EJMR
ERA'S JOURNAL OF MEDICAL RESEARCH
p-ISSN: 2348-9839, e-ISSN: 2394-5222 | www.ejmr.org

Volum 12 Issue 1
REVIEW ARTICLE

Microglial Mitigation: A Novel Avenue for Antidepressant Research

Ausaf Ahmad

Received on: 27-01-2025 Published on: 30-04-2025

ABSTRACT

Depression is a serious mental health condition with an average incidence rate of 4.4 percent worldwide. The pathophysiology of depression is generally linked to the monoamine neurotransmitter reduction, disturbed hypothalamus–pituitary–adrenal (HPA) axis, heightened oxidative load and altered neuroplasticity. Antidepressants have historically targeted monoamine neurotransmitters and HPA-axis hyperactivity restoration. However, there is mounting evidence that neuroinflammation and immunological dysregulation, specifically involving microglia, are key factors in depression. Thus, we aimed to explore the insights of antidepressant drugs in terms of their ability to mitigate the microglial activity and modulations of their phenotype functioning. In the present review, we have highlighted the biological basis of some common clinically used antidepressants (like SSRIs, TCAs, MAOIs, NMDA receptor antagonists) and relevant therapeutic targets (like immunomodulators, anti-inflammatory molecules, PPAR γ agonists), and attempted to provide insights about the role of microglial activity and phenotype shifting in normalizing depressive-like behaviours. We observed that most of the antidepressants are working through modulating redox state, maintaining inflammatory response, restoring synaptic plasticity, enhancing neurogenesis factors, and regulating monoamine levels. Interestingly all these mechanisms are directly associated with microglial activation specially in brain structures which are involved in the pathophysiology of depression such as frontal cortex and hippocampus. This review provided a new perspective of evaluating antidepressant potential of various already used and upcoming novel drugs based on microglial perturbations in the CNS.

Keywords: *Antidepressants, Microglial cells, Monoamines, Neuroinflammation, ROS.*

Era's Journal of Medical Research. 12(1);2025 [doi: 10.24041/ejmr.2025.4]

INTRODUCTION

Depression is a severe mental illness marked by a lessened ability to enjoy life and a constant sense of despair. Increasing stress in today's lifestyles is a significant factor contributing to depression. According to the WHO, there are currently over 350 million people who suffer from depression, with an average incidence rate of 4.4% worldwide.[1] Depression is predicted to become the leading cause of non-fatal health loss globally and to have the highest global illness burden by 2030.[1] It involves multiple interacting systems, such as neurochemical, neuroendocrine, immune, and neuroplasticity. So far, the primary focus in explaining the etiology of depression is linked to the monoamine neurotransmitter depletion, perturbed hypothalamus–pituitary–adrenal (HPA) axis, enhanced oxidative load and neuroplasticity hypothesis.[2] Hence the focus of finding antidepressants is also mostly confined to these well-defined pathways. However, there are numerous limitations associated with these pathological mechanisms in terms of explaining the delayed and diverse effects of antidepressants and lack of insights into their biological processes.

Commonly, selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors; SSRIs/SSNIs, tricyclic antidepressants and other medications are used for depression.[3] However, a variety of adverse effects, including nausea, dry mouth, light-headedness, weight gain, sexual dysfunction, withdrawal symptoms, habit formation, or even drug tolerance, may result from these treatments.[3] Furthermore, separate molecular pathways still need to be carefully identified to target different types of depression across diverse age groups and comorbidities, even if there are CNS commonalities in neuroinflammation, neurotoxicity, aging, and depression-related changes. Additionally, most of the antidepressant-related research is focused only on neurons, whereas the involvement of other cells of CNS is generally overlooked. Thus, it is critical to search for antidepressants with different strategies based on new cellular and molecular insights studied in last decade or so.

