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 ORIGINAL PAPERS

Gut Microbiota. Neuropolen for Recovery after an Ischemic Stroke

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Abstract. ***Background*** *The brain possesses an extraordinary ability to heal itself after a stroke. This ability is known as neuroplasticity. The relationship between the gut microbiota and stroke is recent, with early studies dating from 2013. Recent studies support that gut microbiota is associated with ischemic stroke through the gut-brain axis, thereby modulating stroke pathogenesis.* ***Objectives*** *Gut dysbiosis, defined as alterations to the gut microbial communities has been proposed in stroke. To determine whether Neuropolen can be a potential treatment for recovery after a stroke.* ***Material and methods*** *The 2-way communication between the gut and the brain, which involves the brain, the gut microbiota, and the intestinal tissue, has been suggested as a key component of stroke outcome. To arrive at these observations, authors examined how Neuropolen and diet solve disabilities.* ***Results*** *The gut microbiota can increase the risk of a cerebrovascular event, playing a role in the onset of stroke. Conversely, stroke can induce dysbiosis of the gut microbiota. We found that Neuropolen may be important for functional recovery after a stroke. Neuropolen that may help minimize the degree of complications, stimulation enhances plasticity of the brain, in which noninjured parts of the brain can pick up the job of the injured brain areas.* ***Conclusion*** *In this presentation, authors describe the role of the gut microbiota, microbiome and microbiota-derived metabolites in stroke, and their use as therapeutic targets. Neuropolen may be a potential therapy for recovery after a stroke, it can quickly feed oxygen to the brain and protect brain cells.*

Keywords: Neuropolen, neuroplasticity, recovery after a stroke

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Commensal gut bacteria have a profound impact on stroke pathophysiology. Signaling between the brain and the gut occurs through neuronal pathways but also through microbial metabolites as well as hormones, and the immune system (1).

Recent research highlights the contribution of the gut microbiota to stroke pathogenesis and treatment outcomes. Compositional and functional alterations of

the gut microbiota, termed dysbiosis, are linked to stroke risk factors. Alterations in the diversity, abundance, and functions of the gut microbiome, termed gut dysbiosis, results in dysregulated gut-brain signaling, which induces intestinal barrier changes, endotoxemia, systemic inflammation, and infection, affecting post-stroke outcomes. Gut-brain interactions are bidirectional, and the signals from the gut to the brain are mediated by microbially derived metabolites, such as trimethylamine N-oxide (TMAO) and short-chain fatty acids (SCFAs); bacterial components, such as lipopolysaccharide (LPS); immune cells, such as T helper cells; and bacterial translocation via hormonal, immune, and neural pathways (2).

Experimental and clinical studies have demonstrated that the restoration of the gut microbiome usually improves stroke treatment outcomes by regulating metabolic, immune, and inflammatory responses via the gut-brain axis (GBA) (3).

