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Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota

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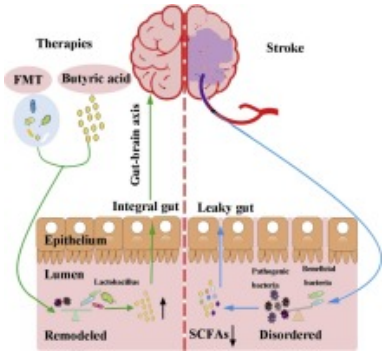
Abstract

The gut microbiota and its short chain fatty acid (SCFA) metabolites have been established to play an important protective role against neurodegenerative diseases. Our previous study demonstrated that cerebral ischemic stroke triggers dysfunctional gut microbiota and increased intestinal permeability. In this study, we aimed to clarify the mechanism by which gut microbiota and SCFAs can treat cerebral ischemic stroke in rat middle cerebral artery occlusion models and use the information to develop new therapies. Our results show that oral administration of non-absorbable antibiotics reduced neurological impairment and the cerebral infarct volume, relieved cerebral edemas, and decreased blood lipid levels by altering the gut microbiota. We also found that ischemic stroke decreased intestinal levels of SCFAs. And that transplanting fecal microbiota rich in these metabolites was an effective means of treating the condition. Compared with other SCFAs, butyric acid showed the highest negative correlation with ischemic stroke. Supplementation with butyric acid treated models of ischemic stroke effectively by remodeling the gut microbiota, enriching the beneficial *Lactobacillus*, and repairing the leaky gut. In conclusion, interfering with the gut microbiota by transplanting fecal bacteria rich in SCFAs and supplementing with butyric acid were found to be effective treatments for cerebral ischemic stroke.

Graphical abstract



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Introduction

Cerebral ischemic stroke, caused by focal occlusion or arterial stenosis in the brain, is a condition of the central nervous system that seriously endangers human life. Unhealthy living habits, excessive life stress, and an aging population has led to an increased threat of cerebral ischemia worldwide [1]. Characterized by complex pathology, including calcium overload, blood–brain barrier disruption, neuronal apoptosis, and cerebral inflammation, ischemic stroke usually causes a series of syndromes such as obstruction of local blood circulation, necrosis of brain tissue, cerebral edema, neurological impairment, cognitive disorder, and paralysis [[2], [3], [4], [5], [6]]. Clinically, intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) is used for treating ischemic stroke [7,8]. According to the guidelines, the standard treatment in China is intravenous rt-PA (0.9 mg/kg) administration to restore blood perfusion [9]. However, the narrow window of time available for thrombolysis (4.5 h), increased risk of intracranial hemorrhage due to activation of the fibrinolytic system, and potential for reperfusion injury limit its clinical application [10,11]. Therefore, effective new therapies for ischemic stroke should be explored.

Increasingly, clinical studies have found that neurological disorders such as Alzheimer's disease, Parkinson's disease, depression, and multiple sclerosis are usually accompanied with gastrointestinal symptoms [[12], [13], [14], [15], [16], [17]]. It has been established that a dysfunctional central nervous system affects gastrointestinal function via the vagus signal, neurotransmitters, endocrine systems, and immune pathways [[18], [19], [20]]. In a previous study, we demonstrated that cerebral ischemia causes gut microbiota dysbiosis, increased intestinal permeability, disruption to the gut barrier, and translocation of gut microbiota. Repairing the leaky gut was found to be beneficial to the blood–brain barrier in cerebral ischemic stroke [21]. Clearly, the "brain-gut axis" is a bidirectional communication system between the central nervous system and the gastrointestinal tract. Increasingly evidences demonstrated that gut microbiota and its short chain fatty acid metabolites (especially butyric acid) appear to be key signaling molecules [22] for the communication of the gut and brain by controlling neurodevelopment, neurotransmitters, and microglia to modulate cerebral biochemistry and behavior [23,24]. However, the influence of gut microbiota and butyric acid in cerebral ischemia is not yet fully understood. Therefore, the purpose of this study was to clarify the mechanism by which the gut microbiota and SCFAs are involved in the treatment of cerebral ischemia to find a new effective therapy for this condition. This study, therefore, provides new insights into the clinical treatment of cerebral ischemic stroke.

Section snippets

Animals

Male Sprague-Dawley rats (240 ± 20 g, Specific Pathogen Free, 9 weeks old) were obtained from the central animal facility of Southern Medical University (Guangzhou, China). The animals were housed under standard conditions of light and dark cycles (12 h:12 h, temperature 25 °C) with free access to food and water. Each rat was housed in separate cage to avoid interference of housing environment. In addition, the cages were regularly cleaned. All the animal studies were carried out according to…

Regulating gut microbiota affected the progression of cerebral ischemic stroke

Our previous study demonstrated that cerebral ischemic stroke triggers dysfunction in the gut microbiota and causes increased intestinal permeability [21]. To investigate whether regulating the gut microbiota affects the progression of cerebral ischemic stroke, non-absorbable antibiotics therapy was supplied orally to rat models. Our results showed that the antibiotics significantly decreased the gut microbiota α-diversity (Fig. S1) and altered its composition in cerebral ischemic stroke (Fig. 1…

Discussion

Cerebral ischemic stroke is caused by an insufficient supply of blood to the brain and triggers neurological impairment and necrosis of brain tissue [31]. Our previous study revealed that cerebral ischemic stroke causes neurological and histomorphological impairments and triggers systemic complications, including hyperlipemia, high blood viscosity, dysfunctional gut microbiota, and a leaky gut [21]. With the widespread recognition of the “gut-brain axis” theory, links between the gut and the…

Compliance with ethical standards

All animal procedures were conducted in strict compliance with the National Institue of Health Guide for Use and Care of Laboratory Animals and approved by Institutional Animal Ethical Care Committee of Southern Medical University Experimental Animal Center. This article does not contain any studies with human participants performed by any of the authors.…

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.…

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