MEDS Clinical Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2022.030508
ISSN 2616-1907 Vol. 3 Num. 5

The Link between Brain Infarction and the Gut Microbiome —— Brain-Gut Axis

Yunyun Li[1], Hai Lin[2,*], Tong Yu[3]

[1]Shaanxi University of Chinese Medicine, Xianyang Shaanxi, 712046, China
[2]Xi'an Trasitional Chinese Medicine Hospital, Xi'an, Shaanxi, 710021, China
[3]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
**Corresponding author*

Keywords: Gut microbiota, Microbial-gut-brain axis, Brain-gut axis, Cerebral infarction, Ischemic stroke

Abstract: Along with research going deep, a bidirectional microbial-gut-brain axis has been found between the brain and gut microbiota, it involves many biological networks such as neural network, neuroendocrine system, immune system and metabolic pathway. Stroke is a high incidence disease in the world, with a high mortality and disability rate. The injury mechanism of ischemic stroke is complex, including calcium overload in nerve cells, cytotoxic effect of excitatory amino acids, free radical and reperfusion injury, nerve cell apoptosis, etc. The current research hotspots have been in-depth into the molecular level, signaling pathway research and targeted therapy [1]. Further understanding of microbial-gut-brain axis can provide more positive help for the prevention, treatment and prognosis of ischemic stroke.

1. Introduction

In the past, traditional intestinal microbiota research methods were limited by their low accuracy. With the development of science and technology, experimental research methods such as Quantitative Real-time PCR, High-throughput sequencing and Metagenomics have become more mature, develop sterile animal models can further analyze the relevant indicators after intervention of normal intestinal microbiota in germ-free mice [2]. At present, through a variety of studies, people have realized that the microbial-gut-brain axis, namely the brain-gut axis, exists in the occurrence and development of a variety of neurological diseases and participates in the deduction of related diseases [3].

2. Microbial-gut-brain axis pathway

The bidirectional communication between the gut microbiota and the brain is mediated by a variety of direct and indirect mechanisms [4]. The most popular ones are :(1) the nervous system (including the enteric nervous system and the autonomic nervous system). The autonomic nervous system is a control system that plays an important role in regulating intestinal homeostasis and intestinal motility [5-6]; (2) The neuroendocrine system (mainly the hypothalamic-pituitary-adrenal

axis HPA). A systematic review has shown that increased cortisol after stroke is associated with morbidity and mortality, and activation of the hypothalamic-pituitary-adrenal axis usually leads to increased cortisol levels [7]. On the other hand, glucocorticoids released by HPA during the body's inflammatory response can regulate excessive immunity [8]; (3) Immune system: hypoxia-ischemia causes abnormal immune signal release and communication, which may lead to the imbalance of peripheral system homeostasis through the two-way feedback of brain-gut circulation, aggravating the outcome of cerebral infarction [9]; (4) Microbiota-derived neuroactive compounds, such as trimethylamine positive oxide (TMAO), short-chain fatty acids, lipopolysaccharide (LPS) and other complex pathways, undergo bacterial translocation [10]. Other scholars have found that after stroke caused by inflammatory response after the activation of the intestinal immune system will further lead to the body bacteria translocation, based on blood brain barrier damage will increase local brain tissue inflammation response, but at the same time some of the intestinal flora metabolites can inhibit inflammation after a stroke and promote restoration of the nerve function to alleviate ischemia-reperfusion injury [11]. At present, brain-gut axis is a hot research field in biology and medicine in recent years. Many recent studies have shown that gut microbiota is related to many diseases, including depression, autism, anxiety, schizophrenia and other psychiatric diseases, Alzheimer's disease, Parkinson's disease, irritable bowel syndrome and obesity [12].Some researchers have proposed that human intestinal microbiota may even play the role of "second brain", and the dysregulation of intestinal microbiota can lead to the increase of intestinal permeability and systemic inflammation, which may lead to the pathology of some diseases and the development of related symptoms through neural, immune, endocrine and metabolic pathways [13]. In the future, studying and understanding the underlying mechanisms of the microbial-gut-brain axis is still a hot topic for many researchers.