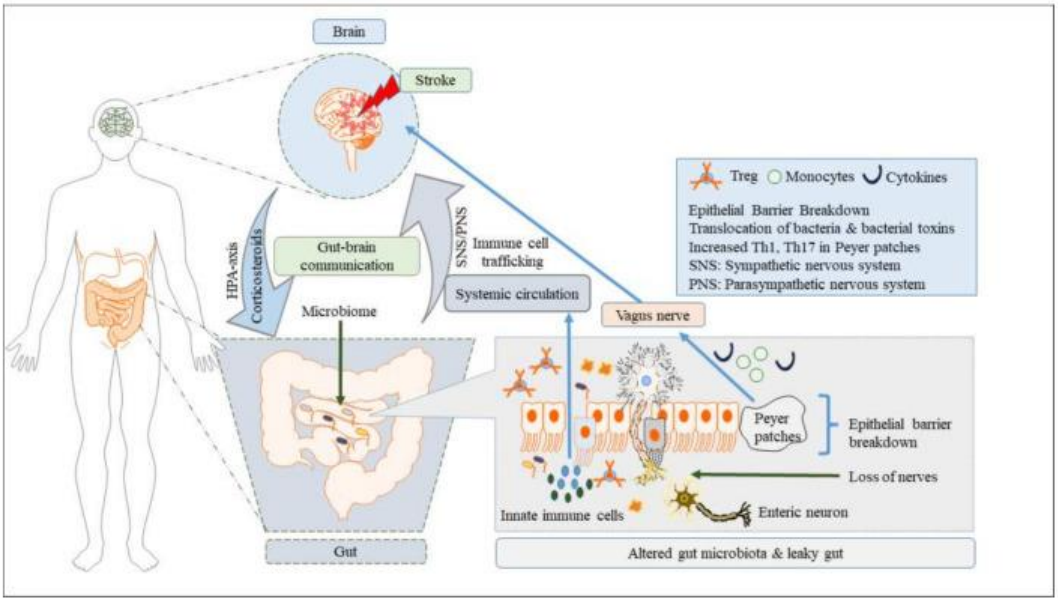


Fig. 1. Effects of stroke on the gut–brain axis. Following cerebral stroke, gut dysbiosis causes loss of enteric nerves, increased intestinal-barrier permeability, reduced mucus production, loss of goblet cells, thinning of the mucus barrier, and increased sympathetic activity in the intestinal wall, all of which contributes to intestinal inflammation and an exaggerated immune response. These events in turn disrupt intestinal and systemic immune homeostasis, resulting in poor stroke treatment prognosis (4).

When a stroke occurs, the brain's blood supply in certain regions is disrupted and a core of neuronal tissue dies (5). There is swelling within the brain as well as a loss of oxygen and nutrients. Numerous studies have identified microbial sequences or epitopes in pathological and non-pathological human brain samples

(6). It has not been resolved if these observations are artifactual, or truly represent population of the brain by microbes (7). Given the tempting speculation that resident microbes could play a role in the many neuropsychiatric and neurodegenerative diseases that currently lack clear etiologies, there is a strong motivation to determine the "ground truth" of microbial existence in living brains (8).

Intestinal bacteria produce neuroactive compounds and can modulate neuronal function, which affects behavior after an ischemic stroke. In addition, intestinal microorganisms affect host metabolism and immune status, which in turn affects the neuronal network in the ischemic brain (9).

The intestinal microbiome, the largest reservoir of microorganisms in the human body, plays an important role in neurological development and aging as well as in brain disorders such as an ischemic stroke (10).

Moreover, several reports have revealed the impact of an ischemic stroke on gut dysfunction and intestinal dysbiosis, highlighting the delicate play between the brain, intestines and microbiome after this acute brain injury. Despite our growing knowledge of intestinal microflora in shaping brain health, host metabolism, the immune system and disease progression, its therapeutic options in an ischemic stroke have not yet been fully utilized (11).

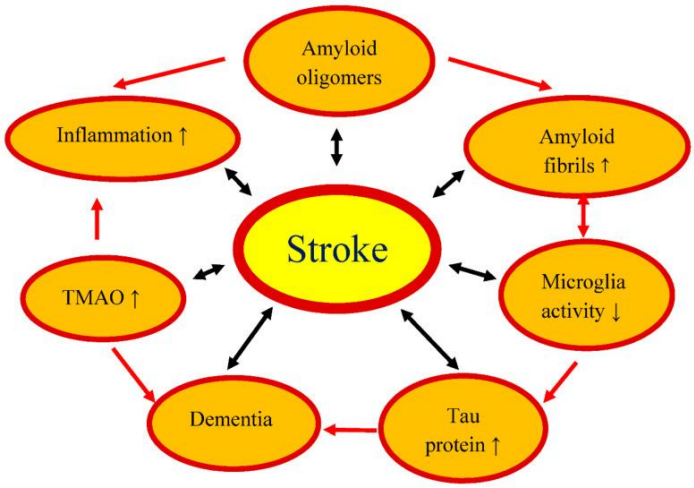


Fig. 2 Influence of intestinal microflora dysbiosis on the development and outcome of an ischemic stroke. ↑: increase, ↓: decrease, TMAO: trimethylamine-n-oxide (12)

Aging has been identified as a risk factor for neurodegenerative disorders by influencing the composition of the gut microbiota, microglia activity and cognitive performance. Aging has been identified as a risk factor for neurodegenerative disorders by influencing the composition of the gut microbiota,

microglia activity and cognitive performance. The microbiota-gut-brain axis is a two-way communication path between the gut microbes and the host brain. The aging intestinal microbiota communicates with the brain through secreted metabolites (neurotransmitters), and this phenomenon leads to the destruction of neuronal cells (13).

