Advances in Clinical Medicine 临床医学进展, 2023, 13(7), 10651-10655
Published Online July 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.1371486

Hans汉斯

肠道微生物与动脉粥样硬化性脑卒中的研究进展

柴逢梅

青海大学研究生院，青海 西宁

收稿日期：2023年6月3日；录用日期：2023年6月28日；发布日期：2023年7月4日

摘　要

肠道微生物群是人体内最大的微生物库，在神经发育和衰老以及缺血性脑卒中等脑部疾病中发挥着重要作用。肠道细菌产生神经活性化合物可以调节神经元功能，从而影响缺血性脑卒中后的行为。此外，肠道微生物会影响宿主代谢和免疫状态，进而影响缺血性大脑的神经元网络。在这里，我们讨论了动物和人类研究在缺血性脑卒中中沿肠－脑轴双向交流的结果。

关键词

肠道菌群，脑卒中

Advances in the Study of Gut Microbes and Atherosclerotic Stroke

Fengmei Chai

Graduate School of Qinghai University, Xining Qinghai

Received: Jun. 3rd, 2023; accepted: Jun. 28th, 2023; published: Jul. 4th, 2023

Abstract

The gut microbiota is the largest reservoir of microorganisms in the body and plays an important role in neurodevelopment and aging as well as in brain diseases such as ischemic stroke. The production of neuroactive compounds by gut bacteria can modulate neuronal function and thus influence behavior after ischemic stroke. In addition, gut microbes affect host metabolism and immune status, which in turn influence neuronal networks in the ischemic brain. Here, we discuss the results of animal and human studies on bidirectional communication along the gut-brain axis in ischemic stroke.

文章引用: 柴逢梅. 肠道微生物与动脉粥样硬化性脑卒中的研究进展[J]. 临床医学进展, 2023, 13(7): 10651-10655.
DOI: 10.12677/acm.2023.1371486

Keywords

Intestinal Flora, Stroke

1. 引言

脑卒中会导致由脑血流短暂或永久性停止引起的脑损伤，从而导致永久性神经功能缺损、痴呆或死亡[1]。脑卒中是一个全球性的健康问题，现已成为全球第二大死亡原因和第三大最常见的残疾原因[2]。在人类中，脑卒中根据潜在的神经病理学分为缺血性或出血性[2]。缺血性脑卒中占所有病例的 85%，出血性脑卒中约占 15% [2]。缺血性脑卒中主要由大脑中动脉闭塞引起，这会导致受影响区域的脑实质受损，随后出现神经炎症和免疫反应[3]。缺血性脑卒中引起的脑损伤是一系列复杂的神经病理结果，包括兴奋性毒性、氧化应激、神经炎症、细胞凋亡、淀粉样蛋白产生和蛋白功能障碍[4] [5]。缺血后大脑的特征是淀粉样蛋白斑块和神经原纤维缠结的积累，随后发展为痴呆。因此，如果不能预防或减缓这种疾病，它将成为一个严重的公共卫生问题，在未来几十年内发病率和流行率将达到流行病的程度。尽管脑卒中会增加痴呆导致的神经功能缺损，但感染是脑卒中导致死亡的主要原因[6]。大约 90%的脑卒中病例已被证明与行为因素有关，包括营养不良、低体力活动和吸烟，以及代谢因素，包括糖尿病、肥胖、高脂血症和高血压[7]。根据全球疾病研究，脑卒中将是一个非常严重的健康问题；其负面影响将随着世界人口老龄化而增加[8]。

2. 肠道菌群代谢产物

多样化的肠道微生物群是由上皮屏障的完整性以及肠道免疫和代谢平衡所介导[9] [10]。肠道内部消化的膳食纤维被盲肠和结肠的微生物群代谢，它们的主要终端产品是短链脂肪酸(SCFAs)，特别是丙酸盐、乙酸盐和丁酸盐等[11] [12]。丙酸是人体的内源性 SCFAs，既是脂肪酸代谢的媒介，也是传统肠道食品防腐剂中肠道细菌的代谢终产物[13]。虽然大多数丙酸是由肠道细菌的氨基酸和碳水化合物发酵产生的，但丙酸会立即通过肠道－血液和血液－大脑屏障，通过被动和主动途径进入中枢神经系统(CNS)，并穿过细胞膜，到达细胞内[14]对中枢神经系统功能产生广泛影响，如改变神经递质的产生、线粒体功能、免疫激活、脂质代谢和基因表达[15]。SCFAs 在细胞内积累后随着 pH 值的轻微降低诱发细胞内酸化[16]。细胞内酸化可以改变钙的信号传递、神经递质的释放和间隙连接的抑制，也有可能改变神经元的通讯和行为[17]。最近的调查显示，厌氧菌作为膳食纤维发酵的代谢物，提供相对较高的 SCFAs 水平[18]。

