"ALTSGEYMER KASALLIGI PATOGENEZIDA ICHAK MIKROBIOTASINING ROLI"

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ARTICLE INFORMATION

ARTICLE HISTORY:

Received: 18.05.2026
Revised: 19.05.2026
Accepted: 20.05.2026

KEYWORDS:

Alzheimer's disease, gut microbiota, neurodegeneration, amyloid-beta, gut-brain axis, dysbiosis, neuroinflammation, lipopolysaccharides, short-chain fatty acids, microglia.

ANNOTATION

This scientific article extensively analyzes the role of gut microbiota in the pathogenesis of Alzheimer's disease, one of the most pressing issues in modern medicine. Recent studies demonstrate that communication carried out through the "gut-brain axis" significantly influences neurodegenerative processes in the brain, particularly the accumulation of amyloid-beta proteins. The article provides a detailed explanation of mechanisms such as the impact of intestinal dysbiosis on systemic inflammation, the increased permeability of the blood-brain barrier caused by bacterial endotoxins, and the activation of microglial cells. Furthermore, the article discusses promising approaches for the prevention and treatment of Alzheimer's disease through microbiota modulation.

Alzheimer's disease is a chronic neurodegenerative disorder characterized by the irreversible loss of memory and cognitive functions. For a long time, the causes of this disease were believed to be limited only to genetic and molecular changes in the brain. However, today scientists are increasingly focusing on other parts of the body, particularly the intestinal microbiota.

The collection of microorganisms living in the human intestine functions almost like a separate organ due to its metabolic activity. The bidirectional communication between the microbiota and the central nervous system — known as the "gut–brain axis" — is considered one of the key mechanisms involved in the development of Alzheimer's disease. This interaction occurs through neural, endocrine, and immune pathways. One of the main hallmarks of Alzheimer's disease is the formation of amyloid beta (Aβ)

plaques in brain tissue. Interestingly, certain intestinal bacteria, such as Escherichia coli and Salmonella, produce amyloid-like proteins. These bacterial proteins may stimulate the immune system and accelerate amyloid accumulation in the brain.

Disruption of the intestinal microbiota composition, known as dysbiosis, increases intestinal permeability. This phenomenon is scientifically referred to as “leaky gut.” As a result, bacterial metabolites and toxins can enter the bloodstream and trigger systemic inflammation throughout the body. Lipopolysaccharides (LPS), toxic substances found in the outer membrane of pathogenic bacteria, have been detected at elevated levels in the brain tissues and amyloid plaques of Alzheimer’s patients. These toxins damage the blood–brain barrier, allowing harmful substances to enter the brain more easily. Immune cells in the brain, called microglia, normally help clean and protect brain tissue. However, continuous inflammatory signals originating from the gut can push microglia into a hyperactive state. In this condition, instead of removing amyloid deposits, microglia begin producing cytokines that also damage healthy neurons.

Beneficial bacteria, particularly Bifidobacterium and Lactobacillus species, produce short-chain fatty acids (SCFAs). These acids, especially butyrate, possess neuroprotective properties by reducing inflammation in the brain and strengthening synaptic connections between neurons. In Alzheimer’s disease, the number of these beneficial bacteria decreases significantly.

Research suggests that the pathogenesis of Alzheimer’s disease may begin decades before clinical symptoms appear. A diet low in fiber and high in animal fats alters the microbiota in ways that create conditions favorable for cognitive decline. The intestinal microbiota also participates in the synthesis of neurotransmitters. Substances such as gamma-aminobutyric acid (GABA), acetylcholine, and dopamine are partially produced in the gut with the help of bacteria. Deficiency of these substances weakens the brain’s ability to process information and contributes to memory loss. Oxidative stress is another important factor in Alzheimer’s disease. Free radicals generated as a result of harmful bacterial overgrowth can damage the mitochondria of brain cells. In contrast, a healthy microbiota helps protect neurons by producing antioxidants that counteract these destructive effects.

In clinical experiments, animals modeled with Alzheimer’s disease showed improved memory test performance and reduced amyloid burden in the brain after receiving probiotic treatment. These findings suggest that targeted modification of the microbiota may become a promising strategy for controlling or slowing the progression of Alzheimer’s disease.

The gut–brain axis represents a communication network connecting the intestinal microbiota with the central nervous system. This communication occurs through several pathways:

Neural pathways involving the vagus nerve;

Immune pathways mediated by cytokines and inflammatory molecules;

Endocrine pathways involving hormones and neurotransmitters;

Metabolic pathways through microbial metabolites such as short-chain fatty acids. Disruption of these pathways can negatively affect brain function and may contribute to neurodegenerative disorders, including Alzheimer's disease.