Numerous external factors, such as living conditions and internal factors related to the age of the host, affect the condition of the intestinal microbiota in the form of dysbiosis. Dysbiosis is defined as changes in the composition and function of the gut microflora that affect the pathogenesis, progress, and response to treatment of a disease entity. Dysbiosis occurs when changes in the composition and function of the microbiota exceed the ability of the microflora and its host to restore equilibrium. Dysbiosis leading to dysfunction of the microbiota-gut-brain axis regulates the development and functioning of the host's nervous, immune, and metabolic systems. Dysbiosis, which causes disturbances in the microbiota-gut-brain axis, is seen with age and with the onset of stroke, and is closely related to the development of risk factors for stroke (14,15).

Acute brain ischemia induces a local neuroinflammatory reaction and alters peripheral immune homeostasis at the same time. Recent evidence has suggested a key role of the gut microbiota in autoimmune diseases by modulating immune homeostasis. Therefore, we investigated the mechanistic link among acute brain ischemia, microbiota alterations, and the immune response after brain injury. Using in vivo cell-tracking studies, we demonstrate the migration of intestinal lymphocytes to the ischemic brain. These results support a novel mechanism in which the gut microbiome is a target of stroke-induced systemic alterations and an effector with substantial impact on stroke outcome (16).

Growing evidence has proved that alterations in the gut microbiota have been linked to neurological disorders including stroke. Structural and functional disruption of the blood-brain barrier (BBB) is observed after stroke. In this context, there is pioneering evidence supporting that gut microbiota may be involved in the pathogenesis of stroke by regulating the BBB function. However, only a few experimental studies have been performed on stroke models to observe the BBB by altering the structure of gut microbiota, which warrant further exploration. Therefore, in order to provide a novel mechanism for stroke and highlight new insights into BBB modification as a stroke intervention, this review summarizes existing evidence of the relationship between gut microbiota and BBB integrity and discusses the mechanisms of gut microbiota on BBB dysfunction and its role in stroke (17).

Increasing evidences have demonstrated that the compositional changes of gut microbiota complexity are involved in diverse gastrointestinal disorders and metabolic dysfunctions such as obesity and diabetes, which may also contribute to the nutrition status after stroke. Moreover, gut microbiota is recently considered to

communicate with central nervous system in a bidirectional pattern. The metabolic products of gut microbiota regulate not only normal brain development but also various brain disorders through neural, immunological, endocrinal and metabolic pathways. Therefore, deep insights into the relationship between gut microbiota and stroke could provide novel avenues to improve post-stroke recovery and prevent stroke recurrence. More than 85% of stroke events are caused by the blockage of blood flow, namely ischemic stroke, thus we focused on ischemic stroke in this review (18).

In acute cerebral ischemia, the gut microbiota plays a key role in bidirectional interactions between the gut and brain, referred to as the microbiota-gut-brain axis. Gut dysbiosis prior to ischemic stroke affects outcomes. Additionally, the brain affects the gut microbiota during acute ischemic brain injury, which in turn impacts outcomes. Interactions between the gut microbiota and stroke pathogenesis are mediated by several factors including bacterial components (e.g., lipopolysaccharide), gut microbiota-related metabolites (e.g., short-chain fatty acids and trimethylamine N-oxide), and the immune and nervous systems. Modulation of the gut microbiota or its metabolites improves conditions related to stroke pathogenesis, including inflammation, cardiometabolic disease, atherosclerosis, and thrombosis (19).

