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Retraction

Retracted: Microglia Involves in the Immune Inflammatory Response of Poststroke Depression: A Review of Evidence

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This article has been retracted by Hindawi, as publisher, following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of systematic manipulation of the publication and peer-review process. We cannot, therefore, vouch for the reliability or integrity of this article.

Please note that this notice is intended solely to alert readers that the peer-review process of this article has been compromised.

Wiley and Hindawi regret that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] W. Xia, Y. Xu, Y. Gong, X. Cheng, T. Yu, and G. Yu, "Microglia Involves in the Immune Inflammatory Response of Poststroke Depression: A Review of Evidence," *Oxidative Medicine and Cellular Longevity*, vol. 2022, Article ID 2049371, 11 pages, 2022.

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Review Article

Microglia Involves in the Immune Inflammatory Response of Poststroke Depression: A Review of Evidence

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Poststroke depression (PSD) does not exist before and occurs after the stroke. PSD can appear shortly after the onset of stroke or be observed in the weeks and months after the acute or subacute phase of stroke. The pathogenesis of PSD is unclear, resulting in poor treatment effects. With research advancement, immunoactive cells in the central nervous system, particularly microglia, play a role in the occurrence and development of PSD. Microglia affects the homeostasis of the central nervous system through various factors, leading to the occurrence of depression. The research progress of microglia in PSD has been summarized to review the evidence regarding the pathogenesis and treatment target of PSD in the future.

1. Microglia

Microglia can be transformed into activated microglia post-brain trauma, infection, or other central nervous system diseases. Rapid proliferation and activation of microglia can have various forms and move to the lesion area. Its activation process includes proliferation, chemotaxis, and cytokine secretion. Microglia can secrete many inflammatory cytokines and molecules, inducing immune-inflammatory reactions and increasing the blood-brain barrier (BBB) permeability. On the other hand, activated microglia promote the regeneration of the nerve cells, facilitating nerve repair after acute cerebral stroke [1–3]. When the external stimulus is eliminated, activated microglia gradually return to the resting state. Microglia can be divided into two polarized phenotypes based on their secreted cytokines, namely, M1 and M2 types [4]. M1 microglia account for most activated microglia, mainly expressing surface antigens such as CD16, CD32, and CD86 [5]. M1-type microglia can exert a phagocytic effect through contact with nerve cells or activating the colony-stimulating factor (CSF) and tumor necrosis factor-α (TNF-α). Moreover, it promotes the synthesis and secretion of interleukin-1 (IL-1), IL-4, and other inflammatory factors, thereby triggering the immune-inflammatory cascade reaction [6–8]. M2 microglia can be divided into M2a, M2b, and M2c subtypes based on different stimuli. M2a microglia can be generated by IL-4, IL-13, and other stimuli and release IL-10 and other anti-inflammatory factors, thus achieving inflammatory response inhibition and neuroprotection [9–11]. In general, cytokines secreted by activated M1-type microglia have proinflammatory effects, while activated M2-type microglia are essential in nerve repair and plasticity.

2. Microglia and Stroke

Different stimuli and pathological environments determine the phenotypes of microglia. Several studies have demonstrated that nerve cells can release cytokines to promote the transformation of M2 to M1. When a stroke occurs, microglia exhibits the characteristics of dynamic change. The early stage of stroke is dominated by the M2 type, which appears 1~3 days after stroke, peaking at 3~5 days, and is sustainable for 14 days. M1-type microglia appeared on

day three and peaked on day 14, revealing the dynamic process of microglia from neuronal protection to nerve injury after stroke [12]. Based on physiological conditions, M1 and M2 microglia maintain a dynamic balance. However, this balance will be disrupted when stimulated with stroke, trauma, inflammation, and other stimuli. Ultimately, the different substances induced by stimulation directly affect whether microglia could protect or damage the nervous system [13].