The immune cells that reside in the brain are called microglial cells. They are referred to as the "housekeepers" of the brain and are representative of the main immune system of the CNS. Microglial populations, which make up 10% of all glial cells, are widely dispersed throughout the brain, with higher densities observed in the substantia nigra and hippocampus regions.[4,5]

Amity Institute of Biotechnology, Amity University, Lucknow, UP, India-226028
Corresponding Author: Ausaf Ahmad
Email: aahmad@lko.amity.edu
How to cite: Ahmad A.Microglial Mitigation: A Novel Avenue for Antidepressant Research. Era J Med Res. 2025;12(1):19-22.

In some recent reports, there are clear indication that depression is associated with microglial cell activity.[6] Reports suggest that microglial phenotype functional changes are associated with accumulation of genetic instability/ mutations, epigenetic regulations, altered synaptic plasticity, buildup of toxic substances (iron, free radicals, misfolded/aggregated proteins), impaired proteostasis and mitophagy, mitochondrial and lysosomal dysfunctions, heightened neuroinflammation, impaired cell cycle arrest, reduced cognition and impaired neurotransmission.[4, 7-11]

Careful examination of these pathways indicated that microglial-induced changes are mostly related to the pathological alterations and molecular pathways that are common to the development of microglial-induced aging and progression of depression.[6] This intrigued us to review the possible involvement of microglial mitigation in various known and novel antidepressant strategies and discuss their probable direct or indirect involvement in modulating the treatment of depression like pathologies. Microglial mitigation refers to strategies aimed at reducing or modulating the activation of microglia, especially in pathological conditions like depression, neurodegenerative diseases, and chronic stress. The objective of this review is offering the understanding of a new path of study of antidepressant drugs in terms of their ability to mitigate the microglial activity and modulations of their phenotype functioning.

Crosstalk between Microglial Activity and Antidepressants

In this section we have encompassed various antidepressants agents and therapeutic targets to analyze how they are exerting their antidepressant effects, and whether there is an association of their biological activity with microglial activation and phenotypes. Knowing how microglia modulate in antidepressants activity could help researchers create fresh approaches in treating this debilitating mental health condition. Microglia regulation has been suggested as a potentially useful treatment approach for several neurological conditions that resemble depression.

Selective Serotonin Reuptake Inhibitors

The most used class of antidepressants are Selective Serotonin Reuptake Inhibitors (SSRIs), which include citalopram and fluoxetine. They increase serotonin (5-HT) availability in the synaptic gap by preventing its reabsorption into presynaptic neurons. According to some recent reports, SSRIs may modulate microglial activation in addition to serotonin neurotransmission to partially alleviate depression.[12] The biological basis of such effects of SSRIs can be linked with their ability to reduce pro-inflammatory cytokines (IL-1β and TNF-α etc) produced by primed microglia.[4,10] Microglial morphology can be broadly categorised into three phenotypes (resting, M1 and M2), which are indicative of their functional condition.[13] Resting morphology involved in maintaining homeostasis.[14-16] M1 helps inflammation through enhancement of immune mediators like TNF-α, IL-1β, IL-6 and promoting oxidative stress with a stimulus of LPS, IFN-γ, DAMPs and pathogens.[10,17] M2 suppresses inflammation and leads to repair and regeneration mechanisms and involved in expressing anti-inflammatory interleukins such as IL-10, stimulated by IL-4 and IL-13 etc.[4,14] SSRIs may shift microglia from M1 to M2 phenotype, thereby reducing neuroinflammation and promoting neuroplasticity. The primary initiators of antidepressant activity are neurogenesis and synaptic remodelling; SSRIs and microglial-derived substances, like brain-derived neurotrophic factor (BDNF), may act synergistically to reduce depressive like symptoms.[18]

