ECRONICON OPEN ACCESS

EC PSYCHOLOGY AND PSYCHIATRY
Review Article

Gut Microbiota-Brain Axis and Mental Health

Hongxing Wang* and Yuping Wang

Department of Neurology, Xuanwu Hospital, Capital Medical University, China

***Corresponding Author:** Hongxing Wang, Department of Neurology, Xuanwu Hospital, Capital Medical University, No 45 Chuangchun Street, Xicheng District, Beijing 100053, China.

Received: April 05, 2016; **Published:** June 03, 2016

Abstract

Gut microbiota-brain axis is the two-way information communication network between intestinal microbiota and brain, whose composition includes gut microbes and their metabolite, intestinal tract, enteric nervous system and the sympathetic and parasympathetic branch of the autonomic nervous system, neural immune system, neuroendocrine system and central nervous system. Gut microbiota-brain axis has become one of the hotspots in the field of neuroscience. A growing body of evidences have revealed that gut microbes not only play an important role in maintaining normal healthy homeostasis, but also can affect the individual's mental health through inflammation, immune system, stress reaction and HPA axis. Dietary changes gut microbes associated with the risk of suffering from mood disorders. Probiotics supplementation not only plays an important role in the treatment of mental disease and regulating gut microbes, but also is a valuable therapy pathway for developing the new treatment methods to treat the brain disorder.

Keywords: *Gut microbiota; Inflammation; Immune system; Stress; HPA axis; Dietary; Antibiotics; Probiotics; Mental health*

Abbreviations

HPA: Hypothalamic Pituitary Adrenal; CRH: Corticotrophin Releasing Hormone; ACTH: Adreno Cortico-tropic Hormone

Introduction

Many studies have shown that gut microbiota affect brain's physiological, behavioral and cognitive functions [1-5], and its precise mechanism has not yet been fully understood, with possible 5 routes including the gut-brain's neuroanatomical pathway, neuroendocrine-HPA axis (hypothalamic-pituitary-adrenal axis, HPA axis) approach, gut immune system approach, path of many neurotransmitters and neural regulators synthesized by gut bacteria and path by intestinal mucosal barrier and blood-brain barrier [6] (see Figure 1). Both clinical and prenatal research show that the gut microbiota plays an important role in maintaining homeostasis of normal health, and if the gut microbiota is damaged, there will be high risk factors for suffering from mental illness and other central nervous system disorders [7].

Gut Microbiota

In human gut, it is estimated to have about 100 trillion "symbiotic" bacteria [7], the total number of cells is at least 10 times that of human cells, over 100 varieties, and the gene is 150 times that of human genome [8,9]. More than 99% of microbiotia are anaerobic bacteria in gut, the rest are fungi, protozoa, archaea, and other microbiotia. Gut microbiome refers to bacterial colonies and their genes in the gut [10], which also includes human host evolving archaea, protozoa, fungi and viruses. Gut microbiome are mainly determined by 2 major bacterial colonies of firmicutes (about 51%) and bacteroidetes (about 48%), and proteobacteria, actinomyces, fusobacterium and verrucomicrobia are relatively small in number [11].

Human and gut microbiota are of "mutually beneficial and symbiotic relationship" [12]. The human body provides habitat and nutrition for gut microbiota, and gut microbiota play an important function of human body via immune system, intestinal system, endocrine

system, and nervous system, such as food processing, digesting complex and difficult-to-digest polysaccharides, synthetic vitamins and inhibition of pathogen.

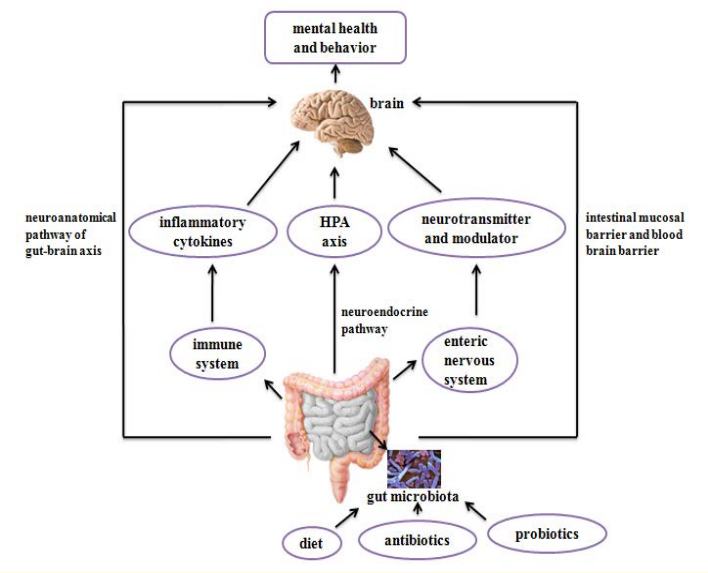

Figure 1: *Gut microbiota-brain axis.*

Gut Microbiota-Brain Axis

Gut microbiota-brain axis refers to two-way information flow network between gut microbiotia and brain, with its components including gut microbiota and their metabolic products, enteric nervous system, sympathetic and parasympathetic branch within autonomic nervous system, neural immune system, neuroendocrine system and central nervous system [6].

