Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/63/20241649

The relationship between gut microbiota and Alzheimer's disorder

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Abstract. The pathology of Alzheimer's disorder: neuron degeneration is the main cause of Alzheimer's disorder. Several ways will stimulate the degeneration of cells. The links between gut microbiota and Alzheimer's disorder consist of three major pathways: the vagus nerve, blood circulation, and release of chemical molecules. This paper discusses not only the pathology of Alzheimer's disorder but also explores the connections between gut microbiota and Alzheimer's disorder, as well as potential treatments based on gut microbiota. Probiotics are mainly discussed in this paper to present possible treatments for Alzheimer's disorder. To conclude, this paper mainly discusses the link between Alzheimer's disorder and gut microbiota. Moreover, the conclusion highlights unresolved issues and unknown aspects of the interaction between Alzheimer's and gut microbiota, urging further research and increased attention from scientists.

Keywords: gut microbiota, Alzheimer's, the relationship between gut microbiota and Alzheimer's.

1. Introduction

Alzheimer's disorder is a progressive neurodegenerative disorder, and although it has been discovered for over 100 years, the pathology and effective treatment is still unclear [1]. Recently, the links between Alzheimer's disorder and gut microbiota have been revealed, and efforts have been made to investigate how the gut microbiota influences the development of Alzheimer's disorder. Alzheimer's disease is the main cause of dementia and is quickly becoming one of the most expensive, lethal, and burdening diseases of this century [2]. With ongoing advancements in understanding the relationship between Alzheimer's disorder and gut microbiota, future research is expected to focus on utilizing gut microbiota for developing treatments. Thus, this paper aims to deliver the latest understanding of the relationship between Alzheimer's disorder and microbiota, encouraging people to conduct further investigations.

2. The pathology of Alzheimer's disorder

2.1. Degeneration caused by the deposition of A-beta plaque

A-beta plaque consists of peptides of A-beta. The formation of A-beta begins with the cleavage of amyloid precursor protein (APP) by beta-secretase, producing a C-terminal membrane attached to fragments of 89 or 99 amino acids. The C-terminal bound with 99 amino acids will be further cleavage by the gamma-secretase, giving rise to the formation of Aβ1-42, a special form of the product [3]. Aβ1-

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42 is prone to accumulate and form the A-beta plaque. When the A beta forms, it will deposit in the human brain, which will cause inflammation and an immune response because the A beta is identified as a foreign material, causing the emission of cytokines by microglia. Finally, the neuron cells start to degenerate due to the immune response.

2.2. Neurofibrillary degeneration

Tau protein is mainly gathered in the microtubule, where it plays a crucial role in maintaining their stability and supporting their proliferation. The Tau protein overgoes phosphorylation, when the cytokine calcium overloads, the kinases CDK5 will be hyperactivated, leading to the hyperphosphorylation of Tau protein [4]. The affinity of Tau protein decreases, resulting in its deposition so that the Tau protein cannot maintain the stability of the microtubule anymore. Moreover, this deposition also influences the ability to transport neuron signals, as a result, the brain cannot function properly: the brain cannot process information and store information, which is the diagnosis of Alzheimer's disorder.

2.3. Immune response

Inflammation is one major immune response that happens in the brain, and it can protect the brain from antigens and injury. However, when the A-beta plaque accumulates in the brain, the microglia are not capable of removing all of the plaque, such that the microglia are persistently activated, releasing pro-inflammatory cytokines. The pro-inflammatory cytokines can disable the microglia, divesting its ability to clear A-beta peptide. Also, it can increase the peptide's ability to aggregate and make it more potent in suppressing synaptic plasticity [2-5].

Besides, the release of cytokines affects Tau protein by activating cyclin-dependent kinases (CDKs), leading to hyperphosphorylation of Tau protein. This hyperphosphorylation, as described in section 2.2, results in neuronal injury.

3. How gut microbiota influences Alzheimer's disorder

3.1. Brief introduction of gut microbiota

Gut microbiota consists of symbiotic bacteria and eukaryotic cells, while the human body is closely related to the activity of gut microbiota [6]. About 1500 species of bacteria benefit from humans, as a result, the gut microbiota releases chemical materials to maintain the stability of pH and other chemical circumstances as well. Besides, the total number of the genome in gut microbiota is several times greater than that of humans, so if the human body is regarded as a whole, most of its genome is not derived from humans. As the gut microbiota is a key factor that exerts various effects on our body, it is necessary to discover the links between gut microbiota and the brain, thus inspiring new solutions for brain injury and brain disorders.

3.2. The vagus nerve

There are many pathways that can transfer signals between the gut and the brain, such as the vagus nerve, connecting the intestine with the autonomic nervous system, and the chemical materials, which can cross the blood-brain barrier thus controlling the brain activity [7]. The vagus nerve consists of neuronal cells that establish a direct connection between the gut and the brain [8]. Through this connection, the brain can release afferent and efferent fibrils to the gut; the enteric nervous system can exchange messages with the central nervous system via the intestine. The most crucial function of the vagus nerve is its ability to transmit signals to the central nervous system, often directly to the brain. Thus, the bacteria and fungus in the gut can release chemical materials that bind to receptors within the intestine. These chemical signals can be transformed into electrical signals, which will be passed through the neuron synapse till they reach their destination—the brain. To conclude, the gut microbiota can use the vagus nerve as a medium to pass signals to the brain, ordering the brain to regulate the body.