Microglia can exert a neuroprotective effect by releasing factors such as glial cell-derived neurotrophic factor (GDNF), transforming growth factor-β (TGF-β), and P2X7 receptor, involved in Ca^{2+} overload inhibition, angiogenesis, and remodeling of the cytoskeleton. On the other hand, microglia can promote the induction of matrix metalloproteinases (MMPs), nitric oxides (NOS), TNF-α, and other inflammatory factors involved in BBB disruption, vasospasm, cellular death, and thrombosis, aggravating the brain injury poststroke [14, 15].

The activation of microglia in the inflammatory response is a "double-edged sword" which plays a dual role in the occurrence and development of ischemic stroke as the first line of defense for central nervous system injury [16, 17]. M1-type microglia mainly produces proinflammatory mediators and additionally plays a cytotoxic role in damaging the nervous system. In contrast, M2-type microglia has protective factors supporting neuronal repair and regeneration. Due to the pleiotropy of microglia during ischemic stroke, its clinical significance deserves further study. Therefore, regulating the activation of microglia and exploring the dynamic changes of microglia after stroke is crucial in the prognosis of ischemic stroke. Future studies will continue to explore how to promote the M2-type polarization of microglia, thus enabling brain injury repair. Moreover, methods to inhibit the M1-type differentiation of microglia need to be explored to reduce the secretion of inflammatory factors, attenuate the brain damage, and ultimately reduce the degree of cerebral ischemia injury and promote functional recovery of the brain tissue [18].

3. Ischemic Stroke and Depression

Stroke is the leading cause of death, disability, and reduced life span worldwide, and its incidence and prevalence are increasing with age [19, 20]. According to the World Health Organization (WHO) report, 15 million people suffer from stroke yearly, which significantly burdens society [20, 21]. Poststroke depression (PSD) is the most common noncognitive neuropsychiatric complication, and about 30% of patients after stroke have depression [22]. The major clinical manifestations are depressed mood, significant changes in appetite or body mass, low self-worth, sleep disorders, fatigue, inattention, and suicidal tendencies [23]. PSD harms physical, cognitive, and functional rehabilitation, reduces the survival rate, and delays the recovery among stroke patients, thereby becoming a severe social and public health problem [24–27].

The prevalence of PSD is associated with the time point of stroke onset, and about 30% of stroke survivors are affected within five years after stroke [28]. Previous studies have shown that the cumulative incidence of depression after stroke is 39%-52%, usually occurring in the first month after stroke, then gradually increasing and reaching its peak around six months [29]. Another study assessed the occurrence of PSD at three and 12 months after stroke, with a rate of 27.6% at three months and 24.8% at 12 months [30]. Based on the severity of PSD, it is divided into mild, moderate, and severe types. A previous study revealed that 57% of patients after stroke have PSD, 33% with mild depression, 20% with moderate depression, and 4% with severe depression [31]. The prevalence of PSD varies among different studies. In the investigation of outpatients after stroke, it was observed that the prevalence of mild PSD was about 23.9%, and that of severe PSD was approximately 24.0%. Community patients had the lowest prevalence, 14% with severe depression and 9% with low depression. In hospitals, including emergency and convalescent patients, the prevalence of major depression was 21.6%. However, among the discharged patients after stroke, the prevalence rate of major depression was 24.0% [32].

The etiology of PSD includes psychosocial and biological factors. In the first year after stroke, patients with PSD depicted more neurological dysfunction, poorer recovery outcomes, and higher morbidity and mortality. Therefore, it is vital to identify the risk factors for PSD at an early stage. PSD risk factors include smoking, mild global cognitive impairment, female gender, less education, exposure to stressful life events in the months leading up to stroke, and comorbidities like diabetes and hypertension [33, 34]. Gender is the most frequently studied risk factor in PSD with controversial results [35, 36]. Other risk factors of PSD include stroke severity and lesion location [37–41].

