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The Role of Microglial Polarization in Adult Hippocampal Neurogenesis and Possible Depression Therapy

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Abstract: Depression is a complex psychiatric disorder that is closely related to neuroinflammation and adult hippocampal neurogenesis (AHN). Microglia polarised into pro-inflammatory M1 and anti-inflammatory M2 states play a key role in the regulation of AHN. M1 microglia release inflammatory cytokines, leading to neuroinflammation and neuronal damage, while M2 microglia promote neuroprotection and neurogenesis by secreting anti-inflammatory factors. Microglia produce BDNF (brain-derived neurotrophic factor), which is essential for neuronal survival and synaptic plasticity. BDNF is often attenuated in depression, further damaging the AHN. This study explores the role of BACE1 (β-secretase 1) in regulating microglial polarisation. Increased BACE1 expression promotes M1 polarisation and inflammation, while BACE1 knockout transitions microglia to the M2 state, enhances BDNF production and restores AHN. The study uses a chronic mild stress model in mice, hypothesising that BACE1 knockout will reduce neuroinflammation, improve AHN, and attenuate depression-like behaviour. These findings aim to elucidate how targeting microglial polarisation and the BDNF pathway can provide a new therapeutic strategy for the treatment of depression by promoting hippocampal neurogenesis and reducing neuroinflammation.

Keywords: Microglial polarization, BACE1, BDNF, neurogenesis, depression therapy

1. Introduction

1.1. Background

Depression is a mental disorder that presents an increasing hazard to the general public, with complicated and multifaceted causes [1]. Hippocampal plasticity has a close connection to adult hippocampal neurogenesis (AHN). The hippocampus is essential for cognitive processes including memory, learning, and stress and anxiety management [2]. There is strong evidence that neurogenesis continues throughout the life span of animals, but it is confined to certain areas of the brain. AHN is responsible for transforming neural stem cells (NSCs) into mature neurons, a process closely tied to depressive behaviours and responses to stress [3].

Neurotrophic factors aid in the survival, growth, and differentiation of neurones. Reduced hippocampus neurogenesis is linked to lowered neurotrophic support [3]. Antidepressant treatments have been shown to reverse this effect by upregulating neurotrophic factors, thereby restoring neurogenesis. Among the several neurotrophic factors are neurotrophin-3, neurotrophin-4, and nerve growth factor (NGF) [4]. The most widely spread substance in the nervous system's central region is

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the brain-derived neurotrophic factors (BDNF) [5]. It is in control of the growth and operation of the nervous system throughout life by activating three signalling pathways: MAPK, PLC-g, and PI3 kinase. They trigger by binding to the receptor, TrkB (tropomyosin receptor Kinase B) [6]. In Alzheimer's disease mice models, increasing both hippocampus neurogenesis and BDNF levels has been demonstrated to improve cognitive performance [4].

1.2. Microglial polarization and their effects on AHN

The brain's indigenous immune cells, known as microglia, patrol the brain parenchyma and preserve homeostasis by phagocytosing and engulfing extracellular particles [4]. Their ability to phagocyte freshly formed neural progenitor cells (NPCs) that experience apoptosis before becoming neuroblasts is crucial for preserving the homeostasis of the grownup hippocampus neurogenic niche [7]. The pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype are the two main phenotypes that microglia may select when they are activated. Usually triggered by stimulation by inflammatory substances, M1-polarized microglia release cytokines that fuel inflammation. Studies have shown that depression is associated with neuroinflammation and the activation status of microglia, which might affect memory and learning about space [7]. Numerous investigations suggest that reducing microglial overactivation, lowering the release of pro-inflammatory cytokines, and increasing neurotrophic factors secreted by microglia are critical for neurogenesis and cognitive functions [8]. BDNF produced by neurones and microglia is essential for axonal development, neuronal differentiation, survival, and synaptic flexibility [9]. Given this relationship, it is important to explore how microglial polarization towards either the M1 or M2 state affects BDNF levels and AHN [10].

