ART & TECHNOLOGY PUBLISHING PTE. LTD.

Gene Science and Engineering

2021 Volume 1, Issue 1

ISSN: 2529-7651

Neuroinflammation Hypothesis in the Pathogenesis of Depression and Its Potential Therapeutic Targets

Minori Koga[1]*, Hiroyuki Toda[1], Manabu Kinoshita[2], Aihide Yoshino[1]

[1]Department of Psychiatry, National Defense Medical College, Tokorozawa, Saitama 359-8513, Japan

[2]Department of Immunology and Microbiology, National Defense Medical College, Tokorozawa, Saitama 359-8513, Japan

Corresponding author: Minori Koga, mkoga3@ndmc.ac.jp

Abstract

Most of the current depression drugs have been developed based on the monoamine hypothesis. However, about 30% of patients indicate resistance to medication, and patients with relatively mild depression get only a small benefit from antidepressants. In addition, although an increase in monoamine concentration in synaptic gaps by monoamine transporter inhibition occurs within a relatively short time, it takes about six weeks to show an antidepressant effect in actual clinical settings. There are cases in which an antidepressant effect is observed for drugs that do not regulate the amount of monoamine. These facts suggest the presence of a variety of pathophysiologies in depression and depressive symptoms. Recently, a relationship between the onset of depression and the expression levels of immune-related molecules such as cytokines in the blood and the brain-derived from patients with depression has been pointed out. Although there is so far no medication targeting neuroinflammation, many recent studies have shown that inflammation is not negligible and is a significant factor in the pathogenesis of depression. Therefore, it is meaningful to focus on inflammation for elucidating the pathogenesis and developing medications. In this paper, we describe the pathogenesis pathways known to be involved in inflammation, the serotonin hypothesis, the hypothalamic-pituitary-adrenal axis hypothesis, and the neurodegeneration/neurogenesis hypothesis and describe the applications to therapy and prevention based on them.

Keywords

Neuroinflammation hypothesis
Depression
Microglia
Cytokines

1. Introduction

The socioeconomic burden of depression exceeds 2 trillion yen, and there is an urgent need for measures to combat this disease, not only for the patients themselves but also for society as a whole. In the 1960s, the monoamine hypothesis was proposed that

this drug exerts its antidepressant effects through an increase in the concentration of monoamines (norepinephrine and serotonin) in the synaptic cleft by inhibiting the monoamine transporter. Since then, most drugs for depression have been developed based on the monoamine hypothesis. However, it has been observed that 10%–30% of treated patients show resistance to medication and that antidepressants are less effective in cases of relatively mild depression. In addition, although the increase in monoamine concentration in the synaptic cleft caused by monoamine transporter inhibitors is relatively short-lived, the time lag of approximately six weeks before the effect appears in clinical practice has not been adequately explained, and the fact that drugs that do not regulate monoamine levels have also been found to have antidepressant effects. The fact that antidepressant effects are sometimes observed even with drugs that do not modulate monoamine levels suggests the existence of a variety of pathological states in depression and depressive symptoms. In this context, neuroinflammation is being focused on as a keyword for the elucidation of new pathological mechanisms.

In the 2000s, a variety of studies, both clinical and basic, began to focus on inflammation and central nervous system (CNS) disease. Diverse studies have reported numerous results suggesting a link or causal relationship between inflammation and the pathogenesis of CNS diseases. Although most of the reports on immune system abnormalities were initially focused on neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, since around 2004, inflammation has also become a focus of attention as a pathophysiological factor in psychiatric disorders such as schizophrenia, bipolar disorder, and depression. A PubMed search using the keywords depression and inflammation showed that there were several dozen to less than 100 cases per year before 2004, but in recent years the number has reached 500–600, suggesting that inflammation is attracting a lot of attention as one of the various pathological conditions of depression and depressive symptoms that are still not fully understood. The number of studies reported to date has been large. The results of numerous studies reported so far leave no doubt that inflammation is related to depression and depressive symptoms, but several patterns have been proposed and are still being debated as to their causal relationship. The first relationship between inflammation and depression is that inflammation in the brain may contribute to the pathogenesis of depression (Figure 1A). This is because patients with severe sepsis are at high risk of developing depressive symptoms and anxiety disorders after recovery [1], and

