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THE SPECIFICS OF THE INTESTINAL MICROFLORA AND THE RELEVANCE OF IMPROVING THE INTESTINAL MICROBIOTA IN STROKE PATIENTS

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ABSTRACT

The gut microbiota and its connection to different neurological conditions have been the subject of an increasing number of investigations. In addition to having a significant influence on blood pressure, blood glucose, and atherosclerosis—all risk factors for ischemic stroke—the gut microbiota can also have an impact on the body's metabolic state. In order to provide new concepts for the prevention and treatment of ischemic stroke, we compiled research on the physiological role of the gut microbiota and gut microbiota disorders associated with the central nervous system in this review. The gastrointestinal tract hosts complex microbial communities, the largest pool of immune cells, and forms a bidirectional regulation brain-gut axis with the brain. Recent experimental and clinical studies have highlighted the significance of the relationship between the intestinal microenvironment and stroke. Over time, the influence of the intestine on stroke has emerged as an important and dynamic research direction in biology and medicine. Stroke is not only a major cause of disability but also the third leading cause of death, after heart disease and cancer. Nevertheless, there are few treatment options for this patient population. In this review, we discuss the intestinal microenvironment's structure and function and emphasize how it interacts with stroke. Furthermore,

we address possible approaches that target the intestinal microenvironment while treating stroke. Neurological function and the outcome of cerebral ischemia can be influenced by the structure and function of the intestinal environment. Targeting the gut microbiota to improve the intestinal milieu could be a novel approach to stroke treatment.

Introduction. One of the most serious health issues in the world, ischemic stroke is a prevalent disorder of the central nervous system (CNS). An essential intestine microecosystem that is crucial to the internal environment's balance is the gut microbiota. The host and intestinal microbes typically maintain a dynamic ecological balance, and gut microbiota homeostasis is strongly linked to health. Recent research has revealed that the development and occurrence of ischemic stroke are significantly influenced by the gut flora. In addition to being closely linked to gastrointestinal conditions like ulcerative colitis, colon cancer, and irritable bowel syndrome, an imbalance in the gut microbiota is also linked to the onset and progression of metabolic diseases, diabetes, obesity, hypertension, and atherosclerosis, all of which are risk factors for ischemic stroke. In this study, we outlined the impact and processes of gut microbiota problems on the pathophysiology of stroke and chronic metabolic diseases, and we offered fresh suggestions for stroke treatment or prevention [1-5]. Up to 50% of stroke survivors have been shown to experience gastrointestinal problems, such as dysphagia, intestinal motility issues, fecal incontinence, leaky gut, intestinal hemorrhage, and even enterogenic sepsis. Gastrointestinal problems in stroke patients frequently result in decreased cerebral function, higher death rates, and poor prognoses. Significant advancements in proteomics, metabolomics, and genomes have been made during the last ten years, making it possible to investigate the relationship between the gut and stroke. The intestine has emerged as a research hotspot in recent years because to the widespread belief that it plays a significant role in the pathophysiological events following stroke. It's interesting to note that the intestine produces over 25% of the T cells in the ischemic brain hemisphere [6-10]. It is now known that the intestine and brain work together to produce a complex "brain–gut axis" through a number of routes that regulate each other in both directions. immunological imbalance results from ischemic stroke's alteration of the intestinal microenvironment; on the other hand, the intestinal microenvironment can also affect stroke outcomes by modifying immunological responses. Understanding the intestinal milieu and how it interacts with stroke could help create new therapeutic approaches, although research on the gut-brain axis in stroke is still in its early stages. In this study, we outline the anatomy and physiology of the intestinal environment, give a thorough summary of current findings about its relationship to stroke, and talk about potential therapeutic approaches and tenets. The field of gut microbiota research and its possible impact on illness is expanding quickly [11,12,13]. The gut microbiota has been linked to a number of diseases in numerous studies, which has resulted in a significant rise in research articles on this topic. This increase emphasizes how important it is to

comprehend the relationship between gut microbiota and illnesses. In recent years, research on the relationship between ischemic stroke and the gut flora has advanced significantly. There is still a need for a thorough and up-to-date review that documents the development of this field of study, even though there are numerous evaluations available from different perspectives. Because these studies are more trustworthy than individual animal and human studies, this evaluation gave priority to studies that support conclusions across both animals and humans. In order to help readers rapidly grasp the historical background, consensus, disagreements, unanswered questions, and developmental trends regarding the gut microbiota and ischemic stroke association, this narrative review attempts to provide a concise summary of the current state of the study. This evaluation also suggests future research directions while admitting existing constraints in research gaps [14-20].