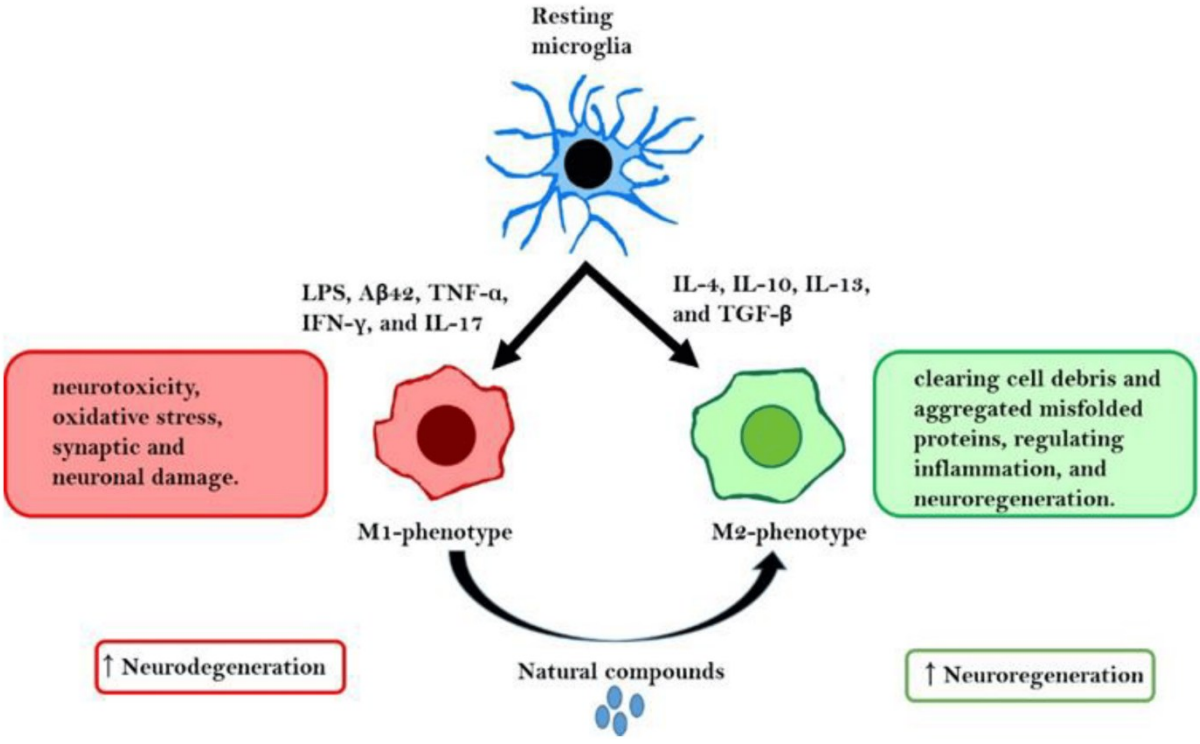


Figure 1: Microglia polarization

Microglia can polarize into two states: M1, which promotes neurodegeneration in response to stimuli like lipopolysaccharide (LPS), amyloid-beta (Aβ), TNF-α, IFN-γ, and IL-17; and M2, which supports neuroprotection and regeneration, triggered by IL-4, IL-10, IL-13, and TGF-β. Natural compounds can shift microglia from the M1 to the M2 phenotype, aiding in brain repair [11].

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1.3. The role of BACE1 in modulating microglial states

Beta-amyloid (Aβ) peptide is created when β-secretase (BACE1) and γ-secretase successively digest amyloid precursor protein (APP) [12]. Amyloid plaque develops when Aβ peptides build up abnormally. Studies employing conditional BACE1-deficient models or BACE1 knockout mice have validated BACE1's function in synaptic function and appropriate hippocampus axonal organization [13]. Research focussing on BACE1 deletion in microglia has demonstrated a decreased burden of amyloid plaque in 5xFAD mice, a model for Alzheimer's disease [13]. Aβ accumulation leads microglia to become M1 polarized, resulting in the production of pro-inflammatory chemicals including TNF-α and IL-1β. This promotes neuroinflammation and neuronal damage. Increased BACE1 expression, therefore, likely promotes M1 polarization, exacerbating the inflammatory response in pathological conditions [3]. Nevertheless, BACE1 deletion may reduce M1 polarization, which promotes a shift to the anti-inflammatory M2 phenotype that aids in the removal of harmful proteins and the repair of injured tissue.

