Psychiatria Danubina, 2024; Vol. 36, Suppl. 2, pp 83-85
Conference paper

Original research

GUT MICROBIOTA AND MOOD DISORDERS: HOW BOTTOM-UP TECHNIQUES CAN IMPROVE MENTAL HEALTH

Alessandro Lepri
Department of Philosophy, Social and Human Sciences and Education, University of Perugia, Perugia, Italy

SUMMARY

The microbiome is dynamic and changes with early development, environmental factors such as diet and antibiotics, and in response to disease. Recently, its role in psychiatric disorders has gained interest. A new class of probiotics, psychobiotics, has emerged as a non-toxic intervention for psychiatric conditions. The relationship between gut microbial metabolism and mental health is gaining attention, with the gut microbiome playing a role in major depressive disorder. Understanding the microbiota offers new therapeutic opportunities for various medical conditions.

Key words: *mood disorders – microbiome - gut*

* * * * *

INTRODUCTION

The microbiome is dynamic and changes with early development, environmental factors such as diet and use of antibiotics and especially in response to disease (Lozupone et al. 2012). The most dramatic changes in composition occur in infancy and early childhood (Palmer et al. 2007). The intestinal microbiome of an infant is affected by gestational age (full term or premature), mode of delivery (vaginal birth or caesarean section), type of feed (breast milk or formula feeds), maternal nutritional status (overweight or under-nourished) and use of antibiotics (Meropol & Edwards 2015). The intestinal microbiota performs a range of important physiological functions, including food digestion, vitamin production, regulation of the immune system, and prevention of harmful pathogen colonization. Recently, there has been growing interest in the intestinal microbiota because it not only represents a crucial part of our digestive system and overall health but also plays a significant role in psychiatric disorders. Through the gut-brain axis, the intestinal bacterial flora communicates with the nervous system, utilizing various pathways such as the HPA axis (Hypothalamic-Pituitary-Adrenal axis), the vagus nerve, and the involvement of immune system molecules, namely cytokines involved in the inflammatory process. Regarding the neurologic pathway includes the vagus nerve, the enteric nervous system, and the activity of neurotransmitters within the gastrointestinal tract. Neurologic modulation of afferent sensory nerves directly produces molecules that can act as local neurotransmitters, such as gamma aminobutyric acid (GABA), serotonin, melatonin, histamine, and acetylcholine; this pathway also generates biologically active forms of catecholamines in the lumen of the gut (Mayer et al. 2014). In addition, the gut microbiome appears to be essential for normal gut intrinsic primary afferent neuron excitability (McVey Neufeld et al. 2017). Bacterial metabolites, most importantly short-chain fatty acids (SCFAs) produced by the bacterial fermentation of dietary carbohydrates, are decisive humoral influencers. SCFAs also regulate the release of gut peptides from enteroendocrine cells and have been shown to regulate the synthesis of gut-derived serotonin from enterochromaffin cells, both of which in turn affect gut–brain hormonal communication (Wang & Kasper 2014). The gut provides approximately 95% of total body serotonin, most of which exists in plasma. Although serotonin has intrinsic roles in the intestines and peripheral metabolism, it is capable of locally activating afferent nerve endings that are connected directly to the central nerve system (MacFabe 2013).

SUBJECTS AND METHODS

A new class of probiotics, known as psychobiotics or psychomicrobiotics, has emerged in the last decade and is being fervently embraced by many health care practitioners as a nontoxic intervention for various psychiatric conditions (Fond et al. 2015, Evrensel & Ceylan 2015). Several clinical trials have now documented effects, or lack thereof, of certain probiotics for depression and anxiety:

Gruenwald and colleagues (2002) in a pre- and postintervention assessment of adults suffering from stress or exhaustion (N = 34), find that a combination of L acidophilus, B bifidum and B longum improved subjects' general condition by 40.7% after 6 months.

Benton and colleagues (2007) in a randomized, double-blind trial (N = 124) find that a consumption of probiotic-containing yogurt had no effect on profile of mood states results, although there was improved self-reported mood of those whose mood was initially poor.

Messaoudi and colleagues (2011) find that inn subjects with reduced urinary free cortisol, consumption of the probiotics reduced anxiety and depression scores.

Steenbergen and colleagues (2015) tested the effects of a multistrain probiotic formula (Ecologic

BARRIER, Winclove, Amsterdam) in a randomized, triple-blind, placebo-controlled trial (N=40 nonsmoking healthy young adults, mean age 20 y). The formula contained specific strains of B bifidum, B lactis, L acidophilus, L brevis, L casei, L salivarius, and L lactis at a dose of 5 billion colony-forming units (CFUs) per day. Consumption of this multispecies probiotic significantly reduced overall cognitive reactivity to depression, in particular aggressive and ruminative thoughts, as assessed by the Leiden index of depression sensitivity. This study is noteworthy because many patients, especially in young people with no prior history of depression, would prefer non-pharmaceutical interventions as a first-line treatment (Messaoudi et al. 2015).

In a systematic review by Wallace and Milev (2017) of 10 clinical trials, most of the studies found positive results on measures of depressive symptoms.

RESULTS

Studies from animal models conducted by independent research groups have corroborated findings of gut dysbiosis and its relation to monoamine disruptions seen in clinical depression, connecting gut microbiota with mood (Diaz Heijtz et al. 2011, Anisman et al. 1999). Those with symptoms of depression frequently exhibit increased expression of proinflammatory cytokines, such as Interleukin-1 beta (IL-1β), Interleukin 6 (IL-6), tumor necrosis factor-α, as well as interferon gamma, and C-reactive protein (Howren et al. 2009, Owen et al. 2001, Maes et al. 1994). Depression is increasingly recognized as having an inflammatory component; indeed, anti-inflammatory drugs, such as Cyclooxygenase-2 inhibitors, have previously demonstrated efficacy in major depression (Muller et al. 2006).