3. 脑卒中的风险因素

肠道微生物群作为脑卒中的风险因素目前已受到广泛关注。越来越多的文献表明，肠道细菌与一些危险因素如糖尿病、高血压和肥胖症介导的脑卒中的发病机制密切相关[19]。通过移植粪便样本，高血压供体的肠道微生物群给实验小鼠的高血压肠道菌群研究带来了进展[20]。一种来自肠道细菌的致动脉粥样硬化的代谢产物－甲胺 N-氧化物(TMAO)，是高血压个体脑卒中风险的增加因素。一项临床调查描述了急性缺血性卒中患者的肠道菌群失调，其肠杆菌科细菌明显增多[21]。在 Zheng 等人的一项先驱研究中[22]，他们评估了脑卒中风险和肠道细菌之间的关系。Zheng 研究的主要发现是，脑卒中高危人群的肠道

内机会性细菌病原体的比率明显高于低危人群，粪便中的丁酸盐水平也与脑卒中风险增加有关[22]。大脑在管理和协调肠道系统平衡方面发挥着不可缺少的作用[22]。肠道细菌在脑卒中后也会发生变化，也许它们是脑卒中的一个危险因素[21]。有研究显示，机会性细菌病原体如肠杆菌科以及变形杆菌科的比率在高危组中更为常见，而丁酸盐形成菌如鲁米诺球菌科以及拉氏杆菌科的比率在同一组中不太常见，这清楚地表明在评估脑卒中风险时应考虑肠道微生物群[22]。肠杆菌科被认为是肠道上皮功能障碍的标志，也是细菌群落组成不稳定的标志[23]。肠杆菌在健康人中的是有益的，但当宿主的平衡被各种因素(包括炎症和低纤维饮食)打断时，会加剧机体炎症[24]。基于高纤维饮食被推荐的事实，以及为什么它被认为可以减少脑卒中的风险，可能是介于肠道细菌产生的 SCFAs，如丁酸盐[25]。研究发现丁酸盐可以减少体内饮食诱发的肥胖、高甘油三酯血症和高胰岛素血症，主要是通过降低食欲、刺激棕色脂肪组织，增加膳食纤维的消化[26]。另外，丁酸盐还能抑制肠杆菌科的呼吸源硝酸盐和氮化物的形成[27]。根据 Zheng 的研究结果[22]，丁酸盐形成的细菌而不是机会性细菌病原体可以改善脑卒中风险增加有关的特定条件，包括糖尿病、高血压和肥胖症。有证据表明，丁酸盐有神经保护的功能，可以减少脑卒中的风险，这表明膳食纤维、丁酸盐和丁酸盐形成菌的服用可以减少心血管疾病的风险[22]。综上所述，已经发现脑卒中风险与机会性细菌病原体增强、丁酸盐形成菌率低以及粪便中丁酸盐水平降低有关[22]。然而，还需要进一步的体外和体内调查来证明这些结论。