3. Research status of brain-gut axis

The brain-gut axis was first proposed in 1980 in a study report on the regulation of bombesin on cholecystokinin [14]. In 2016, Benakis C et al. found that intestinal microbiota imbalance leads to the destruction of immune homeostasis in the small intestine, which leads to the increase of regulatory T cells and the reduction of interleukin (IL) -17-positive γδT cells by altering dendritic cell activity, thereby inhibiting the transport of effector T cells from the intestine to the leptomeninges after stroke. Thus, the effect of gut microbiota on cerebral ischemic injury through the brain-gut axis was recognized [15]. In recent years, some scholars have confirmed through animal experiments that ischemic stroke may reduce the metabolic rate of equol in mice induced by middle cerebral artery occlusion (MCAO) in a time-dependent manner, and this study provides indirect support for the brain-gut axis hypothesis [16]. At present, the commonly used methods to study the gut microbiota-gut-brain axis include sterile animals and gnotobiotic animals models, antibiotic intervention, and microbiota transplantation. However, the specific qualitative definition of gut microbiota is still unclear, and there are differences in the expression of gut microbiota in individuals. Therefore, the specific definition of healthy gut microbiota and bacteria with potential diseases is a difficult problem to be solved urgently.

4. Bidirectional effects of cerebral infarction and gut microbiota

Some animal studies have shown differences in the microbiota composition between stroke models and controls. Microbiota effects on cerebral ischemia reflected in many aspects of metabolism and the immune, such as short chain fatty acid, acetate, butyrate and propionic acid salt related microbial metabolites by free fatty acid receptor affect the immune cells, and cerebral ischemia caused by inflammation intestinal flora caused by immune system steady state change, the

process is reversible [6] [17]. Brain-gut axis plays an important role in connecting gastrointestinal tract and neurogenic diseases [18]. Recent studies have confirmed that gut-brain interaction is bidirectional, and the signals from gut to brain are mediated by microbial derived metabolites, such as trimethylamine-positive oxide (TMAO), short-chain fatty acids (SCFA), lipopolysaccharide (LPS), and T cells exchange with bacteria in neural pathways through hormones and immunity; Ischemic stroke can affect intestinal microbial composition through nerve and hypothalamic-pituitary-adrenal (HPA) pathways [10]. This bidirectional connection between intestinal flora and neural pathways has certain guiding significance for the prevention and prognosis of disease diagnosis and treatment.

5. The positive significance of brain-gut axis as a therapeutic target for cerebral infarction

Studies have shown that the immune system is closely involved in the process of ischemic cascade, and the digestive tract is the main organ of immune response, accounting for more than 70% of the total immune system. More and more evidence shows that intestinal inflammation and immune response play an important role in the pathophysiology of stroke [19-20]. A next-generation DNA sequencing experiment showed that acute cerebral ischemia induces a local neuroinflammatory response, which simultaneously causes changes in peripheral immune homeostasis, further leading to gut microbiota dysbiosis, identifying bidirectional communication along the brain-gut microbiota-immune axis, and showing that the gut microbiota is a central regulator of immune homeostasis. The findings suggest that the gut microbiota is a key regulator of the neuroinflammatory response to brain injury [21]. Recent experimental and clinical studies have shown that the gut microbiota can regulate metabolic, immune, and inflammatory responses through the gut-brain axis (GBA) to improve stroke treatment outcomes [22]. These findings reasonably support the gut microbiota as a potential therapeutic target for ischemic brain injury.

Some experiments have shown that the change of gut microbiota homeostasis may predict the prognosis of stroke, which undoubtedly enricifies the prevention and treatment after stroke [19]. More and more studies have confirmed the gut microbiota as a potential therapeutic target for ischemic stroke [23-25]. Based on this observation, it may provide more theoretical support for the use of antibiotics or probiotic modulators in the clinical treatment of ischemic stroke [26]. In conclusion, the authors agree that further research on brain-gut axis is expected to provide more targets for the clinical treatment of cerebral infarction, and also provide more diagnosis and treatment ideas for the prevention and prognosis of cerebral infarction.

References

[1] Wu Yongmei, Tao Ruying, Meng Xiangbao, Sun Xiaobo, Sun Guibo, Zhang Hui. Ischemic stroke damage mechanism research progress [J]. Journal of jilin of traditional Chinese medicine, 2018, 38 (03): 368-372. The DOI: 10.13463/j.carol carroll nki jlzyy.2018.03.034.