The pathogenesis of PSD is complex, with many processes. The widely studied mechanism is the neurotransmitter imbalance, a popular theory for the pathogenesis of PSD [42–45]. Neurons can secrete a variety of monoamine neurotransmitters, such as 5-hydroxytryptamine (5-HT) and norepinephrine (NE). 5-HT exists in mammalian brain tissues, especially in the cortex and synapses. 5-HT is catalyzed by monoamine oxidase into 5-hydroxytryptophan and 5-hydroxyindoleacetic acid, excreted through the urine. Decreasing 5-HT concentration can lead to depressive symptoms, including low mood and lack of confidence. In contrast, the reduction of NE concentration causes the decline of emotion, cognitive function, and activity regulation ability [46–48]. A decrease in monoamine transmitters is inversely related to the severity of depression. The possible explanation for this may be because, among the brain regions involved in emotion regulation, the amygdala, prefrontal lobe, and hypothalamus are dominant, which play a transmitter regulation role by influencing the release of NE and 5-HT [49–51]. Stroke lesions interrupt the neural pathways of NE and 5-HT release, reducing monoamine neurotransmitters in the brain, which contribute to depression [52–54]. Previous studies depicted that the increased activity of monoamine oxidase in PSD patients increases 5-HT catabolism and decreases its function, causing neurological dysfunction of the limbic system, reticulate structure, and midline region of the brain stem, thereby aggravating depressive symptoms [55–57].

In addition, PSD is associated with dysregulation of BDNF, an essential neurotrophic factor in the hippocampus, cerebral cortex, and cerebellum. It binds to tyrosine kinase receptor B (TrkB) and plays a crucial neurotrophic role [58–61]. Its functions include nourishing damaged neurons, regulating neural plasticity, depicting a vital role in the survival, differentiation, growth, and postinjury repair of neurons, and participating in the initiation and development of depression, regarded as a landmark indicator for the diagnosis of depression [62, 63]. Many studies have revealed that the expression of BDNF and its high-affinity receptor TrkB protein in the thalamus decrease after PSD, indicating PSD occurrence is tightly associated with BDNF level, and the lesser the production of BDNF, the more likely PSD will occur [64, 65]. Infantino et al. found that the MED1/BDNF/TrkB pathway is involved in thalamic hemorrhage-induced pain and depression by regulating the activation of microglia [66]. A recently published prospective multicenter cohort study that enrolled 530 patients with minor stroke indicates that the important markers affecting PSD at three months are BDNF in females [67].

Moreover, inflammation is also involved in PSD development [68, 69]. Considerable evidence indicates that inflammation is involved in the occurrence and development of PSD through related inflammatory pathways by producing inflammatory mediators [70, 71]. Studies have suggested that brain injury during stroke stimulates the body to produce a rapid immune regulatory response. The peripheral immune system recruits inflammation-related cells and develops inflammation-related factors, which migrate to the brain injury area through the damaged blood-brain barrier for immune regulation [72–75]. The imbalance of homeostasis in the inflammatory state alters the endocrine function of nerve cells. It influences the balance of neurotransmitter secretion in the brain, reducing the synthesis and secretion of monoamine neurotransmitters, causing PSD [76–78]. P2X4 receptors on the immune cells modulate the inflammatory response, and receptor deletion protects against stroke acutely. However, it predisposes depression-like behavior chronically after stroke, associated with the P2X4 receptors-induced regulation of BDNF release [79]. Kozak et al. reported no significant relationship between major depression and basal proinflammatory cytokines such as TNF-α, IL-1 β, IL-18, and BDNF expression in patients who have experienced an acute ischemic stroke [80]. Other researchers have proposed that stroke causes neurological deficits and loss of daily living and social functions, putting patients in a slow and long-term stress response that activates the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, it causes excessive corticosteroid releasing hormone and sympathetic nerve activity [81–83]. Excessive hormones have toxic effects on nerve cells and affect the production of neurotransmitters; overactivated sympathetic nerve activity causes mood changes in patients leading to corresponding mood and behavior changes. In addition, the activation of the HPA axis can stimulate the upregulation of the expression of inflammatory factors, further promoting the activity of the HPA axis and forming a vicious cycle leading to the onset and persistence of PSD [84]. Presently, there are various studies on inflammatory factors involved in PSD occurrence. Studies have shown that elevated levels of cytokines such as IL-1β, IL-6, and TNF-α in serum are related to the incidence of depression [85, 86]. Effective antidepressant therapy reduces serum levels of inflammatory cytokines, including IL-1β, TNF-α, and IL-6, in depressed patients [87]. Neutrophil-to-lymphocyte (NLRs) and platelet-to-lymphocyte ratios (PLRs) are also associated with depression. Higher NLRs and PLRs are associated with depression six months after stroke, and the combined index is more meaningful than being alone in the early clinical detection of PSD [88]. A clinical study that enrolled 299 ischemic stroke patients showed that increased NLRs at admission are associated with PSD and could add prognostic information for the early discovery of PSD [89].