4. 肠道菌群与脑卒中的联系

肠道微生物群对宿主脑卒中结果的影响沿脑－肠轴的双向交流[28]。在猴子中证实了缺血后类杆菌的生长[29]，在小鼠发生缺血性脑卒中三天后，也发现类杆菌丰度增加，这被认为是脑卒中后菌群失调的一个特征。相反，在一项临床研究中，入院后两天的粪便样本显示急性缺血性脑卒中和短暂性缺血发作患者的类杆菌水平下降[21]。在对局灶性脑卒中后的猴子的研究中，发现普雷沃特菌的相对丰度增加，表明这种类型可能与脑卒中后的炎症反应有关[29]。在局部脑卒中后的猴子中，观察到粪菌、链球菌、乳酸菌的相对水平降低[29]。粪菌和物种被认为是宿主体内丁酸盐的主要来源[30]。丁酸盐在维持肠道屏障的完整性方面起着关键作用，可抑制促炎症细胞因子的产生，被认为是脑部疾病的治疗目标[25]。猴子在局灶性脑卒中后的 6~12 个月内观察到血浆丁酸盐浓度下降，这可能与杆菌水平下降有关[29]。在局灶性脑卒中后的猴子身上发现短链脂肪酸的血浆水平降低，且生存期为 6~12 个月，这表明慢性肠道菌群失调也可能影响短链脂肪酸的产生。有人指出，乳酸菌是宿主益生菌的一个重要类型，在猴子脑卒中后拥有相对水平的降低[29]。补充乳酸菌已被证明可以改善认知功能、情绪和缓解与衰老有关的炎症[31]。脑卒中后的痴呆和抑郁是动物和脑卒中幸存者的常见并发症[32]，同时有慢性全身性和脑部炎症。补充乳酸菌是否对脑卒中后的病人有益，应该在未来的临床试验中进行调查。也有研究发现，脑卒中后链球菌的相对丰度会降低。链球菌属包括益生菌如嗜热链球菌和致病菌如肺炎链球菌[33]。目前，肠道链球菌在脑卒中中的确切作用还有待今后的研究来澄清。已发现血液中脂多糖的增加会导致脑神经炎症、血脑屏障改变、脑水肿，并使脑卒中后的生存变得复杂[34]。这与缺血后猴子的血浆脂多糖增加有关，特别是在脑卒中后 6 个月和 12 个月[29]。因此，脂多糖可能在脑卒中后的慢性系统性炎症中发挥重要作用，这一点被缺血后肠粘膜屏障的损伤和肠粘膜的形态学损伤所证实。肠粘膜屏障受损可能与肠道释放到血液中的脂多糖增加有关。研究证实，局灶性脑卒中后 12 个月内，血浆中促炎症细胞因子 IFN-g、IL-6 和 TNF-α 升高，提示脑卒中后全身性炎症长期存在[29]。这些观察结果表明，脑梗死后不仅出现了肠道微生态失调，而且还出现了慢性全身性炎症。相关研究还显示，血浆脂多糖或炎症细胞因子水平的增加与类杆菌的过度生长密切相关[29]。我们可以得出结论，脑卒中后的慢性全身性炎症反应会影响大脑，因为已经证明这种炎症反应与认知障碍、学习和记忆障碍、抑郁和焦虑有关[31]。从肠道释放到循环中的促炎症细胞因子直接

与大脑沟通，加剧了病理变化。因此，脑卒中后肠道微生物群和慢性全身性炎症可能是治疗脑卒中的目标。

参考文献

[1] Chen, Y., Fu, A. and Ip, N.Y. (2019) Synaptic Dysfunction in Alzheimer's Disease: Mechanisms and Therapeutic Strategies. *Pharmacology & Therapeutics*, **195**, 186-198. https://doi.org/10.1016/j.pharmthera.2018.11.006

[2] Parr, E., Ferdinand, P. and Roffe, C. (2017) Management of Acute Stroke in the Older Person. *Geriatrics*, **2**, Article No. 27. https://doi.org/10.3390/geriatrics2030027

[3] Radenovic, L., Nenadic, M., Ulamek-Koziol, M., *et al*. (2020) Heterogeneity in Brain Distribution of Activated Microglia and Astrocytes in a Rat Ischemic Model of Alzheimer's Disease after 2 Years of Survival. *Aging*, **12**, 12251-12267. https://doi.org/10.18632/aging.103411

[4] Pluta, R., Ułamek-Kozioł, M., Kocki, J., *et al*. (2020) Expression of the Tau Protein and Amyloid Protein Precursor Processing Genes in the CA3 Area of the Hippocampus in the Ischemic Model of Alzheimer's Disease in the Rat. *Molecular Neurobiology*, **57**, 1281-1290. https://doi.org/10.1007/s12035-019-01799-z

[5] Ułamek-Kozioł, M., Czuczwar, S.J., Januszewski, S. and Pluta, R. (2020) Proteomic and Genomic Changes in Tau Protein, Which Are Associated with Alzheimer's Disease after Ischemia-Reperfusion Brain Injury. *International Journal of Molecular Sciences*, **21**, Article No. 892. https://doi.org/10.3390/ijms21030892

[6] Chamorro, Á., Urra, X. and Planas, A.M. (2007) Infection after Acute Ischemic Stroke: A Manifestation of Brain-Induced Immunodepression. *Stroke*, **38**, 1097-1103. https://doi.org/10.1161/01.STR.0000258346.68966.9d

[7] Li, N., Wang, X., Sun, C., *et al*. (2019) Change of Intestinal Microbiota in Cerebral Ischemic Stroke Patients. *BMC Microbiology*, **19**, Article No. 191. https://doi.org/10.1186/s12866-019-1552-1