[2] Wang J, Zhang H, He J, Xiong X. The Role of the Gut Microbiota in the Development of Ischemic Stroke. Front Immunol. 2022 Mar 28; 13: 845243. doi: 10.3389/fimmu.2022.845243. PMID: 35418976; PMCID: PMC8995494.

[3] Nam HS. Gut Microbiota and Ischemic Stroke: The Role of Trimethylamine N-Oxide. J Stroke. 2019 May; 21(2): 151-159. doi: 10.5853/jos.2019.00472. Epub 2019 May 31. PMID: 31161760; PMCID: PMC6549071.

[4] Gwak MG, Chang SY. Gut-Brain Connection: Microbiome, Gut Barrier, and Environmental Sensors. Immune Netw. 2021 Jun 16; 21(3): e20. doi: 10.4110/in.2021.21.e20. PMID: 34277110; PMCID: PMC8263213.

[5] Wehrwein EA, Orer HS, Barman SM. Overview of the Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System. Compr Physiol. 2016 Jun 13; 6(3): 1239-78. doi: 10.1002/cphy.c150037. PMID: 27347892.

[6] Houlden A, Goldrick M, Brough D, Vizi ES, Lénárt N, Martinecz B, Roberts IS, Denes A. Brain injury induces specific changes in the caecal microbiota of mice via altered autonomic activity and mucoprotein production. Brain Behav Immun. 2016 Oct; 57: 10-20. doi: 10.1016/j.bbi.2016.04.003. Epub 2016 Apr 6. PMID: 27060191; PMCID: PMC5021180.