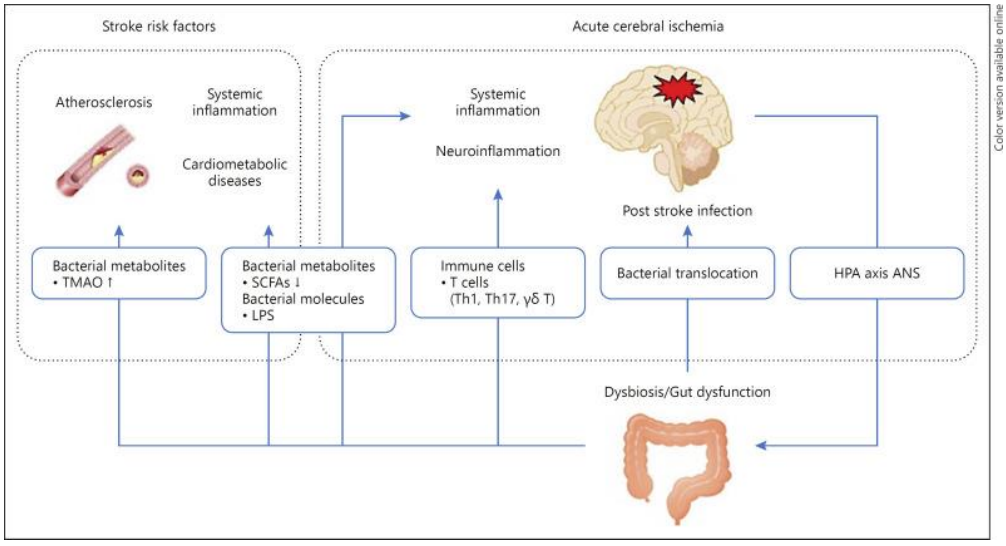


Fig. 3 Gut Gut microbiota and stroke pathogenesis (20).

Alteration of gut microbiota (dysbiosis) contributes to the development of stroke risk factors such as systemic inflammation, cardiometabolic diseases, and atherosclerosis. In acute cerebral ischemia, dysbiosis induces neuroinflammation, systemic inflammation, and infection, which affect stroke outcomes. These

interactions are mediated by several pathways including bacterial components (e.g., LPS), gut microbiota-related metabolites (e.g., SCFAs and TMAO), immune cells (e.g., T cells), or bacterial translocation. Additionally, the ischemic brain influences the gut microbiota composition via either the neural or hypothalamic-pituitary-adrenal pathways, which in turn also contribute to stroke outcomes. ANS, autonomic nervous system; HPA, hypothalamus-pituitary-adrenal; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide (20).

Stroke leads to inflammatory and immune response in the brain and immune organs. The gut or gastrointestinal tract is a major immune organ equipped with the largest pool of immune cells representing more than 70% of the entire immune system and the largest population of macrophages in the human body (21).

The bidirectional communication between the brain and the gut is commonly known as brain-gut or gut-brain axis. Stroke often leads to gut dysmotility, gut microbiota dysbiosis, "leaky" gut, gut hemorrhage, and even gut-origin sepsis, which is often associated with poor prognosis (22).

Emerging evidence suggests that gut inflammatory and immune response plays a key role in the pathophysiology of stroke and may become a key therapeutic target for its treatment (23).

Ischemic brain tissue produces damage-associated molecular patterns to initiate innate and adaptive immune response both locally and systemically through the specialized pattern-recognition receptors (e.g., toll-like receptors). After stroke, innate immune cells including neutrophils, microglia or macrophages, mast cells, innate lymphocytes (IL-17 secreting γδ T-cell), and natural killer T-cell respond within hours, followed by the adaptive immune response through activation of T and B lymphocytes. Subpopulations of T-cells can help or worsen ischemic brain injury. Pro-inflammatory Th1, Th17, and γδ T-cells are often associated with increased inflammatory damage, whereas regulatory T-cells are known to suppress postischemic inflammation by increasing the secretion of anti-inflammatory cytokine IL-10. Although known to play a key role, research in the gut inflammatory and immune response after stroke is still in its initial stage (24). A better understanding of the gut inflammatory and immune response after stroke may be important for the development of effective stroke therapies.

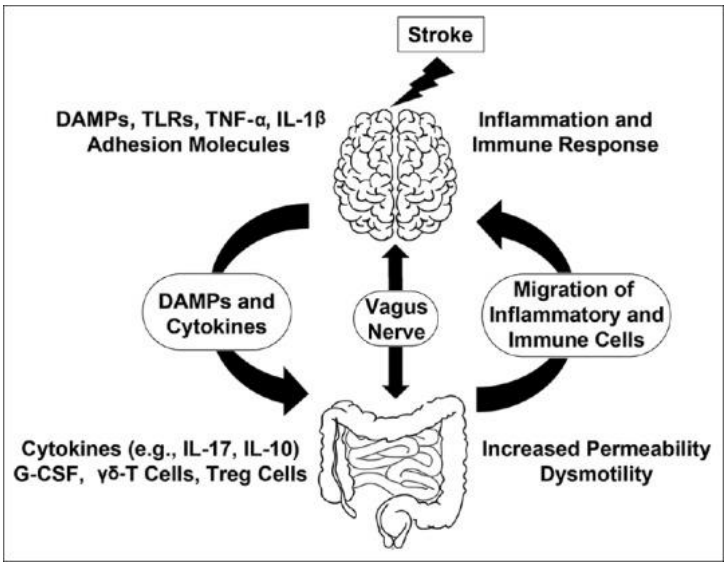


Fig. 4. Changes in brain-gut-microbiota axis after stroke (25)