Tricyclic Antidepressants

Tricyclic Antidepressants (TCAs) like clomipramine and imipramine are known to block the reuptake of 5HT and NE thus increasing their synaptic levels and reversing depressive behaviors. These conventional antidepressants encourage anti-inflammatory microglia to become activated (M1 to M2 phenotype shift) to produce neurotrophic factors like BDNF and anti-inflammatory interleukins, indicating that TCAs may have an anti-inflammatory role.[19] Microglial activation that includes enlarging their cell bodies and shortening their processes casing upregulation of pattern recognition receptors and secreting potentially cytotoxic unstable species such as nitric oxide, reactive nitrogen and oxygen species.[14,20] TCAs are associated with the reduction of ROS produced by microglia, protecting neurons from oxidative damage associated with chronic stress and inflammation in depression. TCAs also modulate neuroinflammation and glial activity via NF-κB pathways[19] Another mechanism proposed is that TCAs can modulate HPA-axis via glucocorticoid receptor sensitivity and thus normalize stress-induced microglial activation.[21] Thus, TCAs, though classically known for altering neurotransmitter levels, may also exhibit immunomodulatory effects via microglial perturbations.

Monoamine Oxidase Inhibitors

This class of drugs includes Phenelzine, Selegiline etc produce their antidepressant effect via inhibiting monoamine oxidase enzymes for example MAO-A and MAO-B, thereby limiting the breakdown of neurotransmitters such as 5-HT, NE and dopamine (DA). Thus, MAOIs primarily work through increasing the availability of monoamines in the brain. It is important to note that microglial cells activation are also associated with neurodegeneration through perturbed synapse density, plasticity and decreased levels of neurotransmitters (5-HT, NE, DA) and their altered biosynthetic processes.[8,22] Monoamine oxidases (MAO) are associated with increase in ROS levels and enhancement of neuroinflammation.[23] Thus, by inhibiting MAO, Monoamine

Oxidase Inhibitors (MAOIs) may mitigate ROS and proinflammatory cytokines, thereby decreasing oxidative stress and neuroinflammation associated with activation of microglia.[24]

NMDA Receptor Antagonists

The noncompetitive NMDA receptor antagonists such as Ketamine known to produce their antidepressant effect and promoting the synaptic plasticity by enhancing the glutamate signalling through AMPA receptors. Although microglia have not traditionally been linked to NMDA receptors, new research indicates that, in some circumstances, they may express functional NMDA receptors.[25] The release of inflammatory promoting interleukins such as TNF-α and IL-1β, contribute to neuroinflammatory processes, has been connected to the activation of these receptors on microglia. Thus, NMDA receptor antagonists may provide therapeutic effects by limiting neuroinflammation and restoring neuroplasticity through the modulation of microglial activity.[26]

Neuroimmune Modulators

These generally belong to anti-inflammatory class of drugs such as Minocycline, Celecoxib and TNF-α inhibitors etc. Few studies showed that prolong administration of minocycline normalizes depressive-like behavior by modulating HPA-axis and microglia hyperactivation.[27] Minocycline mediated a steadiness between pro-inflammation and anti-inflammation responses in the brain regions responsible for depressive-like symptoms such prefrontal cortex, hippocampus and amygdala.[27] In stress scenarios, these medications also contribute to the upregulation of BDNF-mediated synaptic plasticity.[28]

Peroxisome Proliferator-activated Receptor Gamma

Peroxisome Proliferator-activated Receptor Gamma (PPARγ) is a nuclear receptor and transcription factor essential for controlling inflammation, metabolism, and cellular development. Because of its regulatory effects on microglial cells, it has drawn a lot of interest for its role in disorders of the CNS, including depression. PPARγ agonists such as pioglitazone reduce depressive-like symptoms in animal models (Chronic mild stress-treated C57BL/6 mice) primarily by regulating microglial activation and lowering neuroinflammatory responses and reestablishing synaptic plasticity and neurogenesis.[28] According to these results, pioglitazone, an agent that modulates microglia, may be a good option for treating depression. Like mitochondria, peroxisomal function also deteriorates with depression, causing inflammation, neurodegeneration, and oxidative stress.[29] PPARγ has a crucial role in controlling neuroinflammation and microglial activation, two processes that are essential to the onset and course of depression. Thus, a possible treatment option for reducing depression symptoms linked to neuroinflammatory processes is PPARγ activation, which promotes anti-inflammatory microglial states and increases the release of neuroprotective cytokines.