Through this network, the brain affects gut movement, sensory and secretion function. On the contrary, viscera information from the gut also affects brain function. For example, incoming and outgoing branches of vagus nerve allow information to transfer in and out of gut. Activation of the vagus nerve has anti-inflammatory effect. Positive effects of many gut microbiota and probiotics on brain function are dependent on the activity of vagus nerve. But other independent mechanism also plays a role.

Gut, inflammation and immune system

Development of gut immune system depends on gut microbiota [13,14]. Segmented filamentous bacterium in gut can restore the full functions of gut B and T lymphocytes [15-17]. Bacteria communicate with the host through a variety of ways, and the receptor-TLRs of host cell plays a key role in this communication between bacteria and host [18]. These receptors are the first step to produce cytokine reaction and is also widely distributed on neurons [19] So, intestinal epithelial cells can transport microbial composition or metabolites into inner environment, and the nervous system also interacts with these bacterial and viral components [20]. The balance of gut microbiota may change the regulation of inflammatory response and this mechanism may also get involved in the regulation of emotion and behavior.

Gut, stress reaction and HPA axis

Depressive disorder involves inflammation [26,27] and HPA [27,28]. Gut microbiota affect the hypothalamus function via pro-inflammatory factors and anti-inflammatory factors [29]. Among them, pro-inflammatory factors stimulate release of corticotrophin releasing hormone (CRH) which is the main polypeptide regulator of HPA axis [30]. HPA stimulates the adrenal glands to release adreno-cortico-

tropic-hormone (ACTH), and ACTH is necessary component to the normal stress. However, over-expression of CRH promotes stress over-reaction. The system disorder is associated with depression and anxiety [31]. The germ-free mice study indicates that the symbiotic microbiota plays a key role of healthy and balanced immune system [32].

Damage of gut microbiota stimulates HPA activities to release stress hormones, and exogenous stress source direct stimulates HPA. At the same time, HPA also has devastating effects on gut microbiome. Stress leads to changes of intestinal motility and secretion function, which have negative effect on regeneration ability of intestinal mucosa and gut microbiota [33]. Stress reaction releases neuro-transmitters and pro-inflammatory factors, and these neuro-transmitters and pro-inflammatory factors affect intestinal physiology.

Influence of diet on gut microbiota

Gut microbiome is a dynamic entity, which is influenced by factors such as gene, diet, metabolites, age, and treatment with antibiotics [7]. Among above the influencing factors, gene, geography and age can't be changed, but other factors can be artificially adjusted so as to change the balance of gut microbiota.

Many studies have shown that diet is associated with the risk of suffering from affective disorder [34,35]. Imbalance of gut microbiota is also known as intestinal imbalance. Imbalance of gut microbiota is a biological pathway for regulating the relationship between diet and risk of suffering from affective disorder. Diet with high fat and high level of refined sugar are an important factor of gut imbalance [36]. Compared with diet with high fat and high level of refined sugar, diet rich in complex carbohydrates can reduce the variety of gut pathogenic bacteria [37], and complex carbohydrates also increases the variety of beneficial bacteria. Too many dietary fibers help to increase production of short chain fatty acid to prevent the growth of potentially pathogenic bacteria. Refined sugar can also mediate overgrowth of bacteria.

Influence of antibiotics on gut microbiota

Clinically, people use antibiotics to change the gut colonies to improve brain function of certain diseases. For example, to remove metabolltes of gut colonies by regulating intestinal bacteria with application of antibiotics to improve the brain function of hepatic encephalopathy [38,39]. However, rarely to evaluate the role of antibiotics in gut microbiota-the brain axis [4].

In addition, antibiotic treatment can also affect gut balance by eliminating intestinal beneficial bacteria. Probiotics in food such as yogurt, kefir of Russia, kimchi, sauerkraut, and miso etc. can regulate the symbiosis of gut microbiota again, and make gut microbiome rebalancing.