There is no clear consensus on the pathogenesis of PSD. Both depression and stroke should be considered to study the pathogenesis of PSD comprehensively. The biological abnormalities and the interrelation between neurotransmitters involve multiple systems and signaling pathways. One single pathogenesis of a specific system or a particular aspect cannot provide a perfect explanation. Although detailed research progress has been made in the neurobiology of PSD, its pathogenesis's etiology has not been fully clarified. Fragmented studies are not linked together. Therefore, exploring the influence of neural cellular signaling pathways on the regulation of neurotransmitters and then revealing their role in the pathogenesis of PSD could become a hotspot of future research.

4. Microglia and PSD

The imbalance of the neuroimmune system could be an essential factor in the pathophysiology of depression [90]. Compared with the control group, mice exposed to chronic unpredicted stress depict significant depressed-like behaviors and increased corticosterone levels. Moreover, the number of microglia in the hippocampus of stressed mice decreases, while certain microglia present malnutrition forms [91, 92]. Chronic stress may contribute to differences in the clinical presentation of stress-induced depression under the control of sex-specific mechanisms by differentially affecting neurons and microglia [93]. A systematic review and meta-analysis, including 69 studies, examined the cerebrospinal fluid, positron emission tomography, and postmortem brain tissue and observed that increased microglia activity and reduction of astrocytes were associated with major depressive disorder [94]. Another systematic review analyzed 51 articles evaluating inflammatory markers in postmortem bipolar disorder brain samples. Fifteen studies evaluated microglial cell markers, indicating a potential link between microglia activation and the occurrence and outcome of bipolar disorder [95]. Animal experiments and autopsy results suggested that microglia could be involved in the onset and progression of depression (Table 1). Activation of microglia has a vital role in the pathogenesis of major psychiatric disorders associated with hippocampal atrophy and disconnection of cognitive structures [96, 97].

Table 1: Summary of researches regarding the effect of microglia in poststroke depression.