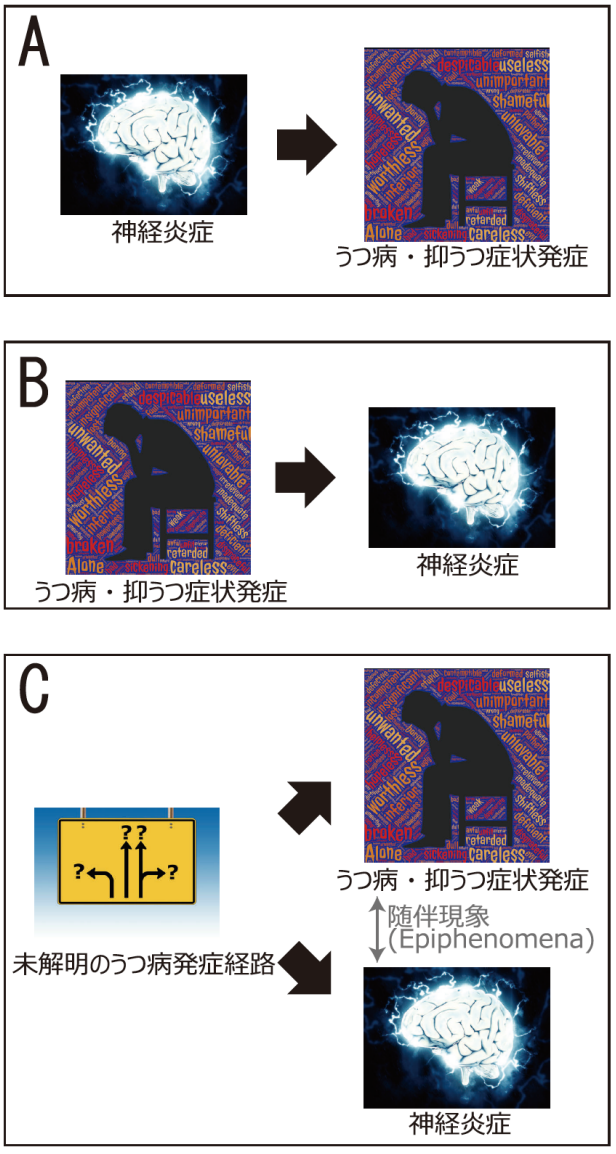

Figure 1. Relationship between depression and depressive symptoms and neuroinflammation

neuropsychiatric symptoms including depression have been reported after interferon treatment [2], and studies in animals have shown that lipopolysaccharide (LPS) administration induces systemic inflammation, which induces depressive symptoms [3]. Contrary to this pathway, some reports suggest that the pathogenesis of depression and depressive symptoms may be a factor in immune system abnormalities (Figure 1B); Song et al. conducted a longitudinal analysis of subjects suffering from psychiatric disorders and found that significantly more patients developed autoimmune disorders after developing psychiatric disorders [4]. The interaction between depression and inflammation may be one or both of these. Another pattern, as shown in Figure 1C, is that inflammation is triggered in parallel with the pathogenesis of depression and depressive symptoms by some mechanism. This is an epiphenomena, in which inflammation may play a role as a biomarker but is not involved in the pathogenesis of depression.

Although inflammation in the pathogenesis of depression and depressive symptoms has not yet been clinically applied, various studies have steadily accumulated results on their association and causal relationship, and are moving in the direction of clarifying the pathophysiology and clinical application. In this article, the pathological pathways in which inflammation has been shown to be involved are described, and their application to treatment and prevention is discussed.

2. Neuroinflammation hypothesis in the pathogenesis of inflammatory depression and depressive symptoms

Cytokines are well known as the most important mediators in the brain-immunity interface and have been shown to play an important role in the formation of various stress responses. When cytokines are dysregulated due to imbalances in the immune system, they induce a state of cytokine overproduction known as cytokine storm, which can even be lethal in some cases. Although cytokines are essentially a defense mechanism, several findings suggest their involvement in a variety of neuropsychiatric and physical diseases. **Figure 2** shows the pathway to depression based on the neuroinflammation hypothesis, which is supported by studies reported to date. Cytokines are mediators with a fundamental role in these pathways shaping inflammation-induced pathologies. Cytokines are