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3.3. The blood circulation

The bloodstream passes along the intestine since there is only one layer on the intestine membrane allow many chemical substances to pass through and start to circulate in the bloodstream [9]. The materials are mainly immune and endocrine molecules, which can affect the microglia and influence the extent of Alzheimer's disorder. Moreover, the gut microbiota can affect the astrocytes, another immune cell in the brain. However, the reason why this happens is still unclear. By contrast, it is acknowledged that the fact of gut microbiota releasing can also emit amino acids, such as phenylalanine and isoleucine, which can promote T cell proliferation. Furthermore, the Fermicutes-Bacteroidet can release short-chain fatty acids, which are also called SFAs. SFAs can regulate the microglia with unknown mechanisms.

3.4. Toxin substances

Another hypothesis is that the gut microbiota can release toxin materials [10]. These particles will harm the neuron cells, causing further development of Alzheimer's disorder. To be specific, two major causes are D-lactic acid and ammonia. Moreover, during a process of inflammation, the gut microbiota releases other proteins potentially harmful to the brain, such as proinflammatory cytokines and other innate immune activators in the host [11]. The toxin particles also aggravate the inflammation reaction in the brain, which will result in neuron degeneration to a larger extent. When the degeneration spreads out in the brain, the brain cannot function anymore, it loses its ability to process and store information, which is the most significant diagnosis of Alzheimer's disorder.

4. Possible treatment--probiotics

The term “probiotics” was first coined in 1974 and has conceptually evolved to its current definition as “live microorganisms that modify microbiota toward a beneficial state” [12,13]. The beneficial effects of probiotics are induction of immunomodulation, protection against physiological stress, pathogen antagonism, and improvement of the intestinal epithelial barrier function [12,14]. In a previous experiment, mice were separated into 2 groups, with one group receiving probiotic supplementation. Mice treated with probiotics showed increased capability of memorizing and significantly lower numbers of a-beta plaques. Probiotic supplementation could also considerably improve synaptic malleability and significantly restore long-term potentiation in the Aβ-administered animals. While the exact underlying mechanisms remain unclear, some aspects have been elucidated. The benefits brought by probiotics could be explained by the inhibition of both TLR4- and retinoic-acid-inducible gene-I-mediated NF-κB signaling pathways in the brain [12,15]. However, the technique of probiotics is not matured yet to be utilized. So far, only one clinical test has been done, in which patients with Alzheimer's disorder were treated with probiotics supplements. The results aligned with scientists’ expectations, showing cognitive function improvement in the patients [16]. These findings highlight the significant potential of probiotics. Therefore, further research into probiotics should be encouraged, with a focus on uncovering their mechanisms of action. Once these mechanisms are better understood, additional clinical trials can be conducted, allowing the process by which probiotics alleviate Alzheimer’s disorder to be optimized for maximum efficacy and minimal side effects.

5. Conclusion

Alzheimer's disease is a complex and devastating condition that affects millions of individuals worldwide. The burden of this disease extends beyond those immediately affected, impacting families, caregivers, and healthcare systems. Understanding the mechanisms underlying Alzheimer’s disease is crucial, as is recognizing the far-reaching implications and the urgent need for effective treatments.

The quest for effective treatments for Alzheimer's disease encompasses a wide range of approaches, from molecular and cellular investigations to clinical trials of potential therapies. The gradual unraveling of the intricate pathology of this disease highlights the need for interdisciplinary collaboration and sustained research efforts. Uniting the expertise of researchers from diverse fields can comprehensively address the multifaceted nature of Alzheimer’s disease and lead to innovative and impactful solutions.

While existing treatments provide some symptomatic relief for individuals with Alzheimer's disease, the development of disease-modifying therapies remains a critical goal. This necessitates a multifaceted approach that considers not only the neurological aspects of the disease but also potential contributions from the gut microbiome and other novel avenues of investigation. Expanding the scope of inquiry may uncover new targets for intervention and pave the way for more effective treatment strategies.

Moreover, the development of personalized approaches to Alzheimer's disease treatment holds promise for addressing the heterogeneity of the disease and tailoring interventions to individual patients. Advances in genomics, proteomics, and other omics technologies offer insights into the unique molecular profiles of patients with Alzheimer's disease, enabling the development of targeted and precise treatment regimens.

In tandem with these efforts, it is important to underscore the significance of ongoing support for individuals impacted by Alzheimer's disease and their caregivers. The provision of comprehensive care, resources, and educational initiatives plays a vital role in enhancing the quality of life for those affected by this condition. Furthermore, continued advocacy and public awareness efforts are essential for fostering understanding, empathy, and support within communities.

Navigating the complexities of Alzheimer's disease requires a steadfast commitment to advancing research, promoting compassionate care, and advocating for the well-being of individuals affected by this condition. By upholding these principles, progress can be made toward a future where the impact of Alzheimer's disease is significantly mitigated, providing hope and solace to individuals and families affected by this condition.

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