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Role of Brain-Derived Neurotrophic Factor Expression Through Microglial Polarization in Adult Hippocampal Neurogenesis with Major Depressive Disorder

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Abstract: In 2021, an estimation of 14.5 million U.S. adults had experienced Major Depressive Disorder (MDD). Among them, nearly 40% of the population doesn't receive treatment. MDD is characterized by cognitive deficits and impaired neurogenesis. Recent studies have identified Brain-Derived Neurotrophic Factor (BDNF) to be a crucial player in neuroplasticity and neurogenesis, with question remaining regarding its complex correlation with microglial cells and ß-site Amyloid Precursor Protein Cleaving Enzyme 1 (BACE-1) Inhibitors. This paper reviews the interplay between BDNF expression, microglial polarization, and adult hippocampal neurogenesis in the context of MDD, highlighting potential therapeutic implications.

Keywords: Brain-Derived Neurotrophic Factor, Microglial polarization, neurogenesis, Major Depressive Disorder, BACE-1.

1. Introduction

1.1. Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a well characterized neurotrophic factor in the central nervous system. Researchers have discovered its function in regulating cellular processes in development, regulating microglial population dynamics, and maintaining neuronal survival and plasticity. In recent studies regarding the relationship between BDNF and depression, low levels of BDNF have been implicated as risk factors in the pathogenesis of MDD. That is, reduced level of BDNF was observed in the presence of amyloid plaques, which can cause inhibition of the proliferation of neural progenitor cells, thus negatively affecting the survival of newly formed neurons in the hippocampus.

1.2. Microglia

Microglia are the resident macrophages of the central nervous system. Studies have found *in vitro,* that classically activated (M1) microglia release destructive proinflammatory mediators, while alternatively activated (M2) microglia clear cellular debris through phagocytosis and release numerous protective and trophic factors. The two forms of microglial polarization can either increase neuroinflammation or promote neuroprotection, which can lead to alternately reversed effects on neurogenesis. Researchers argue that depression is led by the imbalance between M1 and M2 microglial polarization. Elevated levels of proinflammatory cytokines such as TNF-a and IL-1ß can

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enhance M1 polarization, leading to decreased BDNF expression and impaired neurogenesis. Particularly, looking into postoperative depression (POD) after cardiac surgeries, which sleep disturbance before surgery is a common phenomenon affecting patients' recovery. Results have shown that POD is potentially led by exacerbated microglial M1 polarization caused by sleep disturbance, and microglial BDNF-TrkB signaling dysfunction induced by surgery.

1.3. BACE-1 inhibitors

BACE-1 is an enzyme that cleaves amyloid precursor protein (APP) to produce amyloid-beta (Aß) peptides, which are hallmarks of neurodegeneration. Elevated level of BACE-1 can cause increased production of Aß, which can be detrimental to proliferation of neurons and thus lead to neurodegeneration. Increased BACE-1 activity can also lead to decreased BDNF levels, further impairing the neurogenic process. Moreover, BACE-1 inhibitors also modulate and promote M2 microglial polarization.

2. Methods

BACE-1 modified microglial cells are first generated. Microglial cells are isolated from the wild mice, where they should be transfected with lentiviral vectors containing either BACE-1 shRNA for knockdown or a BACE-1 overexpression construct. Then, *in vitro*, microglial cells are cultured and polarized. LPS can be used to induce M1 microglial polarization, while IL-4 can be used to induce M2 microglial polarization. iNOS and Arg1 can then be used to verify that M1 and M2 polarization have been activated. Then, the microglial cells are co-cultured with Neural Progenitor Cells (NPCs). The NPCs are collected from the subventricular zone or hippocampal dentate gyrus of mice, allowing the NPCs to be co-cultured with the microglia modified with BACE-1 gene. By secreting various factors affecting the proliferation of cells, differentiation and survival of NPCs, the effect of microglia on neurogenesis can be investigated. Neurogenesis can then be assessed. DCX can be used to determine the neurogenesis of microglial cells. By conducting BrdU incorporation assays, cell proliferation can thus be quantified. For behavioral analysis of mice, BACE-1 modified microglial cells are implanted into the mice's brains. By using TST and OFT test, mice can be measured and analyzed for depress-like behavior. Lastly, by utilizing qPCR to analyze BDNF expression in the mice tissue and inducing phosphorylation by TrkB, the activation of BDNF can be investigated. The detection of expression level of BDNF can help the understanding of whether BACE-1 modified microglia function by influencing the BDNF signaling pathway.

3. Expected results

Expected results include changes in the proportion of M1 and M2 microglial polarization in response to polarization treatments in the MDD model. That is, M1 polarization would lead to the decrease in BDNF expression, while M2 polarization would lead to an increase in BDNF. Moreover, altered BDNF levels correlated with the microglial polarization sats with M2 polarization are expected to enhance BDNF expression. The expression level of BACE-1 may promote the polarization of microglia towards M1 (pro-inflammatory) or weaken M2 (anti-inflammatory) states. Unmodified microglia would, on the other hand, provide a reference for the natural polarization state of microglia without BACE-1 intervention.

4. Conclusion

This experiment will elucidate the role of BDNF expression mediated by microglial polarization in adult hippocampal neurogenesis within the context of MDD. However, till the present, there hasn't

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yet been animal studies that succeeded to improve the outcomes after 2 weeks. Potentially, it could be due to the lack of a dose-response curve and long-term end points. Also, rodent immune cells exhibit many differences from their human counterparts. In rodent adult brains, neurogenesis is mainly restricted to the subventricular zone and the subgranular zone of the dentate gyrus in the hippocampus and olfactory bulbs. Whether all features of polarization in rodent cells are truly application to humans remains questioned. It would be essential for translation of microglial phenotype research into clinical practice. Still, the findings may provide insights into therapeutic strategies targeting microglial functions and BDNF signaling for improving neurogenesis and alleviating depressive symptoms.

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