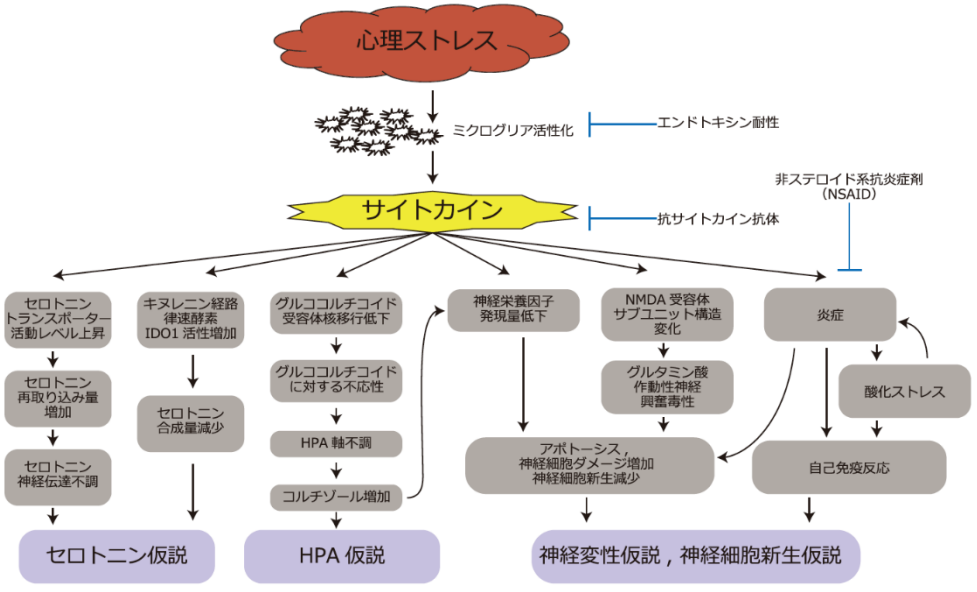

Figure 2. Pathways for the development of depressive and depressive symptoms based on the neuroinflammation hypothesis

also often used as markers reflecting the level of inflammation in individuals.

2.1. Serotonin hypothesis.

Two pathways have been reported in relation to the serotonin hypothesis of the neuroinflammation hypothesis. One is serotonin neurotransmission dysfunction caused by cytokines altering the affinity of serotonin in serotonin transporters, resulting in increased activity of the serotonin transporter and serotonin reuptake. Another is that inflammatory cytokines activate indoleamine 2,3-dioxygenase 1 (IDO1) in a metabolic pathway that synthesizes kynurenine from the same substrate rather than the pathway in which serotonin is synthesized using tryptophan as a substrate, resulting in reduced serotonin synthesis. These two pathways are known as the molecular mechanisms of the serotonin hypothesis in depression.

2.2. Hypothalamic-pituitary-adrenal axis hypothesis

The hypothalamic-pituitary-adrenal (HPA) axis is a well-known biological response to various stresses. There is a feedback mechanism in this system via glucocorticoid receptors to prevent the stress response from becoming excessive. Previous clinical studies investigating the response to cortisol in healthy and depressed subjects have shown that this feedback mechanism is impaired in depressed patients, resulting in an excessive release of cortisol. There are also reports that inflammatory cytokines such as interleukin-1 (IL-1) inhibit the nuclear translocation of cytoplasmic glucocorticoid receptors, which is a known mechanism of CNS-endocrine dysfunction in the neuroinflammatory hypothesis. It has also been suggested that abnormal levels of cortisol release lead to reduced expression of brain-derived neurotrophic factor (BDNF), resulting in reduced neurogenesis. These abnormalities are restored by depression treatments such as antidepressants and electroconvulsive therapy, suggesting that they are a mechanism in the pathogenesis of depression.