Furthermore, chronic stress is known to drive microglial polarization towards the M1 state, decreasing BDNF levels and impairing AHN. It is hypothesized that knocking out the BACE1 gene could prevent M1 polarization, encourage a shift towards the M2 phenotype, increase BDNF production, and restore normal AHN levels. Such a mechanism presents a potential therapeutic strategy for treating depression by addressing the neuroinflammation and neuronal damage linked to microglial polarization.

2. Materials and methods

2.1. Animal model

Male and female C57BL/6 mice aged 8–10 weeks were used in the experiment. The mice will have complete access to food and drink and be kept in a typical laboratory environment with a 12-hour light/dark cycle. Institutional guidelines for animal care should be followed in all research [14]. The mice will be divided into four groups (n = 10 per group): (1) Chronic mild stress (CMS)-induced stress with microglial polarization towards M1. (2) CMS-induced stress with microglial polarization towards M2. (3) Control group with no stress and microglia polarized to M1. (4) Control group with no stress and microglia polarized to M2.

2.2. Stress induction

A Chronic Mild Stress (CMS) protocol will be used to induce stress in the mice. (1) Restraint stress: Mice will be immobilized in restraint tubes for 2-3 hours daily for one week. This method effectively models chronic psychological stress by limiting movement. (2) Cortisol injections: To chemically produce stress, 20 mg/kg body weight of cortisol will be administered intraperitoneally once daily. Both methods will reduce Adult Hippocampal Neurogenesis (AHN), mimicking stress-induced depressive conditions in the mice.

2.3. BACE gene knockout

The BACE1 gene will be conditionally knocked out in microglia alone using the Cre-LoxP system to examine the function of BACE1 in microglial polarization. This will be achieved by crossing BACE1-floxed mice (BACE1^fl/fl) with microglia-specific Cre-expressing mice (Cx3cr1-CreERT2). Tamoxifen (75 mg/kg) will be administered via oral gavage for 5 consecutive days to induce Cre recombinase activity in microglia, resulting in specific BACE1 gene knockout [15]. Genotyping via

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PCR will be performed to verify BACE1 knockout efficiency. Hippocampal tissue will be collected for PCR analysis 1-week post-tamoxifen treatment.

2.4. Behavioural assessment

To evaluate depressive-like behaviours induced by stress, the Tail Suspension Test (TST) will be conducted. Adhesive tape will be used to suspend the mice by their tails, which are attached to a hook around 60 centimetres above the ground. Each mouse will be observed for a total of 10 minutes, and the immobility time (time spent without movement) will be recorded. Increased immobility time is indicative of depressive-like behaviour, and this will be compared across the stressed and control groups [7].

2.5. Microglial polarization and AHN measurement

Brain slices (particularly those from the hippocampus) will be analysed for microglial polarisation using specific markers for M1 and M2 microglia. The anti-IBA1 antibody will be used to identify all microglia. Anti-CD11B antibody will be utilised to identify M2-polarized microglia [15]. Brain tissue will be preserved in 4% paraformaldehyde and sectioned at 40 μm with a cryostat. Sections will then be antigen-retrieved and blocked before being incubated with primary antibodies. Brain slices will also be immunofluorescence stained for BDNF (brain-derived neurotrophic factor), a critical marker of neurogenesis [16]. BDNF protein levels will be quantified and microglial polarisation markers (M1 and M2) will be verified using Western Blot.