Effect of probiotics on treating mental disease

Probiotics are not only good for treatment of antibiotic, but also can prevent and offset attack and damage by high fat and/or high protein diet on gut microbiota. So food containing probiotics should be introduced into food guide as well [40].

Probiotic supplementary treatment not only plays an important role in the treatment of mental diseases and regulating gut microbiota, but also is valuable treatment way of treating brain disorder [41,42]. Research shows that these bacteria can secrete neural active substances, such as gamma-aminobutyric acid and serotonin, and these neural active substances have an effect on gut microbiota-brain axis [43]. It is likely that these probiotics will become a new variety of psychobiotics or antipsychotics in the future [43]. Therefore, it, for patients with mental diseases, may be a reasonable way to improve or reverse their mental diseases via altering their diet and their life way.

Conclusion

It can be predicted in the foreseeable future that, study on regulating gut microbiota to affect the brain will be an important achievement and significant progress in the field of neuroscience and will change people's concept of "stop-gap responses". With the deepening of

research, there will be more evidences to support the concept of altering the brain's physiology, function and behavior via administering gut microbiota, and to provide a new way for people to "know the brain, protect the brain and exploit the brain", including treating patients with mental disorders.

Acknowledgments

This study was partly supported by grants from Beijing Municipal Administration of Hospitals Clinical Medicine Development of special funding support (No. XMLX201401), the National Natural Science Foundation of China (No. 81301138), National High-tech R&D Program of China (863 Program) (No. 2015AA020514), National Hundred, Thousand, and Ten Thousand Talents Project of Beijing (2010-005).

Conflict of Interest

The author declares no conflict of interest associated with this manuscript.

Bibliography

1. Jenkins TA., *et al.* "Influence of Tryptophan and Serotonin on Mood and Cognition with a Possible Role of the Gut-Brain Axis. Nutrients". 8.1 (2016): E56.

2. Schmidt C. "Mental health: thinking from the gut". *Nature* 518.7540 (2015): S12-S15.

3. Smith PA. "The tantalizing links between gut microbes and the brain". *Nature* 526.7573 (2015): 312-314.

4. Mayer EA., *et al.* "Gut microbes and the brain: paradigm shift in neuroscience". *The Journal of Neuroscience* 34.46 (2014): 15490-15496.

5. Diaz Heijtz R., *et al.* "Normal gut microbiota modulates brain development and behavior". *PNAS USA* 108.7 (2011): 3047-3052.

6. Wang HX., *et al.* "Gut microbiotia-brain axis and its application". *Chinese Journal of Psychiatry* 49.4 (2016): 265-269.

7. Foster JA and McVey Neufeld KA. "Gut-brain axis: how the microbiome influences anxiety and depression". *Trends in Neurosciences* 36.5 (2013): 305-312.

8. de Vos WM and de Vos EA. "Role of the intestinal microbiome in health and disease: from correlation to causation". *Nutrition Reviews* 70 Suppl 1 (2012): S45-S56.

9. Lozupone CA., *et al.* "Diversity, stability and resilience of the human gut microbiota". *Nature* 489.7415 (2012): 220-230.

10. Cryan JF and Dinan TG. "Mind-altering microorganisms: the impact of the gut microbiota on brain and behavior". *Nature Reviews Neuroscience* 13.10 (2012): 701-712.

11. Galland L. "The gut microbiome and the brain". *Journal of Medicinal Food* 17.12 (2014): 1261-1272.

12. Bäckhed F., *et al.* "Host-bacterial mutualism in the human intestine". *Science* 307.5717 (2005): 1915-1920.

13. Furusawa Y., *et al.* "Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells". *Nature* 504.7480 (2013): 446-450.

14. Mayer EA., *et al.* "Gut/brain axis and the microbiota". *Journal of Clinical Investigation* 125.3 (2015): 926-938.

15. Umesaki Y., *et al.* "Segmented filamentous bacteria are indigenous intestinal bacteria that activate intraepithelial lymphocytes and induce MHC class II molecules and fucosyl asialo GM1 glycolipids on the small intestinal epithelial cells in the ex-germ-free mouse".

Microbiology and Immunology 39.8 (1995): 555-562.

16. Umesaki Y., *et al.* "Differential roles of segmented filamentous bacteria and clostridia in development of the intestinal immune system". *Infection and Immunity* 67.7 (1999): 3504-3511.

17. Talham GL., *et al.* "Segmented filamentous bacteria are potent stimuli of a physiologically normal state of the murine gut mucosal immune system". *Infection and Immunity* 67.4 (1999): 1992-2000.