Ischemic brain tissue and activated microglia release DAMPs and cytokines, resulting in the activation of endothelial cells to express adhesion molecules and to recruit inflammatory and immune cells from the circulation to the sites of stroke injury. Meanwhile, release of DAMPs and cytokines as well as activation of the vagus nerve induce gut dysmotility, gut dysbiosis, and increased gut permeability, resulting in translocation of intestinal bacteria and migration of gut inflammatory and immune cells through the circulation into the sites of stroke injury. Treg=Regulatory T-cell, G-CSF=granulocyte colony-stimulating factor, DAMPs=damage-associated molecular patterns (25).

The present paper will discuss recent advances in the studies of the brain-gut axis after stroke, the key issues to be solved, and the future directions. We also discuss the interaction between microbiota, microglia and neurons in the aged individuals in the brain after ischemic stroke. This study shows the role of the gut microbiota-brain axis in an ischemic stroke and assesses the potential role of intestinal microbiota in the onset, progression and recovery post-stroke. Finally, we presented preclinical and clinical studies on the role of the aged microbiota-gut-brain axis in the development of risk factors for stroke and changes in the post-stroke microbiota.

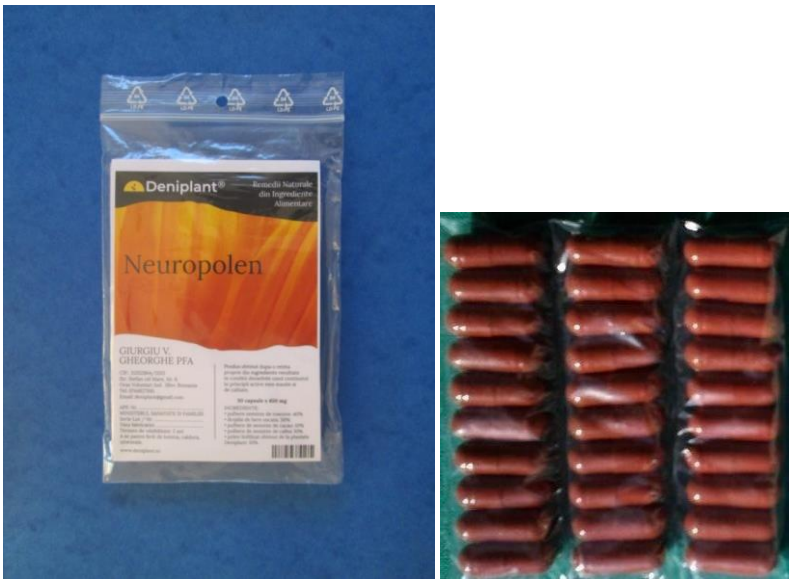
It is currently being studied whether indoles can stimulate the timing of the formation of neurons during brain development.

The objective of the study was to determine whether Neuropolen can be a potential treatment for recovery after a stroke.

The present study suggested the role of Neuropolen in the development of recovery after ischemic stroke. The key to treating a stroke and minimizing long-

term damage is quickly and effectively restoring blood flow to the brain. To arrive at these observations, the authors analyzed how Neuropolen and the diet solve disabilities.

The study found that Neuropolen may be important for functional recovery after ischemic stroke. Stroke patients can have access to Neuropolen, which can help minimize the degree of complications, the stimulation improves brain plasticity, where the uninjured parts of the brain can take over the function of the damaged areas. Neuropolen enables recovery of movement and other abilities after ischemic stroke.