Ref	Model	Animals	Main findings
92	MCAO/R+CUMS	Sprague-Dawley rats	Foraging exercise improves the behavioral scores, reduces the number of microglia in the frontal lobe and striatum, and downregulates serum levels of IL-6 and the IL-6/IL-10 ratio.
90	MCAO/R+CUMS	Wistar rats	LCN2 may affect PSD by regulating microglial activation in the hippocampus, with the involvement of the P38 MAPK pathway.
134	tMCAO+CUMS	Sprague-Dawley rats	Morinda officinalis oligosaccharides attenuate depressive-like behaviors after stroke by inhibiting hippocampal inflammation through modulating microglial NLRP3 inflammasome.
11	MCAO/R+CUMS	Wistar rats	The mRNA expression of proinflammatory markers (IL-1, TNF-α, iNOS, and IL-1β), anti-inflammatory markers (CD206), and the M2 microglia marker Arg1 upregulate in the hippocampal region in the PSD group.
61	MCAO+CUMS	Sprague-Dawley rats	Amygdala microglia contribute to PSD pathogenesis and depression-like behaviors by reducing the level of BDNF and TrkB.
25	BCCAO	ICR mice	Inhibition of the fractalkine/CX3CR1 signaling pathway improves depression and cognition via inhibiting microglia activation, promoting OPC maturation and remyelination after cerebral ischemia.
13	MCAO/O+SIR	ICR mice	Neurons and microglia-released IN-18 contribute to depression-like behavior poststroke through activating the IL-18 receptor/NKCC1 signaling pathway.
18	MCAO/R+CUMS	Sprague-Dawley rats	Xingnao Jieyu alleviates PSD by attenuating neuroinflammation, including reduction of Iba1-positive cells, and downregulation of the TNF-α, IL-6, and IL-1β expressions.
129	MCAO/R+CUMS	Sprague-Dawley rats	Curcumin improves PSD by inhibiting neuroinflammation via diminishing the P2X7R-mediated Ca^{2+} accumulation in microglia.
96	BCCAO	C57BL/6 mice	Minocycline administration exerts antidepressant and anxiolytic effects by inhibiting microglial activation.
97	BCCAO	ICR mice	Minocycline exerts an antidepressant effect by inhibiting microglia activation, promoting OPC maturation and remyelination.
45	MCAO/R+SIR	C57BL/6 mice	Microglia function-induced IDO1-dependent neurotoxic kynurenine metabolism contributes to the PSD pathogenesis. Aripiprazole reduces depressive-like behavior and cognitive impairment by inhibiting IDO1, HAAO, QUIN, and ROS.
79	MCAO/R	Global or myeloid-specific P2X4R KO and wild-type mice	Global and myeloid-specific P2X4R KO mice show intermediate microglia activation after stroke, with shorter processes, less arborization, and larger soma. Myeloid-specific P2X4R KO mice show increased mRNA levels of proinflammatory cytokines, decreased depression-related gene expression, and reduced proinflammatory cytokine IL-1β in plasma after stroke.
68	Social defeat+4-VO	Sprague-Dawley rats	Progesterone attenuates stress-induced microglia activation by regulating polarized microglia and the inflammatory environment in the hippocampus after ischemic injury.
69	Transient BCCAO	Gerbils	DXT is widely used for the treatment of major depressive disorders. Pretreated DXT exerts neuroprotective effect by attenuating microglia and astrocyte activation and decreasing oxidative stress.
26	MCAO/R	Young and aged Sprague-Dawley rats	HTR2B expression in the infarcted territory may render degenerating neurons susceptible to attack by activated microglia and thus aggravate the consequences of stroke, including anhedonic behavior.
27	Microsphere embolism model	Wistar rats	Anxiety-like behavior is increased in males despite a significant increase in microglial activation following microembolic stroke in both males and females.
14	MCAO/R	C57Bl/6 male	Pair housing enhances sociability and reduces avolitional and anhedonic behavior, which is associated with reducing serum IL-6 and enhancing peri-infarct microglia arginase-1 expression. Social interaction reduces PSD and improves functional recovery.

Table 1: Continued.

Ref	Model	Animals	Main findings
15	Microembolism model	Wistar rats	Microembolism infarcts are sufficient to lead to an increase in anxiety- and depressive-like behaviors followed by spatial memory impairment, with no trigger response of microglia, macrophages, or astrocyte.
135	MCAO/R	Sprague-Dawley rats	Fluoxetine is a selective serotonin reuptake inhibitor that is widely used in the treatment of major depression including after stroke. Fluoxetine exerts neuroprotective effects associated with marked repressions of microglia activation, neutrophil infiltration, and proinflammatory marker expressions.

CUMS: chronic unpredictable mild stress; BCCAO: bilateral common carotid artery occlusion; SIR: spatial restraint stress; 4-VO: four-vessel occlusion; PSD: poststroke depression; DXT: duloxetine; LCN2: lipocalin-2; IDO-1: indoleamine 2,3-dioxygenase 1; HAAO: hydroxyanthranilate 3,4-dioxygenase; QUIN: quinolinic acid (QUIN); ROS: reactive oxygen species; KO: knock-out; HTR2B: serotonin receptor 2B.

