today has a proven scientific background as the intestine-brain bidirectional communication makes it possible for emotional experiences originating in CNS, especially anxiety and depression, to be represented and registered as *intestinal feeling* (gastrointestinal distress). It has been shown that trillions of bacteria that live as commensals in human intestine are able to produce and consume neurotransmitters and therefore, interact with enteric nervous system and indirectly with CNS, and in the case of GABA production can even directly act on CNS, which literally makes them a *nervous system of the intestine*. Based on the available preclinical data intestinal dysbiosis has been proven to be a well-established pathophysiological phenomenon contributing to the development and/or severity of symptoms in anxiety, depression, psychosis (schizophrenia), autism, epilepsy, migraine, but the exact clinical implications are yet to be clarified. There have been some clinical evidence showing that microbiota-based therapeutic interventions could be helpful in reducing anxious-depressive behavioral patterns in humans with alleviation of distress experienced centrally in association with GI distress and discomfort, and such implications may also be relevant in ASD, psychosis (which is probably attributable to the attenuation of metabolic aberrations associated with chronic anti-psychotic therapy), epilepsy (ketogenic diet may be associated with the increase of *Bacteroidetes*, which may further be related to clinical improvements, especially in DRE), and even PD as the efficacy of levodopa treatment may be diminished in the presence of *Enterococcus faecalis* and *Eggerthella lenta*. It has also been shown that multiple strain probiotics could be more clinically effective in comparison to single strain probiotics, probably because the specific bacterial imprint for a specific neuropsychiatric condition is yet to be discovered. Identification of the exact bacterial imprint that should be administered for a specific disease or condition will help us design individual and precise microbiome-based therapeutic strategies, but so far we may conclude that there is a clear scientific association between healthy intestinal brain and healthy CNS.

References

- Milani C, Duranti S, Bottacini F, et al. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. *Microbiol Mol Biol Rev* 2017;81(4). <http://doi.org/10.1128/MMBR.00036-17>
- Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018;1693:128–33. <http://doi.org/10.1016/j.brainres.2018.03.015>
- Socała K, Doboszewska U, Szopa A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacol Res* 2021;172:105840. <http://doi.org/10.1016/j.phrs.2021.105840>
- O'Mahony SM, Hyland NP, Dinan TG, Cryan JF. Maternal separation as a model of brain-gut axis dysfunction. *Psychopharmacology (Berl)* 2010;214(1):71–88. <http://doi.org/10.1007/s00213-010-2010-9>
- Dinan TG, Stilling RM, Stanton C, Cryan JF. Collective unconscious: How gut microbes shape human behavior. *J Psychiatr Res* 2015;63:1–9. <http://doi.org/10.1016/j.jpsychires.2015.02.021>
- Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol Clin North Am* 2017;46(1):77–89. <http://doi.org/10.1016/j.gtc.2016.09.007>
- Reardon S. Gut-brain link grabs neuroscientists. *Nature* 2014;515(7526):175–77. <http://doi.org/10.1038/515175a>
- Lyte M. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. *Bioessays* 2011;33(8):574–81. <http://doi.org/10.1002/bies.201100024>
- De Caro C, Iannone LF, Citraro, R, et al. Can we 'seize' the gut microbiota to treat epilepsy? *Neurosci Biobehav Rev* 2019;107:750–64. <http://doi.org/10.1016/j.neubiorev.2019.10.002>
- Pascale A, Marchesi N, Govoni S, Barbieri A. Targeting the microbiota in pharmacology of psychiatric disorders. *Pharmacol Res* 2020;157:104856. <http://doi.org/10.1016/j.phrs.2020.104856>
- Foster JA, McVey Neufeld K-A. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci* 2013;36(5):305–12. <http://doi.org/10.1016/j.tins.2013.01.005>
- Luna RA, Foster JA. Gut brain axis: diet microbiota interactions and implications for modulation of anxiety and depression. *Curr Opin Biotechnol* 2015;32:35–41. <http://doi.org/10.1016/j.copbio.2014.10.007>
- Li N, Wang Q, Wang Y, et al. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice via the gut microbiota-inflammation-brain axis. *Stress* 2019;22(5):592–602. <http://doi.org/10.1080/10253890.2019.1617267>
- Sternbach H, State R. Antibiotics: Neuropsychiatric Effects and Psychotropic Interactions. *Harv Rev Psychiatry* 1997;5(4):214–26. <http://doi.org/10.3109/10673229709000304>
- Hoban AE, Moloney RD, Golubeva AV, et al. Behavioural and neurochemical consequences of chronic gut microbiota depletion during adulthood in the rat. *Neuroscience* 2016;339:463–77. <http://doi.org/10.1016/j.neuroscience.2016.10.003>
- Zhao Z, Wang B, Mu L, et al. Long-Term Exposure to Ceftriaxone Sodium Induces Alteration of Gut Microbiota Accompanied by Abnormal Behaviors in Mice. *Front Cell Infect Microbiol* 2020;10. <http://doi.org/10.3389/fcimb.2020.00258>
- Kaur K, Fayad R, Saxena A, et al. Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: a collaborative investigation by scientists and members of a social network. *J Community Support Oncol* 2016:54–65. <http://doi.org/10.12788/jcso.0167>
- Sun L, Zhang H, Cao Y, et al. Fluoxetine ameliorates dysbiosis in a depression model induced by chronic unpredicted mild stress in mice. *Int J Med Sci* 2019;16(9):1260–70. <http://doi.org/10.7150/ijms.37322>
- Ng QX, Peters C, Ho CYX, Lim DY, Yeo W-S. A meta-analysis of the use of probiotics to alleviate depressive symptoms. *J Affect Disord* 2018;228:13–19. <http://doi.org/10.1016/j.jad.2017.11.063>
- Goh KK, Liu Y-W, Kuo P-H, Chung Y-CE, Lu M-L, Chen C-H. Effect of probiotics on depressive symptoms: A meta-analysis of human studies. *Psychiatry Res* 2019;282:112568. <http://doi.org/10.1016/j.psychres.2019.112568>
- Brown AS, Derkits EJ. Prenatal Infection and Schizophrenia: A Review of Epidemiologic and Translational Studies. *Am J Psychiatry* 2010;167(3):261–80. <http://doi.org/10.1176/appi.ajp.2009.09030361>
- Golofast B, Vales K. The connection between microbiome and