The main purpose of the presented exposition is a brief interpretation of the specifics of the intestinal microflora and the relevance of improving the intestinal microbiota in stroke patients based on scientific research.

The intestinal epithelial barrier's typical form and function. One of the biggest barriers separating the body's internal environment from the external world is the intestinal epithelial barrier (IEB). As a physical barrier and a hub for immunological defense and bacterial–immune cell communication, the IEB is essential for preserving intestinal homeostasis. Four cell types—epithelial cells, goblet cells, Paneth cells, and enterochromaffin cells—have been demonstrated to make up the IEB. Mucin glycoproteins are produced by goblet cells and intestinal epithelial cells. The most prevalent neuroendocrine cells in the digestive tract are called intestinal chromaffin cells, and Paneth cells produce antimicrobial peptides that help fend against pathogen invasion. IEB secretes chemicals to create mucus, which shields epithelial cells from toxins, germs, and digestive enzymes. According to available data, mucus—which is mostly released by intestinal epithelial goblet cells—is heavily glycosylated and is crucial for preserving the integrity of the IEB. Water, proteins, lipids, and electrolytes make up 90–95% of mucus. Goblet cells are the primary producers of proteins, notably mucins, which give mucus its gel-like qualities [1-6]. Additionally, mucus contains immunoglobulin A (IgA) and antimicrobial peptides, which enable mucus to act as an innate defense. It's interesting to note that when inflammation is present, mucous fucosylation is dramatically decreased. The existence of a number of intercellular junctions made up of desmosomes, tight junctions (TJ), adherent junctions (AJ), and apical junction complexes (AJC) is necessary for IEB to function. Transmembrane proteins found in the outer apical region of the epithelial cell make up the TJ structure, which is essential for preserving barrier integrity by blocking antigen transit through the IEB. Auxiliary structures for cell-cell adhesion, adherent junctions and desmosomes are found beneath TJ and are mostly made up of actin filaments, catenin, and e-cadherin. It's interesting to note that adherent junctions create connections between cells and aid in TJ maturation. Additionally, TJ and AJ regulate the entry of gut microorganisms into the intestinal connective tissue and seal off epithelial cells. Desmogleins and desmocollins make up desmosomes, which give epithelial cells' cell-to-cell contact mechanical strength [17-22].

Changes in the intestinal epithelial barrier's structure and function following a stroke. According to available data, stroke damages the intestinal villus epithelium, increases permeability, damages the intestinal tight junction, reduces mucus, and causes enterogenic sepsis by destroying the integrity of the IEB. Using a rat permanent middle cerebral artery occlusion (MCAO) model, Liu et al. found notable alterations in small bowel morphology over time. A few villi's tips had necrotic and exfoliated epithelial cells at six hours. All villi showed signs of epithelial cell necrosis, exfoliation, and epithelial dissociation at 24 hours. Three hours after surgery, Dragana Stanley et al. discovered increased intestinal permeability in a mouse model of MCAO, and the amount of FITC identified in the blood was comparable to that in a mouse model of acute colitis caused by dextran sulfate sodium (DSS) [3,4,5]. When the researchers evaluated the intestinal barrier function in a different photochemically produced stroke mouse model, they discovered that the intestinal permeability of the animals increased one day after the stroke and that the contents of ZO-1, occludin, and claudin-1 in the TJ were dramatically reduced. Additionally, TJ breaking was observed using an electron microscope. Age also has an impact on the IEB's integrity following a stroke. Intestinal homeostasis is more severely disrupted by stroke in older mice than in younger ones, according to animal tests. Additionally, a study discovered that stroke in older mice reduces the number of goblet cells that secrete mucus, ultimately resulting in a lack of mucus production. Microbiota translocation, in which bacteria or bacterial components pass the barrier and invade the extra-intestinal organs, can eventually occur when the integrity of the IEB is disrupted following a stroke. Interestingly, a common commensal bacterium called Enterococcus faecalis was given to germ-free (GF) mice, and its translocation and dispersion following experimental stroke induction were investigated. Only GF mice after MCAO displayed bacterial translocation and dissemination to nearby tissues, including the lung, liver, spleen, and mesenteric lymph nodes (MLNs), 24 hours following E. faecalis colonization [11-17].