Future perspective

The CNS's principal immune cells, microglial cells, are essential for preserving neural homeostasis. According to recent research, microglial activation is a major factor in the pathogenesis of depression.[4] Neuroinflammation, which is really connected to a phenotypic shift of microglia, including morphological alterations, increased production of cytokines, and oxidative stress products, may have an impact on the onset and maintenance of depression.[6] These microglial-induced enhancement of pro-inflammatory cytokines and their neurotoxic response are the chief perpetrators behind CNS disorders.[30] Therefore, the goal of future research should be to restore microglial homeostasis to decrease the progression of neurodegeneration and modulate the antidepressant actions. Finding, evaluating, and applying compounds or treatments that can restore the molecular mechanisms underlying microglial-induced activation such as maintaining an ideal redox state, efficient surveillance and phagocytosis, synaptic plasticity, BDNF activation, hippocampus function, and monoamine maintenance may be the main strategies of the future. Finding treatments that can reduce chronic microglial activation without compromising their neuroprotective role should be the aim of future studies. One such strategy could be targeting microglial phenotype switching from M1 (inflammatory favouring) to M2 (inflammatory limiting) states that may reverse depressive pathology. Also, Potential strategies include using PPARγ agonists, IL-10 modulators, and natural compounds like flavonoids all these generally work through modulating redox state, maintaining inflammatory response, restoring synaptic plasticity, enhancing neurogenesis factors, and regulating monoamine levels.

CONCLUSION

It is becoming more well acknowledged that microglial cells have a part in the pathogenesis and management of depression. Antidepressants have historically targeted monoamine neurotransmitters (5-HT, DA, and NE) and HPA-axis hyperactivity restoration. However, there is mounting evidence that neuroinflammation and immunological dysregulation, specifically involving microglia, are key factors in depression, particularly in cases that are resistant to treatment. In the present review, we have highlighted the biological basis of some common clinically used antidepressants (like SSRIs, TCAs, MAOIs, NMDA receptor antagonists) and relevant therapeutic targets (like immunomodulators, anti-inflammatory molecules, PPAR γ agonists), and try to provide insights about the role of microglial activity and phenotype shifting in normalizing depressive-like behaviours. We observed that most of the antidepressants are working through modulating

redox state, maintaining inflammatory response, restoring synaptic plasticity, enhancing neurogenesis factors, and regulating monoamine levels. Interestingly all these mechanisms are directly associated with microglial activation specially in brain structures which are involved in the pathophysiology of depression such as frontal cortex and hippocampus. This review highlighted a new horizon of evaluating antidepressant potential of various already used and upcoming novel drugs and natural compounds based on microglial perturbations in the CNS. Therefore, it has been suggested that controlling microglia could be a useful treatment approach for several neurological conditions that resemble depression by directly suppressing microglial activation or reprograming their immune responses.