Various bacterial and viral infections could induce depression [98–101]. These infectious pathogens have a particular affinity for the brain and can induce microglial activation [102, 103]. These pathogens can also induce microglia to secrete proinflammatory cytokines, whose concentration levels have been associated with depression-like symptoms [104–106]. Lipopolysaccharide (LPS) can activate microglia to cause depressive symptoms, whose severity is connected with the level of inflammatory cytokines [107, 108]. LPS also induces depression by activating microglia, and many drugs have exerted an antidepression effect by inhibiting the activation of LPS-induced microglia [109–111]. O'Connor et al. revealed a pivotal role for interferon-γ and tumor necrosis factor-α in inducing indoleamine 2,3-dioxygenase and depressive-like symptoms in response to bacillus Calmette-Guerin [112]. A previous study showed that activation of peripheral blood mononuclear cells correlated with depression in patients with chronic hepatitis C. This suggests a pivotal role of immune cell activation in depression and neurocognitive dysfunction among chronic hepatitis C patients [113]. In addition, the injection of interferon-γ and poly(I:C), a Toll-like receptor-3 (TLR3) agonist mimicking the effect of HCV double-strand RNA, caused depression-like symptoms, and the proinflammatory genes were synergistically induced in the hippocampus and prefrontal cortex [105]. The tight association between HCV infection and depression suggests that optimal care for the overall well-being of patients with HCV infection needs adequate knowledge of their psychological status [114]. Infection with human immunodeficiency virus (HIV) has been associated with an increase in the prevalence of depression [115, 116]. HIV infection is associated with neuroinflammation and more significant psychopathological symptoms, which imbalances may mediate in the kynurenic pathway [117]. As the critical kynurenic pathway enzymes that catabolize kynurenine, kynurenine-3-monooxygenase produces neurotoxic metabolites in microglia [118], while kynurenine-aminotransferase II synthesizes kynurenine acid in astrocytes [119]. Targeted intervention that reduces neuroinflammation and increases kynurenine acid in at-risk kynurenine-aminotransferase II-TT-carriers may lessen the depressive symptoms of HIV [120].

The inflammasome is a cytoplasmic protein complex, an essential immune system component [121–123]. Microglia play an important role in activating inflammasome as they carry pattern recognition receptors (PRR) such as the Toll-like receptor, triggering receptor expressed in myeloid cells 2 (TREM2). It recognizes pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP) [124–126]. The microglia membrane is rich in P2X7, activating the NLRP3 inflammasome in the microglia under chronic stress, thus mediating depression-like behavior [127–129]. Therapy such as electroacupuncture, curcumin, and simvastatin exhibit the antidepressant effect and alleviate neuroinflammation by inhibiting the NLRP3 inflammasome and inflammatory mediators [130–135]. Selective serotonin reuptake inhibitors (SSRI) are the first-line treatment for depression. Its representative drug fluoxetine significantly inhibits the NLRP3 inflammasome activation in microglia and relieves depression-like behavior by downregulating NLRP3 [136]. In addition, fluoxetine prevents the exacerbation of cardiovascular dysfunction due to socially isolated depression by activating Nrf2/HO-1 and inhibiting the TLR4/NLRP3 inflammasome signaling pathway [137]. Moreover, clomipramine, perilla aldehyde, cholecalciferol, geraniol, and silymarin also attenuate depressive symptoms by the NLRP3-relative inflammatory response [138–142].

5. Conclusion

PSD is common among stroke patients and has a high recurrence rate. Its risk factors and pathophysiological mechanism are still unclear, so it is significant for preventing and treating PSD. Microglia are a vital part of maintaining mental health and a key mediator in managing stress and lifestyle. In the pathophysiological mechanism of depression, microglia could be involved in many processes and play a regulatory role in neuroinflammation, nerve growth, and neuroplasticity. The function of microglia in depression and the sequence of various mechanisms and their interrelation are not clarified. Therefore, understanding the role of microglia in the pathogenesis of depression is of great significance for developing treatment strategies against depression.

Data Availability

The availability of data and materials is not applicable.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

GCY and TGY conceptualized the research project. WLX, YX, and YDG drafted the manuscript. GCY, TGY, and XJC reviewed and modified the manuscript. GCY and TGY supervised the research and led the discussion. All authors approved the final version of the manuscript.

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