[8] Murray, C.J.L. and Lopez, A.D. (2013) Measuring the Global Burden of Disease. *New England Journal of Medicine*, **369**, 448-457. https://doi.org/10.1056/NEJMra1201534

[9] Rasoul, M., Rokhsareh, M., Mohammad, S.M., Sajad, K. and Ahmadreza, M. (2019) The Human Immune System against *Staphylococcus epidermidis*. *Critical Reviews™ in Immunology*, **39**, 151-163. https://doi.org/10.1615/CritRevImmunol.2019031282

[10] Takiishi, T., Fenero, C.I.M.F. and Câmara, N.O.S. (2017) Intestinal Barrier and Gut Microbiota: Shaping Our Immune Responses throughout Life. *Tissue Barriers*, **5**, e1373208. https://doi.org/10.1080/21688370.2017.1373208

[11] Holscher, H.D. (2017) Dietary Fiber and Prebiotics and the Gastrointestinal Microbiota. *Gut Microbes*, **8**, 172-184. https://doi.org/10.1080/19490976.2017.1290756

[12] Venegas, D.P., De la Fuente, M.K., Landskron, G., *et al*. (2019) Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Frontiers in Immunology*, **10**, Article 277. https://doi.org/10.3389/fimmu.2019.01486

[13] Shultz, S.R., Macfabe, D.F., Martin, S., *et al*. (2009) Intracerebroventricular Injections of the Enteric Bacterial Metabolic Product Propionic Acid Impair Cognition and Sensorimotor Ability in the Long-Evans Rat: Further Development of a Rodent Model of Autism. *Behavioural Brain Research*, **200**, 33-41. https://doi.org/10.1016/j.bbr.2008.12.023

[14] Maurer, M.H., Canis, M., Kuschinsky, W. and Duelli, R. (2004) Correlation between Local Monocarboxylate Transporter 1 (MCT1) and Glucose Transporter 1 (GLUT1) Densities in the Adult Rat Brain. *Neuroscience Letters*, **355**, 105-108. https://doi.org/10.1016/j.neulet.2003.10.056

[15] MacFabe, D.F., Cain, D.P., Rodriguez-Capote, K., *et al*. (2007) Neurobiological Effects of Intraventricular Propionic Acid in Rats: Possible Role of Short Chain Fatty Acids on the Pathogenesis and Characteristics of Autism Spectrum Disorders. *Behavioural Brain Research*, **176**, 149-169. https://doi.org/10.1016/j.bbr.2006.07.025

[16] Bonnet, U., Bingmann, D. and Wiemann, M. (2000) Intracellular pH Modulates Spontaneous and Epileptiform Bioelectric Activity of Hippocampal CA3-Neurones. *European Neuropsychopharmacology*, **10**, 97-103. https://doi.org/10.1016/S0924-977X(99)00063-2

[17] Cannizzaro, C., Monastero, R., Vacca, M., *et al*. (2003) [^{3}H]-DA Release Evoked by Low pH Medium and Internal H^+ Accumulation in Rat Hypothalamic Synaptosomes: Involvement of Calcium Ions. *Neurochemistry International*, **43**, 9-17. https://doi.org/10.1016/S0197-0186(02)00211-5

[18] Nakamura, Y.K., Janowitz, C., Metea, C., *et al*. (2017) Short Chain Fatty Acids Ameliorate Immune-Mediated Uveitis Partially by Altering Migration of Lymphocytes from the Intestine. *Scientific Reports*, **7**, Article No. 11745. https://doi.org/10.1038/s41598-017-12163-3

[19] Sato, J., Kanazawa, A., Ikeda, F., *et al*. (2014) Gut Dysbiosis and Detection of "Live Gut Bacteria" in Blood of Japa-

nese Patients with Type 2 Diabetes. *Diabetes Care*, **37**, 2343-2350. https://doi.org/10.2337/dc13-2817

[20] Li, J., Zhao, F., Wang, Y., *et al*. (2017) Gut Microbiota Dysbiosis Contributes to the Development of Hypertension. *Microbiome*, **5**, Article No. 14. https://doi.org/10.1186/s40168-016-0222-x

[21] Yin, J., Liao, S.-X., He, Y., *et al*. (2015) Dysbiosis of Gut Microbiota with Reduced Trimethylamine-N-Oxide Level in Patients with Large-Artery Atherosclerotic Stroke or Transient Ischemic Attack. *Journal of the American Heart Association*, **4**, e002699. https://doi.org/10.1161/JAHA.115.002699