18. Takeuchi O and Akira S. "Pattern recognition receptors and inflammation". *Cell* 140.6 (2010): 805-820.

19. McKernan DP., *et al.* "Enhanced peripheral toll-like receptor responses in psychosis: further evidence of a pro-inflammatory phenotype". *Translational Psychiatry* 1 (2011): e36.

20. O'Brien SM., *et al.* "Cytokines: abnormalities in major depression and implications for pharmacological treatment". *Human psychopharmacology* 19.6 (2004): 397-403.

21. Forsythe P., *et al.* "Mood and gut feelings". *Brain, Behavior, and Immunity* 24.1 (2010): 9-16.

22. Kumar M., *et al.* "Bioengineered probiotics as a new hope for health and diseases: an overview of potential and prospects". *Future Microbiology* 11 (2016): 585-600.

23. Macpherson AJ and Uhr T. "Gut flora--mechanisms of regulation". *The European journal of surgery* 587 (2002): 53-57.

24. Kopp MV., *et al.* "Lactobacillus GG has in vitro effects on enhanced interleukin-10 and interferon-gamma release of mononuclear cells but no in vivo effects in supplemented mothers and their neonates". *Clinical & Experimental Allergy* 38.4 (2008): 602-610.

25. Lyte M. "Microbial endocrinology: Host-microbiota neuroendocrine interactions influencing brain and behavior". *Gut Microbes* 5.3 (2014): 381-389.

26. Wong ML., *et al.* "Inflammasome signaling affects anxiety- and depressive-like behavior and gut microbiome composition". *Molecular Psychiatry* (2016): 10.1038/mp.2016.46.

27. Kunugi H., *et al.* "Biochemical markers subtyping major depressive disorder". *Psychiatry and Clinical Neurosciences* 69.10 (2015): 597-608.

28. Crupi R and Cuzzocrea S. "Neuroinflammation and Immunity: A New Pharmacological Target in Depression". *CNS & neurological disorders drug targets* 15.4 (2016): 464-476.

29. Mayer EA. "Gut feelings: the emerging biology of gut-brain communication". *Nature Reviews Neuroscience* 12.8 (2011): 453-466.

30. Galley JD and Bailey MT. "Impact of stressor exposure on the interplay between commensal microbiota and host inflammation". *Gut Microbes* 5.3 (2014): 390-396.

31. Aubry JM. "CRF system and mood disorders". *Journal of Chemical Neuroanatomy* 54 (2013): 20-24.

32. Pariante CM and Lightman SL. "The HPA axis in major depression: classical theories and new developments". *Trends in Neurosciences* 31.9 (2008): 464-468.

33. Konturek PC., *et al.* "Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options". *Journal of physiology and pharmacology* 62.6 (2011): 591-599.

34. Beyer JL and Payne ME. "Nutrition and Bipolar Depression". *Psychiatric Clinics of North America* 39.1 (2016): 75-86.

35. Quirk SE., *et al.* "The association between diet quality, dietary patterns and depression in adults: a systematic review". *BMC Psychiatry* 13 (2013): 175.

36. Ghaisas S., *et al.* "Gut microbiome in health and disease: Linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases". *Pharmacology & Therapeutics* 158 (2016): 52-62.

37. Graf D., *et al.* "Contribution of diet to the composition of the human gut microbiota". *Microbial Ecology in Health and Disease* 26 (2015): 26164.

38. Butterworth RF. "The liver-brain axis in liver failure: neuro inflammation and encephalopathy". *Nature Reviews Gastroenterology & Hepatology* 10.9 (2013): 522-528.

39. Bajaj JS., *et al.* "Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy". *PLoS One* 8.4 (2013): e60042.

40. Tamang JP., *et al.* "Review: Diversity of Microorganisms in Global Fermented Foods and Beverages". *Frontiers in Microbiology* 7 (2016): 377.

41. Zhou L and Foster JA. "Psychobiotics and the gut-brain axis: in the pursuit of happiness". *Neuropsychiatric Disease and Treatment* 11 (2015): 715-723.

42. Dinan TG and Cryan JF. "The impact of gut microbiota on brain and behavior: implications for psychiatry". *Current Opinion in Clinical Nutrition and Metabolic Care* 18.6 (2015): 552-558.

43. Romijn AR and Rucklidge JJ. "Systematic review of evidence to support the theory of Psychobiotics". *Nutrition Reviews* 73.10 (2015): 675-693.

Volume 1 Issue 2 June 2016