REFERENCES

1. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. JAMA. 2017;317:1517.
2. Dean J, Keshavan M. The neurobiology of depression: An integrated view. Asian journal of psychiatry. 2017;27:101-11.
3. Gomez AF, Barthel AL, Hofmann SG. Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: a meta-analytic review. Expert opinion on pharmacotherapy. 2018;19(8):883-94.
4. Bachiller S, Jimenez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, et al. Microglia in Neurological Diseases: A Road Map to Brain-Disease Dependent-Inflammatory Response. Front Cell Neurosci. 2018;12:488.
5. Henneman WJ, Sluimer JD, Barnes J, van der Flier WM, Sluimer IC, Fox NC, et al. Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. Neurology. 2009;72(11):999-1007.
6. Deng SL, Chen JG, Wang F. Microglia: A Central Player in Depression. Current medical science. 2020;40(3):391-400.
7. Boje KM, Arora PK. Microglial-produced nitric oxide and reactive nitrogen oxides mediate neuronal cell death. Brain Res. 1992;587(2):250-6.
8. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal transduction and targeted therapy. 2023;8(1):359.
9. Jha MK, Jeon S, Suk K. Glia as a Link between Neuroinflammation and Neuropathic Pain. Immune Netw. 2012;12(2):41-7.
10. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. Transl Neurodegener. 2020;9(1):42.
11. Rogers J, Strohmeyer R, Kovelowski CJ, Li R. Microglia and inflammatory mechanisms in the clearance of amyloid beta peptide. Glia. 2002;40(2):260-9.
12. Mariani N, Everson J, Pariante CM, Borsini A. Modulation of microglial activation by antidepressants. Journal of psychopharmacology (Oxford, England). 2022;36(2):131-50.
13. Bernhardi VR, Tichauer JE, Eugenin J. Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. J Neurochem. 2010;112(5):1099-114.
14. Hanslik KL, Marino KM, Ulland TK. Modulation of Glial Function in Health, Aging, and Neurodegenerative Disease. Front Cell Neurosci. 2021;15:718324.
15. Luo XG, Ding JQ, Chen SD. Microglia in the aging brain: relevance to neurodegeneration. Mol Neurodegener. 2010;5:12.
16. Wang J, Qin J, Wang P, Sun Y, Zhang Q. Molecular Mechanisms of Glial Cells Related Signaling Pathways Involved in the Neuroinflammatory Response of Depression. Mediators Inflamm. 2020;2020:3497920.
17. Damani MR, Zhao L, Fontainhas AM, Amaral J, Fariss RN, Wong WT. Age-related alterations in the dynamic behavior of microglia. Aging Cell. 2011;10(2):263-76.
18. Wu SY, Pan BS, Tsai SF, Chiang YT, Huang BM, Mo FE, et al. BDNF reverses aging-related microglial activation. J Neuroinflammation. 2020;17(1):210.
19. Hwang J, Zheng LT, Ock J, Let al. Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. Neuropharmacology. 2008;55(5):826-34.
20. Contestabile A, Monti B, Polazzi E. Neuronal-glial Interactions Define the Role of Nitric Oxide in Neural Functional Processes. Curr Neuropharmacol. 2012;10(4):303-10.
21. Ramirez K, Sheridan JF. Antidepressant imipramine diminishes stress-induced inflammation in the periphery and central nervous system and related anxiety- and depressive- like behaviors. Brain, behavior, and immunity. 2016;57:293-303.
22. Dahl MJ, Werkle-Bergner M, Mather M. Neuromodulatory systems in aging and disease. Neuroscience and biobehavioral reviews. 2024;162:105647.
23. Ahmad A, Rasheed N, Banu N, Palit G. Alterations in monoamine levels and oxidative systems in frontal cortex, striatum, and hippocampus of the rat brain during chronic unpredictable stress. Stress (Amsterdam, Netherlands). 2010;13(4):355-64.
24. Gao M, Hu P, Cai Z, Wu Y, Wang D, Hu W, et al. Identification of a microglial activation-dependent antidepressant effect of amphotericin B liposome. Neuropharmacology. 2019;151:33-44.
25. Kim JW, Suzuki K, Kavalali ET, Monteggia LM. Ketamine: Mechanisms and Relevance to Treatment of Depression. Annual review of medicine. 2024;75:129-43.
26. Kaindl AM, Degos V, Peineau S, Gouadon E, Chhor V, Loron G, et al. Activation of microglial N-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. Annals of neurology. 2012;72(4):536-49.
27. Zhang C, Zhang YP, Li YY, Liu BP, Wang HY, Li KW, et al. Minocycline ameliorates depressive behaviors and neuro-immune dysfunction induced by chronic unpredictable mild stress in the rat. Behavioural brain research. 2019;356:348-57.
28. Zhao Q, Wu X, Yan S, Xie X, Fan Y, Zhang J, et al. The antidepressant-like effects of pioglitazone in a chronic mild stress mouse model are associated with PPARγ-mediated alteration of microglial activation phenotypes. J Neuroinflammation. 2016;13(1):259.
29. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Frontiers in immunology. 2018;9:586.
30. Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol. 2008;84(4):932-9.

Orcid ID:
Ausaf Ahmad - https://orcid.org/ 0000-0002-1026-497X