[7] Barugh AJ, Gray P, Shenkin SD, MacLullich AM, Mead GE. Cortisol levels and the severity and outcomes of acute stroke: a systematic review. J Neurol. 2014 Mar; 261(3): 533-45. doi: 10.1007/s00415-013-7231-5. Epub 2014 Jan 30. PMID: 24477489; PMCID: PMC4928702.
[8] Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and Cortisol Secretion and Implications for Disease. Endocr Rev. 2020 Jun 1; 41(3): bnaa002. doi: 10.1210/endrev/bnaa002. PMID: 32060528; PMCID: PMC7240781.
[9] Yang Z, Wei F, Zhang B, Luo Y, Xing X, Wang M, Chen R, Sun G, Sun X. Cellular Immune Signal Exchange from Ischemic Stroke to Intestinal Lesions Through Brain-Gut Axis. Front Immunol. 2022 Apr 1; 13: 688619. doi: 10.3389/fimmu.2022.688619. PMID: 35432368; PMCID: PMC9010780.
[10] Chidambaram SB, Rathipriya AG, Mahalakshmi AM, Sharma S, Hediyal TA, Ray B, Sunanda T, Rungratanawanich W, Kashyap RS, Qoronfleh MW, Essa MM, Song BJ, Monaghan TM. The Influence of Gut Dysbiosis in the Pathogenesis and Management of Ischemic Stroke. Cells. 2022 Apr 6; 11(7): 1239. doi: 10.3390/cells11071239. PMID: 35406804; PMCID: PMC8997586.
[11] Hu W, Kong X, Wang H, Li Y, Luo Y. Ischemic stroke and intestinal flora: an insight into brain-gut axis. Eur J Med Res. 2022 May 25; 27(1): 73. doi: 10.1186/s40001-022-00691-2. PMID: 35614480; PMCID: PMC9131669.
[12] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O'Connor R, Cruz-Pereira JS, Peterson VL, Rea K, Ritz NL, Sherwin E, Spichak S, Teichman EM, van de Wouw M, Ventura-Silva AP, Wallace-Fitzsimons SE, Hyland N, Clarke G, Dinan TG. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019 Oct 1;99(4):1877-2013. doi: 10.1152/physrev.00018.2018. PMID: 31460832.
[13] Goyal D, Ali SA, Singh RK. Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 2; 106: 110112. doi: 10.1016/j.pnpbp.2020.110112. Epub 2020 Sep 16. PMID: 32949638.
[14] Banks WA. Evidence for a cholecystokinin gut-brain axis with modulation by bombesin. Peptides. 1980 Winter; 1(4): 347-51. doi: 10.1016/0196-9781(80)90013-3. PMID: 7301638.
[15] Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, Sita G, Racchumi G, Ling L, Pamer EG, Iadecola C, Anrather J. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. Nat Med. 2016 May; 22(5): 516-23. doi: 10.1038/nm.4068. Epub 2016 Mar 28. PMID: 27019327; PMCID: PMC4860105.
[16] Kim JH, Lim C, Cho S. Ischemic-time associated reductions in equol monosulfate plasma levels in a mouse model of ischemic stroke: support the existence of a 'brain-gut axis'. Neuroreport. 2021 Apr 7; 32(6): 458-464. doi: 10.1097/WNR.0000000000001618. PMID: 33657076.
[17] Pluta R, Januszewski S, Czuczwar SJ. The Role of Gut Microbiota in an Ischemic Stroke. Int J Mol Sci. 2021 Jan 18; 22(2): 915. doi: 10.3390/ijms22020915. PMID: 33477609; PMCID: PMC7831313.
[18] Zhao L, Xiong Q, Stary CM, Mahgoub OK, Ye Y, Gu L, Xiong X, Zhu S. Bidirectional gut-brain-microbiota axis as a potential link between inflammatory bowel disease and ischemic stroke. J Neuroinflammation. 2018 Dec 11; 15(1): 339. doi: 10.1186/s12974-018-1382-3. PMID: 30537997; PMCID: PMC6290529.
[19] Li N, Wang X, Sun C, Wu X, Lu M, Si Y, Ye X, Wang T, Yu X, Zhao X, Wei N, Wang X. Change of intestinal microbiota in cerebral ischemic stroke patients. BMC Microbiol. 2019 Aug 19; 19(1): 191. doi: 10.1186/s12866-019-1552-1. PMID: 31426765; PMCID: PMC6700817.
[20] Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med. 2011 Jul 7; 17(7): 796-808. doi: 10.1038/nm.2399. PMID: 21738161; PMCID: PMC3137275.
[21] Singh V, Roth S, Llovera G, Sadler R, Garzetti D, Stecher B, Dichgans M, Liesz A. Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J Neurosci. 2016 Jul 13; 36(28): 7428-40. doi: 10.1523/JNEUROSCI.1114-16. 2016. PMID: 27413153; PMCID: PMC6705544.
[22] Chidambaram SB, Rathipriya AG, Mahalakshmi AM, Sharma S, Hediyal TA, Ray B, Sunanda T, Rungratanawanich W, Kashyap RS, Qoronfleh MW, Essa MM, Song BJ, Monaghan TM. The Influence of Gut Dysbiosis in the Pathogenesis and Management of Ischemic Stroke. Cells. 2022 Apr 6; 11(7): 1239. doi: 10.3390/cells11071239. PMID: 35406804; PMCID: PMC8997586.
[23] Yuan B, Lu XJ, Wu Q. Gut Microbiota and Acute Central Nervous System Injury: A New Target for Therapeutic Intervention. Front Immunol. 2021 Dec 24; 12: 800796. doi: 10.3389/fimmu.2021.800796. PMID: 35003127; PMCID: PMC8740048.
[24] Yamashiro K, Kurita N, Urabe T, Hattori N. Role of the Gut Microbiota in Stroke Pathogenesis and Potential Therapeutic Implications. Ann Nutr Metab. 2021; 77 Suppl 2(Suppl 2): 36-44. doi: 10.1159/000516398. Epub 2021 Jun 9. PMID: 34107468; PMCID: PMC8619778.
[25] Bao Z, Zhang Z, Zhou G, Zhang A, Shao A, Zhou F. Novel Mechanisms and Therapeutic Targets for Ischemic Stroke: A Focus on Gut Microbiota. Front Cell Neurosci. 2022 May 17; 16: 871720. doi: 10.3389/fncel.2022.871720. PMID: 35656406; PMCID: PMC9152006.
[26] Liu C, Cheng X, Zhong S, Liu Z, Liu F, Lin X, Zhao Y, Guan M, Xiao T, Jolkkonen J, Wang Y, Zhao C. Long-term

modification of gut microbiota by broad-spectrum antibiotics improves stroke outcome in rats. Stroke Vasc Neurol. 2022 May 16:svn-2021-001231. doi: 10.1136/svn-2021-001231. Epub ahead of print. PMID: 35577395.