



## Review Article

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# Pathophysiological Role of Neuroinflammation in Neurodegenerative Diseases and Psychiatric Disorders

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Brain diseases and disorders such as Alzheimer disease, Parkinson disease, depression, schizophrenia, autism, and addiction lead to reduced quality of daily life through abnormal thoughts, perceptions, emotional states, and behavior. While the underlying mechanisms remain poorly understood, human and animal studies have supported a role of neuroinflammation in the etiology of these diseases. In the central nervous system, an increased inflammatory response is capable of activating microglial cells, leading to the release of pro-inflammatory cytokines including interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$ . In turn, the pro-inflammatory cytokines aggravate and propagate neuroinflammation, degenerating healthy neurons and impairing brain functions. Therefore, activated microglia may play a key role in neuroinflammatory processes contributing to the pathogenesis of psychiatric disorders and neurodegeneration.

**Keywords:** Inflammation; Brain Diseases; Microglia; Cytokines


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## INTRODUCTION

Today, a growing number of people worldwide have psychiatric disorders and neurodegenerative diseases, characterized by abnormal thoughts, emotions, behaviors, and social communication. Despite decades of research, however, the etiologies of these afflictions remain poorly understood. Inflammation in the peripheral nervous system and the central nervous system (CNS), termed neuroinflammation, is believed to be one of the causes underlying these disorders. Numerous studies have proposed that inflammatory dysfunctions are associated with psy-

chiatric disorders and neurodegeneration in both animal models and human patients [1-3]. Microglial activation has also been linked with brain diseases [4]. Microglia are CNS-resident immune cells activated in response to brain injury [5]. Microglial activation can induce the release of pro-inflammatory cytokines including interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF)- $\alpha$ , leading to neuronal damage and loss [6,7].

In this review, we summarize and discuss the potential roles of neuroinflammation in the etiology of diseases and disorders including Alzheimer disease, Parkinson disease, depression, autism spectrum disorder (ASD), addiction, and schizophrenia.

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## NEURODEGENERATIVE DISEASES

### Alzheimer Disease

Dementia, the severe loss of intellectual abilities, affects over 46 million people worldwide [8]. Dementia has many origins, among which Alzheimer disease (AD) is the major cause.

AD is characterized by progressive loss of memory. The underlying mechanism is believed to be neurodegeneration caused by production and accumulation of  $\beta$ -amyloid ( $A\beta$ ) peptides in the brain [9]. Previous studies have proposed that  $A\beta$  deposition begins a cascade of reactions resulting in synaptic dysfunction, neuronal damage, and ultimately, neurodegeneration [10,11], suggesting that  $A\beta$  accumulation likely plays an important role in the pathophysiological process of AD. Indeed, a recent study reported a potential relationship between  $A\beta$  deposits and AD-related neurodegeneration [12]. However, the findings of clinical and preclinical studies have been inconsistent, suggesting that the etiology of AD is not yet precisely understood.

Interestingly, innate immune activation has been considered a major component of age-related neurodegenerative diseases including AD [13,14]. Inflammatory responses and pro-inflammatory mediators have been found to be capable of inducing neurodegeneration, resulting in neuronal loss and brain injury. Microglia are innate immune cells in the CNS that mediate inflammatory responses to pathogens and injury by inducing release of pro-inflammatory cytokines. In response to innate immune activation, microglia-derived pro-inflammatory cytokines, including TNF- $\alpha$ , aggravate and propagate inflammation throughout brain. These pro-inflammatory factors may induce degeneration of normal neurons through upregulation of nuclear factor-kappa B, mitogen-activated protein kinase, and c-Jun N-terminal kinase [15].

### Parkinson Disease

Parkinson disease (PD) is a chronic and progressive movement disorder marked by muscular rigidity, tremor, and bradykinesia [16-18]. The incidence and prevalence of PD increase with age and are consistently higher in men than in women [19].

PD is triggered by the reduction of dopamine, a brain neurotransmitter involved in control of movement, caused by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [20]. To date, studies have failed to elucidate the precise pathophysiological mechanisms underlying SNpc dopaminergic neurodegeneration in PD.

One of the pathological hallmarks of PD is chronic neuroinflammation [20]. Glial cell activation is a common feature in patients with PD and animal models of PD, and microglia and astrocytes are thought to play critical roles in the neuroinflammatory processes associated with PD [18]. It has been suggested that activated microglia may be beneficial to the host in the early phase of neurodegeneration in PD [11], but excessive activation of microglia leads to the elevated expression of pro-inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and interferon- $\gamma$ . These pro-inflammatory mediators may rapidly induce the degeneration of SNpc dopaminergic neurons [11,21]. Additionally, pro-inflammatory mediators released upon microglial activation can activate astrocytes, which in turn play a role in the neuroinflammatory processes in PD [22]. Overall, these studies suggest that microglia- and astrocyte-mediated inflammatory responses contribute to the pathophysiology of PD through the neurodegeneration of SNpc dopaminergic neurons.

## NEUROPSYCHIATRIC DISORDERS

### Depression

Major symptoms of depression include lack of enthusiasm, sadness, feelings of guilt, low self-worth, and disturbed sleep, all of which contribute to poor functioning in daily life through abnormal cognitive, emotional, and physical behaviors [23]. The World Health Organization estimates that approximately 350 million people worldwide suffer from depression, and nearly 1 million lives are lost yearly due to suicide [23].