[22] Zeng, X., Gao, X., Peng, Y., *et al*. (2019) Higher Risk of Stroke Is Correlated with Increased Opportunistic Pathogen Load and Reduced Levels of Butyrate-Producing Bacteria in the Gut. *Frontiers in Cellular and Infection Microbiology*, **9**, Article 4. https://doi.org/10.3389/fcimb.2019.00004

[23] Litvak, Y., Byndloss, M.X., Tsolis, R.M. and Bäumler, A.J. (2017) Dysbiotic *Proteobacteria* Expansion: A Microbial Signature of Epithelial Dysfunction. *Current Opinion in Microbiology*, **39**, 1-6. https://doi.org/10.1016/j.mib.2017.07.003

[24] Winter, S.E., Winter, M.G., Xavier, M.N., *et al*. (2013) Host-Derived Nitrate Boosts Growth of *E. coli* in the Inflamed Gut. *Science*, **339**, 708-711. https://doi.org/10.1126/science.1232467

[25] Bourassa, M.W., Alim, I., Bultman, S.J. and Ratan, R.R. (2016) Butyrate, Neuroepigenetics and the Gut Microbiome: Can a High Fiber Diet Improve Brain Health? *Neuroscience Letters*, **625**, 56-63. https://doi.org/10.1016/j.neulet.2016.02.009

[26] Li, Z., Yi, C.-X., Katiraei, S., *et al*. (2018) Butyrate Reduces Appetite and Activates Brown Adipose Tissue via the Gut-Brain Neural Circuit. *Gut*, **67**, 1269-1279. https://doi.org/10.1136/gutjnl-2017-314050

[27] Byndloss, M.X., Olsan, E.E., Rivera-Chavez, F., *et al*. (2017) Microbiota-Activated Ppar-γ Signaling Inhibits Dysbiotic Enterobacteriaceae Expansion. *Science*, **357**, 570-575. https://doi.org/10.1126/science.aam9949

[28] Singh, V., Roth, S., Llovera, G., *et al*. (2016) Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. *Journal of Neuroscience*, **36**, 7428-7440. https://doi.org/10.1523/JNEUROSCI.1114-16.2016

[29] Chen, Y., Liang, J., Ouyang, F., *et al*. (2019) Persistence of Gut Microbiota Dysbiosis and Chronic Systemic Inflammation after Cerebral Infarction in Cynomolgus Monkeys. *Frontiers in Neurology*, **10**, Article 661. https://doi.org/10.3389/fneur.2019.00661

[30] Gophna, U., Konikoff, T. and Nielsen, H.B. (2017) *Oscillospira* and Related Bacteria—From Metagenomic Species to Metabolic Features. *Environmental Microbiology*, **19**, 835-841. https://doi.org/10.1111/1462-2920.13658

[31] Chesnokova, V., Pechnick, R.N. and Wawrowsky, K. (2016) Chronic Peripheral Inflammation, Hippocampal Neurogenesis, and Behavior. *Brain, Behavior, and Immunity*, **58**, 1-8. https://doi.org/10.1016/j.bbi.2016.01.017

[32] Liu, Z., Lu, W., Gao, L., *et al*. (2022) Protocol of End-PSCI Trial: A Multicenter, Randomized Controlled Trial to Evaluate the Effects of DL-3-N-Butylphthalide on Delayed-Onset Post Stroke Cognitive Impairment. *BMC Neurology*, **22**, Article No. 435. https://doi.org/10.1186/s12883-022-02957-y

[33] del Carmen, S., Miyoshi, A., Azevedo, V., de LeBlanc, A.M. and LeBlanc, J.G. (2015) Evaluation of a *Streptococcus thermophilus* Strain with Innate Anti-Inflammatory Properties as a Vehicle for IL-10 cDNA Delivery in an Acute Colitis Model. *Cytokine*, **73**, 177-183. https://doi.org/10.1016/j.cyto.2015.02.020

[34] Dénes, Á., Ferenczi, S. and Kovács, K.J. (2011) Systemic Inflammatory Challenges Compromise Survival after Experimental Stroke via Augmenting Brain Inflammation, Blood-Brain Barrier Damage and Brain Oedema Independently of Infarct Size. *Journal of Neuroinflammation*, **8**, Article No. 164. https://doi.org/10.1186/1742-2094-8-164