- schizophrenia. *Neurosci Biobehav Rev* 2020;108:712–31. <http://doi.org/10.1016/j.neubiorev.2019.12.011>
23. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. *Pediatrics* 2014;133(5):872–83. <http://doi.org/10.1542/peds.2013-3995>
 24. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* 2011;11(1). <http://doi.org/10.1186/1471-230X-11-22>
 25. Xie G, Zhou Q, Qiu C-Z, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. *World J Gastroenterol* 2017;23(33):6164–71. <http://doi.org/10.3748/wjg.v23.i33.6164>
 26. Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. *Epilepsy Res* 2018;145:163–68. <http://doi.org/10.1016/j.epilepsyres.2018.06.015>
 27. Crawford J, Liu S, Tao F. Gut microbiota and migraine. *Neurobiol Pain* 2022;11:100090. <http://doi.org/10.1016/j.ynpai.2022.100090>
 28. Arzani M, Jahromi SR, Ghorbani Z, et al. Gut-brain Axis and migraine headache: a comprehensive review. *J Headache Pain* 2020;21(1). <http://doi.org/10.1186/s10194-020-1078-9>
 29. Lorente-Picón M, Laguna A. New Avenues for Parkinson's Disease Therapeutics: Disease-Modifying Strategies Based on the Gut Microbiota. *Biomolecules* 2021;11(3):433. <http://doi.org/10.3390/biom11030433>

Competing interests

The author declares no conflicts of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Abbreviations

GBA, gut-brain-axis ; GABA, gamma-aminobutyric acid; CNS , central nervous system ; BBB, blood-brain barrier ; GI, gastrointestinal; ASD, autism spectrum disorder; DRE, drug-resistant epilepsy ; PD, Parkinson's disease.

Citation

Petric D. The potentially important role of intestinal brain (gut microbiota) in neuropsychiatric health. *Microenviron Microecol Res.* 2023;5(1):1. doi: 10.53388/MMR2023001.

Executive editor: Na Liu.

Received: 30 January 2023, **Accepted:** 20 February 2023, **Available online:** 10 March 2023.

© 2023 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (<https://creativecommons.org/licenses/by/4.0/>).