Neuropolen is a nutraceutical (food with dual role of nutrition and health) for the regeneration of destroyed nerve cells. Neuropolen for solving human medical conditions was made long before the appearance of the product under this name. Neuropolen is a natural neuroregenerator of the nerve cell. Nerve regeneration is the ultimate battle in defending and restoring the body! By combining them, the authors managed to obtain a product with a broad spectrum of action without side effects or side effects. The components themselves are foods that we can consume daily, that's why Neuropolen has the slogan ”Eat and hea”

Neuropolen contains: carob seed powder=40%, dry brewer's yeast=30%, cocoa nib powder=10%, coffee seed powder=10%, lyophilized polen from Deniplant plants=10%

Presentation form: 30 self-dissolving gelatin capsules

The properties of Neuropolen are due to the composition rich in antioxidants, anti-inflammatory agents, amino acids, minerals and natural vitamins, neuroregenerative molecules.

The Neuropolen product offers various possibilities to balance the processes that take place in the nerve cells and the neuromuscular plate, to accelerate the regeneration of the nerve connection and the self-healing of the body, being a nutrient, it is not medically certified, but its components have scientifically proven healing qualities.

We found that Neuropolen may be important for functional recovery after a stroke. Neuropolen, which can help minimize the degree of complications, stimulation improves brain plasticity, where uninjured parts of the brain can take over the function of damaged areas of the brain. Neuropolen may be a potential therapy for stroke recovery, can rapidly oxygenate the brain and protect brain cells.

We summarized recent advances in the interactions between commensal gut microbiota and ischemic stroke: how stroke insult changes gut microbiota composition and how these shifts reversely influence stroke outcome and prognosis. We also attempted to figure out the clues from latest literatures by which gut microbiota may affect the major aspects during post-stroke management, including the controls of body temperature, blood glucose, blood pressure, oxygen and hydration. The concerns on gut microbiota will provide researchers novel therapeutic potentials for ischemic stroke and remind clinicians for special cares in post-stroke management.

Increasing knowledge about mediators and triggered pathways has contributed to a better understanding of the interaction between the gut-brain axis and the brain-gut axis.

Ischemic stroke affects gut microbial composition via neural and hypothalamic-pituitary-adrenal (HPA) pathways, which can contribute to post-stroke outcomes.

Intestinal bacteria produce neuroactive compounds and can modulate neuronal function, which affects behavior after an ischemic stroke. In addition, intestinal microorganisms affect host metabolism and immune status, which in turn affects the neuronal network in the ischemic brain.

We have identified a bidirectional communication along the brain-gut microbiota-immune axis and show that the gut microbiota is a central regulator of immune homeostasis. Acute brain lesions induced dysbiosis of the microbiome and, in turn, changes in the gut microbiota affected neuroinflammatory and functional outcome after brain injury. The microbiota impact on immunity and stroke outcome was transmissible by microbiota transplantation. Our findings support an emerging concept in which the gut microbiota is a key regulator in priming the neuroinflammatory response to brain injury. These findings highlight the key role of microbiota as a potential therapeutic target to protect brain function after injury

Conclusions

Accumulating evidence indicates that the gut microbiota plays a possible role in stroke pathogenesis. Modulation of the gut microbiota may provide a novel therapeutic strategy for the treatment and prevention of stroke. Therefore, restoring healthy microbial ecology in the gut may be a key therapeutic target for the effective management and treatment of ischemic stroke. We and others have shown that the gut microbiome influences stroke outcome by modulating the immune response, in turn stroke itself induces a shift of the microbial community which impacts gut motility and permeability, stress response, and poststroke infection. In particular, these findings highlight a direct connection along the gut-brain axis via intestinal T cells regulating the neuroinflammatory response to brain injury. Understanding on how modification of the gut microbial community impacts the consequences of stroke on the host has the potential for the development of new therapeutic strategy to improve recovery after stroke. When an ischemic stroke occurs, part of the brain is damaged and many of these connections are destroyed, and Neuropolen can be a potential therapy for restoring the connections, it can quickly supply oxygen to the brain, thus protecting the brain cells.

R E F E R E N C E S

[1] Benakis C, Martin-Gallausiaux C, Trezzi JP, et al. The microbiome-gut-brain axis in acute and chronic brain diseases. Curr Opin Neurobiol. 2019; 61: 1-9.

[2] Honarpisheh P, Bryan RM, McCullough LD. Aging Microbiota-Gut-Brain Axis in Stroke Risk and Outcome. Circ Res. 2022; 130(8): 1112-44.