DISCUSSION

The relationship between gut microbial metabolism and mental health is one of the most intriguing and controversial topics in microbiome research. (Valles-Colomer et al. 2019). Patients with anxiety and depression often have bowel symptoms. Until now, studies investigating a link between altered bowel habit and psychological illness have focused on patients with disturbed defecation presenting to gastroenterologists (Gorard et al. 1996) It is certainly plausible to assert the existence of a connection between the intestinal microbiome and a range of complex behaviors linked to the central nervous system, such as moods and emotions, appetite, and anxiety. The enteric nervous system, also known as the "second brain," is composed of a dense network of neurons with around one hundred million neurons present in the inner walls of the gastrointestinal tract and is in constant communication with the central nervous system. The role of the microbiome-gut-brain axis in psychopathology is gaining attention. While past efforts to study major depressive disorder (MDD) have focused on neurological, behavioral, and genetic factors underlying this condition, the role that the gut microbiome plays in the development of MDD has gained attention in recent years. Microbes can influence the functioning of the HPA and immune system and thus it is perhaps not so surprising that there could be a link between microbiota and depression (Dinan et al. 2013).

CONCLUSIONS

In conclusion, the intestinal microbiota represents an important therapeutic target in many diseases, and its understanding can provide new opportunities for the treatment and management of a wide range of medical conditions.The routes of communication between the microbiota and brain are slowly being unraveled, and include the vagus nerve, gut hormone signaling, the immune system, tryptophan metabolism, and microbial metabolites such as short chain fatty acids. The importance of the early life gut microbiota in shaping later health outcomes also is emerging.

Acknowledgements: *None.*

Conflict of interest: *None to declare.*

References

1. *Anisman H, Ravindran A, Griffiths J, et al.: Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical. Mol Psychiatry 1999; 4:182-188*
2. *Benton D, Williams C, Brown A: Impact of consuming a milk drink containing a probiotic on mood and cognition. Eur J Clin Nutr 2007; 61:355-361*
3. *Diaz Heijtz R, Wang S, Anuar F et al.: Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA 2011; 108:3047-3052*
4. *Dinan, Ted G, Cryan John F: Melancholic microbes: a link between gut microbiota and depression? Neurogastroenterology & Motility 2013; 25:713-719*
5. *Evrensel A, Ceylan ME: The gut-brain axis: The missing link in depression. Clin Psychopharmacol Neurosci 2015; 13:239-244*
6. *Fond G, Boukouaci W, Chevalier G, et al.: The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review. Pathol Biol (Paris) 2015; 63:35-42*
7. *Gorard DA, et al.: Intestinal transit in anxiety and depression. Gut 1996; 39:551-555*
8. *Gruenwald J, Graubaum HJ, Harde A: Effect of a probiotic multivitamin compound on stress and exhaustion. Adv Ther 2002; 19:141-150*
9. *Howren MB, Lamkin DM, Suls J: Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med 2009; 71:171-186*

10. *Hughes-Morley A, Young B, Waheed W, Small N, Bower P: Factors affecting recruitment into depression trials: Systematic review, meta-synthesis and conceptual framework. J Affect Disorders 2015; 172:274-290*
11. *Lozupone CA, Stombaugh JI, Gordon JI, et al.: Diversity, stability and resilience of the human gut microbiota. Nature 2012; 489:220–30*
12. *MacFabe D: Autism: Metabolism, mitochondria, and the microbiome. Glob Adv Health Med 2013; 2:52-66*
13. *Maes M, Scharpé S, Meltzer HY, et al.: Increased neopterin and interferongamma secretion and lower availability of l-tryptophan in major depression: further evidence for an immune response. Psychiatry Res 1994; 54:143-160*
14. *Mayer EA, Savidge T, Shulman RJ: Brain-gut microbiome interactions and functional bowel disorders. Gastroenterology 2014; 146:1500-1512*
15. *McVey Neufeld KA, Mao YK, Bienenstock J, Foster JA, Kunze WA: The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterol Motil 2013; 25:183-188*
16. *Meropol SB, Edwards A: Development of the infant intestinal microbiome: a bird's eye view of a complex process. Birth Defects Res C Embryo Today 2015; 105:228–39*
17. *Messaoudi M, Lalonde R, Violle N, et al.: Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. Br J Nutr 2011; 105:755-764*
18. *Müller N, Schwartz MJ, Douhe A, et al.: The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: Results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Molecular Psych 2006; 11:680-684*
19. *Owen BM, Eccleston D, Ferrier IN, et al.: Raised levels of plasma interleukin-1β in major and postviral depression. Acta Psychiatr Scand 2001; 103:226-228*
20. *Palmer C, Bik EM, Di Giulio DB, et al.: Development of the human infant intestinal microbiota. PLoS Biology 2007; 5:e177*
21. *Steenbergen L, Sellaro R, van Hemert S, et al.: A randomized controlled trial to test the effect of multi-species probiotics on cognitive reactivity to sad mood. Brain Behav Immun 2015; 48:258-264*
22. *Valles-Colomer M, et al.: The neuroactive potential of the human gut microbiota in quality of life and depression. Nature microbiology 2019; 4:623-632*
23. *Wallace CJK, Milev Rumans: A systematic review. Ann Gen Psychiatry 2017; 16:14*
24. *Wang Y, Kasper LH: The role of microbiome in central nervous system disorders. Brain Behav Immun 2014; 38:1-12*

Correspondence:
Alessandro Lepri, MA
Department of Philosophy, Social and Human Sciences and Education, University of Perugia
Perugia, Italy
E-mail: dott.alessandrolepri@gmail.com