Changes in the gut microbiome's composition and function in stroke. There is ample evidence that ischemic stroke modifies the gut microbiome. In one study, collected feces were sequenced using 16S rDNA, and the results showed elevated levels of the phylum *Bacteroidetes* after brain infarction in cynomolgus monkeys. *Prevotella,* a member of the phylum *Bacteroidetes*, is known to play a crucial pro-inflammatory role in chronic inflammatory illnesses in humans. Furthermore, the elevated relative abundance of the *Prevotella* genus following cerebral infarction induction in cynomolgus monkeys may also be connected to the inflammatory response following a stroke. Three days following acute ischemia surgery in mice, reduced species diversity of the gut microbiota and an increase in the phylum *Bacteroidetes* were found to be indicators of post-stroke microbiota dysbiosis [4-9]. However, a case-control research revealed that patients with large-artery atherosclerotic ischemic stroke and transient ischemic attack had higher microbial alpha diversity and lower abundance levels of *Bacteroides, Prevotella* and *Faecalibacterium*. The daily diet of stroke patients and conditions like obesity, diabetes, and hypertension may have an impact on the gut flora, which could explain why this conclusion is at odds with the results seen in animal model research. Additionally,

following 6–12 months of cerebral infarction induction, butyrate concentrations and the quantities of *Faecalibacterium* and *Oscillospira* species in monkey feces reduced. The main sources of butyrate generation in the host are generally believed to be *Oscillospira* and *Faecalibacterium*. Butyrate is essential for preserving the intestinal barrier's integrity and preventing the synthesis of pro-inflammatory cytokines. In conclusion, intestinal immune cell formation and activity, as well as the integrity of the IEB, depend heavily on the gut microbiota and its metabolites. Stroke-related dysbiosis of the gut microbiota can change a number of vital bioactive molecules and increase the number of pathogenic bacteria. Certain metabolites have the potential to enhance stroke prognosis, aid in neurological rehabilitation, and offer a fresh strategy for repairing stroke injuries [12-19].

Changes in the gut immune system's structure and function following a stroke. The development of stroke is significantly influenced by intestinal immune cells. Immune cells can get to the brain through peripheral circulation following a stroke, despite the microbiota controlling immune cells in the gut. It's interesting to note that after three days, mice with cerebral ischemia-reperfusion showed increased Th17 cell differentiation in the lamina propria of the small intestine (SI-LP), along with an increase in the expression of IL-23 and IL-17A in the small intestine. On the other hand, in the small intestine, Treg cell differentiation and release of the anti-inflammatory cytokine IL-10 were both reduced. Furthermore, the majority of γδT cells in the human body primarily reside on the intestinal epithelium's surface and take part in the intestine's innate immune response [7-12]. It's interesting to note that during an ischemic stroke, γδT cells go from the gut to the brain membrane via the peripheral circulation and release IL-17 into the injured brain tissue. IL-17 then causes the brain parenchyma to produce more chemokines, which increases neutrophil infiltration and exacerbates ischemic neuroinflammation. Treg cells in the small intestine release Il-10, which has neuroprotective properties and can prevent γδT cells from differentiating. Following an acute ischemic stroke, there may be changes to traditional Th1 and Th2 responses in addition to Th17/Treg or γδT/Treg responses. The cytokines IFN-γ and IL-4, which represent Th1 and Th2 effector phenotypes, respectively, were examined for mRNA levels in the small intestine. On day three, the researchers discovered that IFN-γ expression had increased while IL-4 expression had reduced. These results suggested that cerebral ischemia injury could be lessened by pharmacological management of the immunological balance of Th1/Th2 and Th17/Tregs in the small intestine. In conclusion, the many immunological tissues and cells that make up the intestinal immune system cooperate in a typical physiological setting to protect against pathogenic invasion and preserve immune homeostasis. However, this immunological homeostasis is upset following a stroke, and cytokines and intestinal immune cells change. Crucially, distant brain tissue is also impacted by this alteration, which is not limited to the stomach. Treatment and recovery following a stroke might be difficult due to the exacerbation of ischemic neuroinflammation caused by lymphocyte migration and an increase in inflammatory mediators [13-22].