[3] Koszewicz M, Jaroch J, Brzecka A, et al. Dysbiosis is one of the risk factor for stroke and cognitive impairment and potential target for treatment. Pharmacol Res. 2021; 164: 105277.

[4] Chidambaram SB, Rathipriya AG, Mahalakshmi AM, et al. The Influence of Gut Dysbiosis in the Pathogenesis and Management of Ischemic Stroke. Cells. 2022; 11(7): 1239.

[5] Tan C, Wu Q, Wang H, et al. Dysbiosis of Gut Microbiota and Short-Chain Fatty Acids in Acute Ischemic Stroke and the Subsequent Risk for Poor Functional Outcomes. JPEN J Parenter Enteral Nutr. 2021; 45(3): 518-29.

[6] Wang T, Pan C, Xie C, et al. Microbiota Metabolites and Immune Regulation Affect Ischemic Stroke Occurrence, Development, and Prognosis. Mol Neurobiol. 2023

[7] Pu B, Zhu H, Wei L, et al. The Involvement of Immune Cells Between Ischemic Stroke and Gut Microbiota. Transl Stroke Res. 2023

[8] Peh A, O'Donnell JA, Broughton BRS, Marques FZ. Gut Microbiota and Their Metabolites in Stroke: A Double-Edged Sword. Stroke. 2022; 53: 1788-801.

[9] Benakis C, Poon C, Lane D, et al. Distinct Commensal Bacterial Signature in the Gut Is Associated With Acute and Long-Term Protection From Ischemic Stroke. Stroke 2020; 51: 6

[10] Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiol Rev. 2019; 99: 1877-2013.

[11] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci**.** 2017; 20: 145-55.

[12] Pluta R, Januszewski S, Czuczwar SJ. The Role of Gut Microbiota in an Ischemic Stroke**.** Int J Mol Sci 2021; 22(2): 915.

[13] van de Wouw M, Boehme M, Lyte JM, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain-gut axis alterations. J Physiol. 2018; 596: 4923-44.

[14] Yin J, Liao SX, He Y, et al. Dysbiosis of gut microbiota with reduced trimethylamine-N-oxide level in patients with large-artery atherosclerotic stroke or transient ischemic Attack. J Am Heart Assoc. 2015; 4: e002699.

[15] Pluta R, Jabłoński M, Januszewski S, et al. Crosstalk between the aging intestinal microflora and the brain in ischemic stroke. Front Aging Neurosci. 2022; 14: 998049.

[16] Singh V, Roth S, Llovera G, Microbiota Dysbiosis Controls the Neuroinflammatory Response after Stroke. J Neurosci. 2016; 36(28): 7428-40.

[17] Zeng M, Peng M, Liang J, et al. The Role of Gut Microbiota in Blood-Brain Barrier Disruption after Stroke. Mol Neurobiol 2023; doi: 10.1007/s12035-023-03512-7.

[18] Zhao J, Liu S, Yan J, The Impact of Gut Microbiota on Post-Stroke Management. Front Cell Infect Microbiol. 2021; 11: 724376.

[19] Singh V, Sadler R, Heindl S, et al. The gut microbiome primes a cerebroprotective immune response after stroke. J Cereb Blood Flow Metab. 2018; 38: 1293-8.

[20] Yamashiro K, Kurita N, Urabe T, et al. Role of the Gut Microbiota in Stroke Pathogenesis and Potential Therapeutic Implications. Ann Nutr Metab. 2021; 77 Suppl 2(Suppl 2): 36-44.

[21] Spychala MS, Venna VR, Jandzinski M, et al. Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome. Ann Neurol**.** 2018; 84: 23-36.

[22] Sadler R, Cramer JV, Heindl S, Kostidis S, Betz D, Zuurbier KR, et al. Short-chain fatty acids improve poststroke recovery via immunological mechanisms. J Neurosci. 2020; 40: 1162-73.

[23] Tibæk M, Dehlendorff C, Jørgensen HS, et al. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: a registry-based study. J Am Heart Assoc. 2016; 5: 27-8.

[24] Link CD. Is There a Brain Microbiome? Neurosci Insights. 2021; 16: 15 **.**

[25] Arya AK, Hu B Brain-gut axis after stroke. Brain Circ. 2018; 4(4): 165-73.