

Neuron-to-microglia Crosstalk in Psychiatric Disorders

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Long-term studies of psychiatric illness have been continuing, but the development of the cause of disease and new treatment methods are slower than the time and cost. Therefore, the perspective focuses on the inflammation aspects of psychiatric diseases and the related glial cells in the brain and considers new perspectives on causes and treatment methods of psychiatric diseases.

There are three types of glial cells in the human neocortex: oligodendrocytes, astrocytes, and microglial cells [1]. Astrocytes play a particularly important role in brain homeostasis because they supply energy metabolites to the neurons, as well as neurotransmitter recycling, including glutamate and gamma-aminobutyric acid (GABA), and synaptic connectivity functions [2]. In addition, when activated, astrocytes regulate neuroinflammation by production and secretion cytokines (e.g., IL-1, IL-6, IL-10) that affect themselves and other brain cells such as neurons, microglia, and oligodendrocytes, leading to excitotoxicity and inflammation [3]. Microglia are the first immune cells that are immunologically activated during an inflammatory reaction and play a role in cellular defense against brain injury and phagocytosis of invading pathogens [4].

Traditionally, neuroscientists regarded glial functions as simply providing physical support and maintenance for neurons. Thus, in this limited role, glia had been long ignored. Recently, glial functions have been gradually investigated, and increasing evidence has suggested that glial cells perform important roles in various brain functions. Uncovering the glial functions and further understanding these crucial cells, and the interaction between neurons and glia may shed new light on clarifying many unknown aspects including the mind-brain gap, and conscious-unconscious relationships. It is well-known that the central nervous system (CNS) inflammation and immune activation play a major role in the pathophysiology of neurodegenerative diseases. Although the blood-brain barrier is able to protect the CNS from immune activation, it becomes more permeable during inflammation, which renders the brain vulnerable to infections. A better understanding of the interaction between inflammatory mediators, such as cytokines, and the activated immune response, including astrocytes and microglia, is critical for the development of new therapeutic strategies for psychiatric diseases.

Comparing bipolar disorder patients with control subjects, alteration of astroglial and microglial markers was observed in the postmortem frontal cortex, excitotoxicity, and neuroinflammatory reactions. Glial fibrillary acidic protein (GFAP) is a classical astrocyte protein marker, and it is commonly altered in brain areas of patients with bipolar disorder [5]. Lithium and valproic acid are the first-line drugs in the treatment of bipolar disorder. In a study by Li N *et al.*, lithium inhibited astrocyte activation and pro-inflammatory cytokine production, reinforcing the neuroprotective role of this drug [6]. In another study with mouse neurons, the microglia-mediated neuroprotective function of valproic acid was demonstrated in organotypic hippocampal slice cultures [7]. The exact mechanism has not yet been established, but from the evidence described above, changes in inflammatory markers and microglial functions play an important role in neuronal secretion in bipolar disorder patients.

The inflammation-associated changes in glutamate metabolism may also play a key role in the regulation of mood. Regarding depression, an astrocytic deficit may account for the alterations in glutamate/GABA neurotransmission in depression, because astrocytes participate in the uptake, metabolism, and recycling of glutamate. Fullana *et al.* found that in mice, selective knockdown of astrocyte glutamate uptake results in a depressive-like phenotype due to serotonergic hypoactivity in the infra- limbic cortex area [8]. There are also many astrocyte-related studies in which antidepressants affect various neurotransmitters, *i.e.*, serotonin, glutamate, energy homeostasis, and the regulation of blood-brain barrier integrity by astrocytes [9]. There is another study on the association of antidepressants with glial cells. Czéh and Benedetto proposed that antidepressant treatments reactivate cortical plasticity and can lead to the readjustment of abnormal neuronal networks [9]. It is well known that chronic stress aggravates the sympathetic nervous system and degrades the parasympathetic nervous system function. Kim and Won have also clarified the relationship between stress and inflammation, and have studied the changes in mood associated with them. Changes in the sympathetic and parasympathetic nerves increase pro-inflammatory cytokines, which can directly cause

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the neurotoxic effects of cytokines. In addition, when the peripheral inflammatory response increases, microglia can draw monocytes into the brain and produce chemokines. This phenomenon affects the function and structure of the brain area related to emotional processing, making it vulnerable to depression. Anti-inflammatory drugs have a positive effect on neuronal regeneration, suggesting that anti-inflammatory agents may also play an important role in depression, given the relationship between inflammation and brain changes in major depressive disorders [10].

Several studies on schizophrenia have also revealed a link between glial cells and disease. Doorduyn *et al.* found that the people with recent-onset schizophrenia and individuals who were recovering from a psychotic episode both had increases in a marker indicative of microgliosis in grey matter [11, 12]. Several studies on the treatment of schizophrenia have also shown the above results. Atypical antipsychotic quetiapine prevents astrogliosis in mice treated with the neurotoxic copper chelator, cuprizone. These studies support the neuroprotective or anti-gliotic effect of atypical antipsychotic medications *in vivo* [13].

It is well known that the levels of cytokines in the brain of Alzheimer's dementia patients or animal models of this disease are increasing. It has been observed that the inflammatory process can promote the loss of neuronal cells and the loss of cognitive ability. Wang W.Y. *et al.* clarified that the activation of glial cells, including microglia and astrocytes, plays an important role in eliciting the inflammatory signaling pathway involved in neurodegeneration [14]. There is some evidence that Alzheimer's dementia is associated with glial-mediated inflammation, and studies have shown that anti-inflammatory drugs can be used to prevent or halt neurodegeneration. In particular, studies of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, a class of corticosteroids, which have also been investigated for the treatment of Alzheimer's dementia due to their anti-inflammatory and immunosuppressive properties, support this hypothesis. Both drugs were effective in slowing the progression of Alzheimer's dementia in animal models of the disease and reducing glial cell activation [15]. Despite a number of noteworthy studies of this drug in the treatment of AD, clinical trials of these drugs have been mostly disappointing.

