Development of novel drug for age-associated cognitive dysfunction based on the glymphatic system

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Abstract
In Japan, where the population is aging rapidly, the number of dementia patient has surpassed one million, making it one of the countries with the highest prevalence of this condition. Developing treatments and preventive measures for age-related cognitive impairment is a socially urgent and critical issue to extend healthy lifespans while maintaining brain function. Among age-related cognitive impairments, postoperative delirium is a common and significant cognitive complication after major surgery in older people. Nonetheless, the molecular and cellular mechanisms underlying the pathophysiology of postoperative delirium remain poorly understood, delaying advances in its prevention and treatment. Systemic inflammation induces neuroinflammation – largely regulated by brain resident immune cells, resulting in acute cognitive dysfunction. Recent studies suggest that deterioration of glymphatic waste clearance system may contribute to cognitive decline in the elderly. In the current study, using an aged mouse model of abdominal surgery, we are investigating whether abdominal surgery-induced systemic inflammation results in excess glutamate production in the CNS, which may affect glymphatic waste clearance system and cognitive impairments.

1. Aim of Research

Postoperative delirium is a significant complication frequently observed in elderly patients, characterized by cognitive impairments such as decreased attention and impaired thinking. One pathophysiological aspect of postoperative delirium is the inflammation of both the systemic and central nervous systems. Systemic inflammation is thought to induce brain inflammation primarily controlled by glial cells, leading to acute and transient cognitive dysfunction. Our research group previously reported that suppressing the production of excessive glutamate, induced by brain inflammation, ameliorated depression-related behaviors such as social avoidance and decreased motivation in a mouse model of chronic stress-induced depression (Zhu et al., Neuropsychopharmacology, 2019). However, the detailed molecular mechanisms linking brain inflammation and cognitive impairment remain unclear.

In the body, waste products and harmful substances are expelled through the lymphatic system. Similarly, neuronal activity in the brain produces waste, but the central nervous system lacks anatomical lymphatic vessels, leaving its clearance mechanism unknown for many years. Recently, the glymphatic system was discovered, involving cerebrospinal fluid flowing through the perivascular spaces around arteries and entering the interstitial space via aquaporin-4 (AQP4) receptors expressed on astrocytes, a type of glial cell. This fluid then exits the central nervous system through the perivenous spaces, providing a pathway for waste clearance. The potential impact of age-related declines in this system on cognitive function has drawn significant attention.

In this study, we investigate whether abdominal surgery-induced systemic inflammation increases glutamate levels in the central nervous, leading to aberrant glymphatic waste clearance system and cognitive impairments.

2. Method of research & progression

We prepared a model of abdominal surgery involving inhalation anesthesia with intestinal

manipulation. Behavioral experiments were conducted to evaluate cognitive function at two time points: 1) immediately after surgery and 2) three weeks post-surgery.

We injected the tracer with fluorescent proteins directly into the cerebrospinal fluid. After allowing to perfuse throughout the brain, we observed the distribution of the fluorescent signals in brain regions essential for cognitive function. We also extracted the brain from the mice in each group, and glutamate levels were measured.

3. Result of research

3.1 Memory and Spatial Cognitive impairments induced by abdominal surgery in aged mice

To investigate the impact of abdominal surgery on cognitive function, we performed several memory tests including the Novel Object Recognition Test. Transient cognitive impairments were observed in aged mice subjected to abdominal surgery.

3.2 Disturbance of glymphatic waste clearance system and increased glutamate expression in delirium model

Reduction of glymphatic fluid and excess glutamate production in the hippocampus was induced by abdominal surgery.

4. Future area to take note of, and going forward

Our results suggest that abdominal surgery produces transient cognitive impairments in aged mice, which may result from excess glutamate production and disturbance of glymphatic waste clearance system. We are currently investigating the molecular mechanisms underlying these phenotypes. Additionally, we are exploring whether pharmacological inhibition of glutamate signaling can ameliorate these phenotypes.

We hope our research will contribute to the development of molecular mechanism-based pharmacological interventions for the prevention and treatment of postoperative delirium in the elderly.

5. Means of official announcement of research results

5.1 Publications

Yang K*, Hasegawa Y*, Hua J, Dower M, Etyemez S, Prasad N, Duvall L, Paez A, Smith A, Lane AP, Ishizuka K, Kamath V, Kamiya A, Sawa A: Immune-related molecular changes in the olfactory epithelium, structural alteration in the olfactory bulb, and psychosis. Mol Psychiatry, PMID: 38321120, 2024. (*These authors contributed equally to this work.)

Hasegawa Y, Kim J, Ursini G, Jouroukhin Y, Zhu X, Miyahara Y, Xiong F, Madireddy S, Obayashi M, Lutz B, Sawa A, Brown SP, Pletnikov M, Kamiya A.: Microglial cannabinoid receptor type 1 mediates social memory deficits produced by adolescent THC exposure and 16p11.2 duplication. Nat Commun, PMID: 37880248, 2023

5.2 Future plans

Paper submission (Dec 2024)

Conference presentation

(63rd Annual meeting of the American College of Neuropsychopharmacology, Dec 8-11, 2024. Phoenix, Arizona, USA)