Though depression is a common mental disorder, the etiology of this disorder is unclear. Animal and human studies have shown that chronic inflammation is frequently associated with the development of depression. For instance, patients with inflammatory disorders often reveal depressive symptoms [24]. This comorbid relationship is bidirectional, as patients with depressive disorder display increased serum levels of IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$  [25]. In another study, expression of IL-6 and TNF- $\alpha$ , but not IL-1 $\beta$ , was elevated in depressed subjects [26]. Furthermore, increased expression of these pro-inflammatory mediators was observed in postmortem examination [27].

It has been proposed that the inflammatory processes in depression induce alterations of immune regulation in the CNS. Activation of the peripheral immune system leads to increased expression of cytokines that are actively transported into the CNS and stimulate microglia and astrocytes, which in turn produce cytokines through a feedback mechanism. As such, mi-

croglia and astrocytes have been proposed as potential mediators of inflammatory alterations in depression [28].

Stress is known to contribute to the development of depression, and several studies suggest that stress is related to the activation of microglia [29,30]. For instance, stress can cause abnormal activation of microglia related to the increase in the production of inflammatory mediators such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [7,31,32]. In addition, antidepressant drugs such as selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors reduce microglial activation and inhibit inflammatory responses [33,34].

Overall, these findings indicate that the activation of microglia is a potential effector of abnormally increased neuroinflammation in depression. However, the association between abnormal glial activation and depression in humans requires validation from clinical studies [35].

### Autism Spectrum Disorder

ASD is a group of neurodevelopmental disorders characterized by language and intelligence deficits, repetitive behavior, and social communication disability [2]. The pathogenesis of ASD is poorly understood, but recent studies indicate that ASD is associated with immune dysfunction and brain inflammation [1-3,36].

Postmortem studies show that the number of microglial cells in patients with ASD is higher than in healthy individuals [37], and microglial activation is increased in patients with ASD [38,39]. In a study using lipopolysaccharide stimulation to induce the production of inflammatory mediators in pregnant mice, offspring exhibited increased microglia number and autistic symptoms, suggesting a causal link between inflammation and ASD [40,41]. In addition, increased pro-inflammatory cytokines are associated with hippocampal and cerebral damage in virus-infected neonatal rat models of autism [42].

These findings suggest that inflammation may be the origin of symptoms in ASD, and microglia-mediated dysregulation of the inflammatory response may contribute to the pathophysiology of ASD. Further studies focusing on the link between microglial activation and neuroinflammatory processes could help clarify the etiology of ASD.

### Addiction

Addiction is a disorder characterized by persistent and compulsive dependence on a substance [43]. An addicted individual is afflicted by abnormal mental and physical activities that revolve

around the recurrent and uncontrollable urge to seek and use a substance [44]. Causes of addiction vary considerably and remain poorly understood. Nevertheless, it has been suggested that neuroinflammation may play a role in the pathophysiology of addiction [45].

Psychostimulants induce microglial activation and pro-inflammatory cytokine expression. For example, methamphetamine increases the expression of TNF- $\alpha$  in mice [46] and the expression of IL-1 $\beta$  mRNA in human JAR choriocarcinoma cells [47]. Alcohol abuse is considered a source of microglial activation leading to the elevation of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 levels in the brains of rats after chronic alcohol consumption, resulting in neurodegeneration and deterioration of memory and learning processes [48]. Moreover, methamphetamine increases IL-6 and TNF- $\alpha$  levels in cultures of rat microglial cells, resulting in microglial cell apoptosis [49].

### Schizophrenia

Schizophrenia is a chronic and debilitating disorder with positive and negative symptoms. Positive symptoms are characterized by the presence of abnormal feelings or behaviors including hallucinations and delusions, while negative symptoms are characterized by lack of interest and indifference in daily life [6]. Two major hypotheses have been established to explain the etiology of schizophrenia: the dopamine dysfunction hypothesis and the glutamatergic hypofunction hypothesis [50]. More recently, neuroinflammation has been suggested as a cause of schizophrenia [51]. Supporting this hypothesis, increased cytokine levels have been associated with schizophrenia [6]. More specifically, it has been reported that schizophrenia patients have high levels of pro-inflammatory cytokines in cerebrospinal fluid [52]. IL-6 has been shown to play a central role in the neuronal reaction to nerve injury and is involved in microglial and astrocytic activation [53], and TNF- $\alpha$ , produced by lipopolysaccharide-stimulated microglia, is necessary and sufficient to trigger apoptosis in mouse neural precursor cells [54]. Furthermore, activated microglia release pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , leading to neurodegeneration through neuroinflammation. Therefore, the neuroinflammatory process may be associated with schizophrenia.

## CONCLUSION

In conclusion, several studies have shown the potential role of microglial activation pathways related to CNS neuroinflammation

tion in neurodegenerative diseases and psychiatric disorders. A combined dysregulation of microglial activation and pro-inflammatory cytokine production may be an important driver in the pathogenesis of these diseases, as they are associated with neuroimmunological abnormalities contributing to neurodegeneration. Further studies are needed to investigate the detailed mechanisms of microglial activation in the neuroinflammatory process and the subsequent onset of disease.

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