Dysbiosis and Systemic Inflammation

One of the most important mechanisms linking gut microbiota to Alzheimer's disease is chronic systemic inflammation. Dysbiosis occurs when harmful bacteria outnumber beneficial microorganisms within the intestine. This imbalance weakens the intestinal barrier and increases gut permeability, commonly referred to as "leaky gut." Under these conditions, bacterial toxins such as lipopolysaccharides (LPS) can enter the bloodstream. LPS molecules trigger strong inflammatory responses by activating immune cells and promoting the release of pro-inflammatory cytokines. Chronic inflammation caused by circulating bacterial toxins may eventually affect the brain and accelerate neurodegenerative processes.

Studies have demonstrated elevated levels of inflammatory markers and bacterial endotoxins in patients with Alzheimer's disease. These findings support the hypothesis that intestinal inflammation contributes significantly to disease progression.

Amyloid-Beta Accumulation and Bacterial Influence

The formation of amyloid-beta plaques is one of the defining pathological features of Alzheimer's disease. Interestingly, certain intestinal bacteria produce amyloid-like proteins structurally similar to human amyloid-beta. These microbial proteins may stimulate the immune system and increase amyloid aggregation within the brain. Bacterial species such as Escherichia coli and Salmonella have been identified as potential producers of amyloid-like substances. Continuous exposure to these proteins may induce chronic immune activation and enhance neuroinflammation. Furthermore, bacterial endotoxins may weaken the blood–brain barrier, allowing harmful substances to penetrate brain tissue more easily. As amyloid-beta accumulates, neuronal communication becomes impaired, leading to memory loss and cognitive dysfunction.

Microglia are specialized immune cells responsible for protecting and cleaning the brain. Under normal conditions, microglia remove damaged cells and toxic proteins. However, chronic inflammatory signals originating from the gut can transform microglia into a hyperactive state.

Hyperactivated microglia produce excessive amounts of inflammatory cytokines and reactive oxygen species. Instead of protecting neurons, they begin damaging healthy brain tissue. Persistent neuroinflammation contributes to synaptic dysfunction, neuronal death, and progressive cognitive decline.

This mechanism highlights the critical role of intestinal inflammation in the pathogenesis of Alzheimer's disease.

Beneficial gut bacteria produce short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate through the fermentation of dietary fiber. These metabolites possess strong anti-inflammatory and neuroprotective properties.

Butyrate, in particular, supports the integrity of the blood–brain barrier, reduces oxidative stress, and promotes healthy neuronal communication. SCFAs also regulate immune activity and suppress excessive inflammatory responses.

In individuals with Alzheimer's disease, the abundance of SCFA-producing bacteria is often significantly reduced. Consequently, the protective effects of these metabolites diminish, leaving the brain more vulnerable to inflammation and degeneration.

There is also a strong connection between genetic predisposition (for example, the APOE4 gene) and the gut microbiota. Individuals who are genetically susceptible to Alzheimer's disease tend to have intestinal flora that is more sensitive to external influences such as diet and antibiotics, causing it to shift more rapidly into a pathological state. The role of bacteria in the formation of amyloid plaques, one of the major hallmarks of Alzheimer's disease, has been increasingly emphasized. Certain pathogenic bacteria produce "sticky" proteins similar to those found in the brain, which may trigger neurodegeneration.

As a result of dysbiosis, the intestinal wall becomes excessively permeable, a condition known as "leaky gut," allowing toxins such as lipopolysaccharides (LPS) to enter the bloodstream. These toxins can travel through the blood to the brain, where they damage neurons. Research also shows that intestinal bacteria synthesize substances responsible for memory and mood regulation, including serotonin, dopamine, and gamma-aminobutyric acid (GABA). Imbalances in these compounds contribute to the cognitive decline observed in Alzheimer's disease.

The neuroprotective properties of substances such as butyrate and acetate, produced by beneficial bacteria, have also been analyzed. These compounds help protect brain cells and reduce inflammation. It is further explained that microglia, the "cleaning" cells of the brain, may become overly aggressive under the influence of inflammatory signals originating from the gut, eventually leading to the destruction of brain tissue.

Irregular and prolonged use of antibiotics creates a "microbiological vacuum." This not only weakens the immune system but also reduces the brain's ability to repair itself. Therefore, antibiotic therapy in older adults should be approached with caution. Modern medicine increasingly promotes the concept of "personalized nutrition." By studying an individual's microbiota composition, it may become possible to prescribe specific prebiotics and dietary regimens tailored to that person, which could serve as an effective strategy during the early stages of Alzheimer's disease.

In conclusion, Alzheimer's disease is not merely a pathology of the brain but rather a disorder involving the entire organism, including dysfunction of the intestinal microbiota. Maintaining balance between the microbiota and the brain opens new possibilities for

slowing or even preventing neurodegeneration. The role of the gut microbiota in the pathogenesis of Alzheimer's disease is undoubtedly significant and multifaceted. Imbalances in intestinal microorganisms directly contribute to systemic inflammation, weakening of the blood–brain barrier, and accumulation of pathological proteins in the brain. Understanding these connections creates opportunities for early diagnosis and the development of innovative treatment methods, including probiotic therapy and dietary correction. In the future, therapies targeting the gut–brain axis are expected to become a key component in preserving cognitive health.

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