Similar studies have been conducted for other diseases of neuropsychiatric disorders. In particular, several previous studies have demonstrated increased levels of inflammatory markers in PTSD. These studies showed that peripheral serum concentrations of proinflammatory cytokines such as IL-1 β , IL-2, IFN- γ , and TNF- α were increased and anti-inflammatory cytokines such as IL-4 were decreased in patients with PTSD [16]. The above-mentioned cytokines activate the kynurenine pathway. This increases the neurotoxic kynurenine metabolite, such as quinolinic acid and 3-hydroxykynurenine, and ultimately affects the structure of the brain [10]. Thus, quinolinic acid causes oxidative stress and, together with increased glutamate, results in excitotoxicity and nerve cell apoptosis [17]. In PTSD, the activity of this immune system was increased and shown to have altered brain structure and function, *e.g.*, in the amygdala, hippocampus, medial prefrontal cortex, anterior cingulate cortex, and insula. This chronic inflammation can cause problems in the brain area that is important in controlling emotional behavior and fear, which can be associated with PTSD [16].

As has been emphasized in this article, over the past few years, there has been a strong connection between glial cells and neuropsychiatric disorders, and there are many meaningful studies in the development of new therapies, but they are not yet fully understood. More research is needed to improve knowledge of neuropsychiatric disorder-glial cell interactions and mechanisms that enhance the etiology and treatment of neuropsychiatric disorders.

REFERENCES

- [1] Pelvig, D.P., Pakkenberg, H., Stark, A.K., Pakkenberg, B. Neocortical glial cell numbers in human brains. *Neurobiol. Aging*, **2008**, 29(11), 1754-1762.
- [2] Sampedro-Piquero, P., Moreno-Fernandez, R.D. The forgotten cells: Role of astrocytes in mood disorders during the Aging. *Curr. Neuropharmacol.*, **2019**, 17(5), 404-405.
- [3] Pinto, J.V., Passos, I.C., Librenza-Garcia D., *et al.* Neuron-glia interaction as a possible pathophysiological mechanism of bipolar disorder. *Curr. Neuropharmacol.*, **2018**, 16(5), 519-532.
- [4] Fakhoury, M. Microglia and astrocytes in Alzheimer's Disease: Implications for therapy. *Curr. Neuropharmacol.*, **2018**, 16(5), 508-518.
- [5] Rao, J.S., Harry, G.J., Rapoport S.I., Kim, H.W. Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. *Mol. Psychiatry*, **2010**, 15(4), 384-392.
- [6] Li, N., Zhang, X., Dong, H., Zhang, S., Sun, J., Qian, Y. Lithium ameliorates LPS-induced astrocytes activation partly *via* inhibition of toll-like receptor 4 expression. *Cell Physiol. Biochem.*, **2016**, 38(2), 714-725.
- [7] Masuch, A., Shieh, C.H., van Rooijen, N., van Calker, D., Biber, K. Mechanism of microglia neuroprotection: Involvement of P2X7, TNF α , and valproic acid. *Glia*, **2016**, 64(1), 76-89.
- [8] Fullana, M.N., Ruiz-Bronchal, E., Ferrer-Coy, A., Juarez-Escoto, E., Artigas, F., Bortolozzi, A. Regionally selective knockdown of astroglial glutamate transporters in infralimbic cortex induces a depressive phenotype in mice. *Glia*, **2019**, 67(6), 1122-1137.
- [9] Czeh, B., Di Benedetto, B. Antidepressants act directly on astrocytes: evidences and functional consequences. *Eur. Neuropsychopharmacol.*, **2013**, 23(3), 171-185.
- [10] Kim, Y.K., Won, E. The influence of stress on neuroinflammation and alterations in brain structure and function in major depressive disorder. *Behav. Brain Res.*, **2017**, 329, 6-11.
- [11] Doorduyn, J., de Vries, E.F., Willemsen, A.T., de Groot, J.C., Dierckx, R.A., Klein, H.C. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J. Nucl. Med.*, **2009**, 50(11), 1801-1807.
- [12] van Berckel, B.N., Bossong, M.G., Boellaard, R., Kloet, R., Schuitmaker, A., Caspers, E., Luurtsema, G., Windhorst, A.D., Cahn, W., Lammertsma, A.A., Kahn, R.S. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. *Biol. Psychiatry*, **2008**, 64(9), 820-822.

- [13] Zhang, Y., Xu, H., Jiang, W., Xiao, L., Yan, B., He, J., Wang, Y., Bi, X., Li, X., Kong, J., Li, X.M. Quetiapine alleviates the cuprizone-induced white matter pathology in the brain of C57BL/6 mouse. *Schizophr. Res.*, **2008**, *106*(2-3), 182-191.
- [14] Wang, W.Y., Tan, M.S., Yu, J.T., Tan, L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann. Transl. Med.*, **2015**, *3*(10), 136.
- [15] Sastre, M., Gentleman, S.M. NSAIDs: how they work and their prospects as therapeutics in alzheimer's disease. *Front Aging Neurosci.*, **2010**, *2*, 20.
- [16] Kim, Y.K., Amidfar, M., Won, E. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, **2019**, *91*, 103-112.
- [17] Guillemin, G.J., Smythe, G., Takikawa, O., Brew, B.J. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia*, **2005**, *49*(1), 15-23.