Discussion. Through a variety of ways, the gut microbiota can interact with the brain. An imbalance in the gut microbiota might increase the risk of stroke, which may

worsen the dysbiosis of the gut microbiota. Several therapies can improve the prognosis following a stroke (Figure 1). The impact of the gut microbiota on stroke outcomes may be altered by the diversity of metabolites and the abundance of gut microorganisms. There are currently significant limits to using gut microbiota to treat stroke, and further study is still needed. Ischemic stroke is a serious hazard to human health due to its high incidence, death, and disability. The onset, course, and prognosis of ischemic stroke are strongly influenced by the gut flora. Brain-gut connections are significantly influenced by gut flora. The study of early warning biomarkers and possible treatment targets for ischemic stroke is made easier by the reflection of changes in the gut and brain brought on by gut bacteria. Based on actual human and animal research, we mainly address three subjects in this narrative review of the connection between gut microbiota and ischemic stroke. First, we looked at the connection between intestinal microbiota and its metabolites and ischemic stroke [1,2,7,8]. We also outlined the general features of intestinal microbiota dysregulation in ischemic stroke and evaluated the potential clinical utility, current research debates, and distinctive phenomena of intestinal microbiota metabolites like trimethylamine N-oxide and short-chain fatty acids in ischemic stroke. Second, using the brain-gut axis as a framework, we investigated the possible mechanisms of communication between intestinal flora and ischemic stroke, including immunological, metabolic, and neurological pathways. Lastly, we summarized the factors that affect the severity of ischemic stroke through intestinal flora, the pharmacological and nonpharmacological interventions that alter intestinal flora in the treatment of ischemic stroke, and the state of intestinal flora research in relation to the aftermath of ischemic stroke [4,9,10,11]. Chinese herbal medicine is the main focus of current research on using gut microbiota regulation as a treatment for ischemic stroke, however antibiotics also play a big part. The particular microbiota targeted for modification differs in the field of Chinese herbal medicine research, probably because different plants are used. This variety suggests that separate distinctive bacteria may be influenced by different herbs during the healing process following an ischemic stroke, indicating the possibility of modulating these varied microbiota as a therapeutic approach. The overall changes in gut microbiota after Chinese herbal medicine treatment for ischemic stroke can predict stroke recovery outcomes, despite the inconsistent specific microbiota linked to Chinese herbal medicine. Improved gut microbiota diversity, fewer opportunistic infections, more symbiotic or beneficial bacteria, fewer bacteria linked to TMAO synthesis, and more bacteria that create SCFAs are some examples of these improvements. Furthermore, the control of systemic and cerebral inflammatory responses in ischemic stroke has been linked to Chinese herbal treatment. Antibiotics have been shown to be effective in treating ischemic stroke through gut microbiota alteration in ischemic stroke animal models, both prophylactically before stroke induction and therapeutically afterward, highlighting the potential of gut microbiota modulation as a treatment strategy [14-21].

Conclusions. The connection between gut microbiota and ischemic stroke is still not fully understood. The majority of human research is observational, with animal studies conducting more in-depth analyses of mechanisms. However, because of possible inconsistencies, results from animal models do not always translate to human research

and should be carefully taken into account when extrapolating to humans. Determining the precise mechanisms of gut microbiota within the human body is extremely difficult due to its unique nature. This review provides a thorough and practical summary of the current state of research in this area, despite the lack of a comprehensive mechanistic explanation of the connection between gut microbiota and ischemic stroke. It seeks to serve as a useful resource for those looking to delve more into this area. Innovative therapy approaches and customized medical approaches may be made possible by further research, which would ultimately improve the care and results of ischemic stroke patients.

Antibiotics, probiotics, and FMT are examples of microbe-targeted therapies that have been demonstrated to improve host health. The gut microbiota has significant therapeutic potential in clinical practice, as evidenced by the fact that external manipulations with intestinal flora may alter the course of several resistant disorders, such as stroke. A significant advancement in the treatment of ischemic stroke could be the restoration of gut microbial balance. Future studies will use high-throughput sequencing of gut microbial genomes to define mechanisms of microbe-microbe and microbe-host interactions in complex microbial-human gut ecosystems and develop medications based on these findings. The possibility for treating a number of illnesses, including stroke, will be greatly impacted by all of these studies. Lastly, to convert these investigations into therapeutic applications, carefully planned, prospective, and longitudinal trials would be required.

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