2.6. Data collection and analysis

The percentage of M1 versus M2 microglia will be quantified by counting the number of CD11B-positive cells (M2) and comparing them to the total IBA1-positive cells (all microglia). These data will be compared across all groups. BDNF expression will be measured through both immunohistochemistry and Western blotting, and the results will be normalized to internal controls (e.g., GAPDH for WB) for accurate comparison. The mean ± standard error of the mean (SEM) will be used to display all data. Tukey's post hoc test for multiple comparisons will be used after a one-way ANOVA to examine differences between the experimental groups. Statistical significance will be established when the p-value is less than 0.05.

3. Results (expected)

This increase in M1 microglial is naturally expected to be associated with a neuroinflammatory process characterized by reduced neurogenesis in the hippocampus. On the other hand, it is predicted that the cohort of mice with BACE1 knockout will be characterized by an increase of M2-polarized microglia cells, which are producers of anti-inflammatory cytokines such as IL-10 and markers of tissue repair [17]. It is probable that this shift of M2 microglia will lead to a decrease in neuroinflammatory processes, hence paving the way for a more neuroprotective environment even under stress. The anticipated findings lend credence to the theory that the inactivation of BACE1 entailed the lowering of M1 microglia activation along with the promotion of M2 microglia polarization, thereby reversing M2-depressant effects on neurogenesis. However, in the BACE1 knockout group, BDNF production levels are anticipated to remain stable even in the case of stress-induced BDNF loss. The gradual rise in M2 microglia, which is responsible for influencing the release of neurotrophic factors, results, probably, in increased NSPC survival and differentiation rate. Consequently, AHN would be as much or as little as that in the physically unstressed control counterparts of the animals, indicating that the BACE1 gene eliminates the harmful impact of stress

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on neurogenesis [18]. Therefore, it becomes evident that keeping BDNF levels intact contributes in stress immunity and protects the hippocampus from deterioration.

In the behavioral test, it is been predicted that mice with higher amounts of M1-classified microglia would yield results the same as mice showing signs of depression, according to the TST or tail suspension test. Specifically, mice in the control group under stress conditions should be expected to display increased immobility time in the TST, which represents higher vulnerability to stress and depressive tendencies compared to the stress-free group. In the opposite direction, mice in the BACE1 knockout, which have a high proportion of M2-polarized microglia, are predicted to have a lesser immobility duration during the TST, indicating development of resilience against stress-induced depression-like behaviors. The M2-microglial polarization, which happens simultaneously with behavioral improvements like better cognitive performance and less anxiety, will be further investigated [7].

4. Discussion

The hypothetical result indicates that long-term stress results in M1 microglial polarization and that this is associated with the reduction of BDNF and decline in AHN. This forms the platform for a new theory that argues that stress-induced alterations in microglia activity to M1 can alter the neurogenesis patterns thereby resulting in behavioral traits like depressive symptoms. In contrast, the gene knockout of BACE1 preferentially increases M2 microglia that may amplify BDNF expression and supply the required BDNF substrate essential for generation of new neurons. These experiments not only affirm the association but also reveal how changing the type of microglia affects BDNF levels and affects function of the hippocampus, which in turn seems to underline depressive symptoms in patients. As such, increasing BDNF secretion by M2 microglia, which can be mediated by modulating BACE1, might alleviate neurogenesis and defend neurons from stress-induced neuronal atrophy. Gene therapy targeting BACE1 could represent a novel strategy for developing therapeutics that influence the inflammation and eventually the brain functioning in a depression disorder.

Despite these promising findings, several limitations exist. Though BDNF is considered a special component in availing neurogenesis and the antidepressant action, studies on its connection to depression are contradictory in nature. Future studies should examine the interplay that environmental and genetic factors have in moderating BDNF levels and their efficacy in managing conditions [8]. An effective intervention and preventive measure will be largely determined by how these factors interact and affect the treatment process.

5. Conclusion

In summary, BACE1 gene knockout looks to be a promising avenue in depression treatment in that it boosts BDNF levels and neurogenesis. Although this investigation has presented valid in vitro research, clinical trials are still necessary to detect the clinical consequences of such a therapy and also to achieve the widest range of patients by establishing a combination of drugs aimed at repairing the function of microglia to cure depressive disorders.

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