ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

LETTER TO EDITOR

Is there a fresh hope for Alzheimer's using butyrate?

Xueyi Yin[1], Mengjiao Zhang[2], and Linlin Shao[1]*

[1]Tianjin Key Laboratory of Modern Chinese Medicine Theory of Innovation and Application, College of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

[2]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China

Dear Editor,

More than 3 billion individuals worldwide suffer from neurodegenerative disorders as of 2021,[1] with Alzheimer's disease (AD) being the most prevalent type. In the affected individuals, their memory and other cognitive processes and behaviors experience gradual decline, which can significantly disrupt their day-to-day activities. According to the existing research, patients who experience neuron loss in certain brain areas will eventually experience cognitive impairment as a result of the hippocampus and cortex atrophy. Numerous factors have been found to be related to the disease's pathogenesis, including: (1) mechanisms underlying the inducible neuronal apoptosis during the disruption of the assembly of the natural amyloid precursor protein, such as: (a) when Aβ-42 subtype formation disrupts the lipid in the neuronal cell membrane, leading to the disruption of calcium homeostasis and neuronal death[2]; and (b) when Tau protein phosphorylation results in amyloid-induced synaptic loss[3]; (2) conversion of glycoprotein to advanced glucose oxidation end products during oxidative stress, which causes the release of inflammatory mediators into the brain and causes neuroinflammation due to high neurotoxicity[4]; and (3) Direct damage of mitochondrial protein by amyloid beta protein, leading to increased oxidative stress and impaired energy generation, and decreased adenosine triphosphate production that impairs the function of neurons and glial cells when mitochondrial function is compromised.[5] Thus, it is crucial to seek and develop new strategies that can improve the conditions experienced by AD patients.

The human gut is the home to tens of thousands of bacteria, and along with their byproducts, they are essential for preserving the body's homeostasis, enhancing health, controlling lipid metabolism, and boosting immunity. Short-chain fatty acids (SCFAs) are produced by the fermentation of difficult-to-digest carbohydrates by certain intestinal flora in the colon,[6] such as butyrate produced by Firmicutes and certain anaerobic bacteria (*Bacteroides*, *Clostridium*, *etc.*), which makes up around 20% of the total SCFAs.[7] It has been discovered that the fermentation of indigestible fibers in the stomach by the aforementioned bacteria mostly produces butyrate through two pathways, such as: (1) butyrate kinase pathway, where two acetyl-coenzyme A (CoA) molecules are converted to butyryl CoA, which is subsequently converted to butyryl phosphate by phosphoric acid and produces butyrate through butyrate kinase activity; and (2) butyryl CoA pathway, where acetate and butyryl CoA undergo a β-oxidase reaction mediated by acetate CoA-transferase, converting them to butyrate and acetyl-CoA.[8] Furthermore, the fermentation of amino acids and peptides by some bacteria can produce butyrate. For instance, *Enteromonas* strain AF211 ferments lysine to generate butyrate.[9] Lysine can be converted to glutamic acid by *Fusobacterium varium*, which can then be converted into butyrate.[10]

***Corresponding author:**
Linlin Shao
(shaollin@tjutcm.edu.cn)

Citation: Yin X, Zhang M, Shao L. Is there a fresh hope for Alzheimer's using butyrate? *Eurasian J Med Oncol*. 2025;9(4):362-364. doi: 10.36922/EJMO025080035

Received: February 20, 2025

Accepted: March 11, 2025

Published online: March 27, 2025

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Butyrate-producing bacteria have been shown to decrease the intestinal flora of AD patients.[11] *Bifidobacterium brevis* supplementation alleviated the cognitive deficits of APP/PS1 mice by inhibiting neuroinflammation and synaptic dysfunction through the generation of acetate and butyrate.[12] In addition, the supplementation of butyrate produced by *Clostridium* lowers the cyclooxygenase-2 (COX-2) and CD11b expression levels, preventing nuclear factor kappa B (NF-κB) p65 from being phosphorylated and mitigating neuroinflammation.[13] Both studies showed that AD is linked to the reduction of particular butyric acid-producing groups. Furthermore, taking butyrate supplements may help with cognitive impairment by: (1) inhibiting superoxide dismutase 1, which is upregulated by NADPH oxidase 2 and p21/nuclear factor erythroid 2-related factor 2 pathways that prevent excessive production of reactive oxygen species (ROS) and reduce amyloid Aβ accumulation,[14] thereby enhancing the epigenetic brain-derived neurotrophic factor promoter H3K18ac to alleviate neurodegeneration in diet-induced obese mice[15]; (2) improving mitochondrial function,[16] preventing microglia from becoming overactive,[17] reducing the buildup of Aβ,[17] and promoting astrocyte development into A2-neuron-protective subtypes in AD mice models; and (3) increasing the expression of brain-derived neurotrophic factor and angiotensin-converting enzyme,[18] activating G-protein-coupled receptors,[18] addressing mitochondrial dysfunction,[18] and lowering ROS production.[19] Taken together, sodium butyrate supplementation can ameliorate AD in the Aβ-induced AD cell model.

The research on the use of butyrate to improve AD is still in its infancy, despite the fact that both *in vitro* and *in vivo* experiments have demonstrated the strong potential of butyrate in improving AD and its related diseases. More research is needed to determine the potential mechanisms of action on AD, the toxic side effects of different butyrate, and whether the drug's effectiveness varies with changes in the intestinal flora.

Conflict of interest

The authors declare that they have no competing interests.

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