2.3. Neurodegeneration/neurogenesis hypothesis

It is known that depressed patients not only suffer from mood disorders such as depressed mood, and decreased motivation and interest, but also impaired cognitive functions including memory. The hippocampus is an important site for these brain functions, and findings on its association with depression have been accumulated. In the late 1990s, it was demonstrated that neurons are also generated in the adult brain, and since then, many findings suggest that this is an important phenomenon that contributes to the pathogenesis of many psychiatric and neurological disorders. Many findings have since suggested that neurogenesis is an important phenomenon contributing to the pathogenesis of many psychiatric and neurological disorders. In the neuroinflammatory hypothesis of depression, inflammatory cytokines induce decreased expression of BDNF, which has a neuroprotective role and is known to reduce apoptosis and neuronal cell renewal. Cytokine-induced excitotoxicity due to changes in the subunit composition of the NMDA receptor also causes apoptosis and reduced neurogenesis. Neurogenesis is known to occur in the periventricular area, the olfactory bulb, and the hippocampus, which acts in an inhibitory manner on the HPA axis. Inhibition of hippocampal neurogenesis by cytokines may lead to abnormalities in the HPA pathway. Oxidative stress, which is closely related to inflammation, is known to be induced by inflammation and also causes inflammation. Apoptosis and reduced neurogenesis due to these factors, as well as autoimmune reactions, are also known to be mechanisms of the neurodegeneration/neurogenesis hypothesis in the pathogenesis of depression.

3. The potential of targeting inflammation in depression for therapeutic and drug discovery applications

3.1. Nonsteroidal anti-inflammatory drugs

Although many studies support the involvement of inflammation in the pathogenesis of depression, it is only recently that investigations into treatments targeting immunological changes, particularly inflammation, in depression have begun. Clinical investigations have proposed the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as monotherapy or as adjuncts to existing antidepressants, and clinical trials have been conducted on selective cyclooxygenase 2 and nonselective cyclooxygenase inhibitor NSAIDs. Although these results support the use of NSAIDs for depression, there is a bias towards celecoxib as the selective cyclooxygenase NSAID under consideration, whereas no significant results have been obtained in retrospective cohort studies investigating nonselective cyclooxygenase inhibitor NSAIDs. Further investigation into the usefulness of anti-inflammatory treatment for depression may be warranted, as the clinical trials examined to date have included patients with acute depression.

3.2. Anti-cytokine and neutralizing antibodies

It has been reported in studies using animal models of depressive symptoms that neutralizing the cytokines that are fundamental to various pathological pathways in depression can prevent the formation of depressive symptoms. It has been reported that administration of antibodies against the inflammatory cytokines IL-1α and tumor necrosis factor-α (TNF-α) to the medial prefrontal cortex of mice alleviated depressive symptoms of mice model. On the other hand, it has been reported that an antibody against the IL-6 receptor alleviated depressive symptoms when administered intravenously in mice. Interestingly, this antibody did not relieve symptoms when administered intracerebroventricularly. These findings suggest the existence of different mechanisms in the pathogenesis of depression in peripheral tissues and the CNS.

3.3. Endotoxin tolerance.

Our group is conducting a molecular biological study to elucidate the mechanisms underlying the development of inflammatory depressive symptoms using a mouse model of depressive symptoms mediated by systemic inflammation induced by LPS administration [3]. It has been reported that high doses of LPS induce systemic inflammation, whereas pre-conditioning with relatively low doses of LPS has been shown to have tissue and organ-enhancing and protective effects. In animal models of cerebral infarction and brain injury, pre-conditioning with LPS has been shown to be neuroprotective, but pre-conditioning focused on psychiatric symptoms has not been investigated. Therefore, we investigated the behavioral and biochemical changes following LPS preconditioning in a model of depressive symptoms caused by systemic inflammation induced by LPS. The results showed that depressive symptoms that appeared after systemic inflammation were reduced, suggesting that LPS preconditioning has a preventive effect on the onset of depressive symptoms. In addition, biochemical changes in brain tissue showed that the activation level of microglia was suppressed by LPS preconditioning, suggesting the involvement of endotoxin tolerance as a mechanism of this behavioral change. Focusing on this phenomenon, we are currently investigating the involvement of inflammation in the pathogenesis of depression using molecular biological and molecular anatomical approaches to elucidate the detailed mechanisms with the aim of applying these findings to therapies and drug discovery.

4. Conclusion

There is no doubt that changes in cytokine and cortisol expression are not a concomitant phenomenon with the pathophysiology of depression. Several

hypotheses have been proposed for the pathogenesis of depression, including inflammation, each of which has been shown to be associated with onset and severity, but the contribution of each pathway to the pathogenesis of depression is unknown. It has been reported that IL-1β and IL-6 levels are higher in patients with refractory depression who do not respond to current standard therapies than in those who do, suggesting that inflammation contributes significantly to the pathogenesis of depression, at least as far as inflammation is concerned. The molecules and cell types involved in the pathogenesis of inflammation have only recently been identified, and the effects of inflammation on metabolic pathways *in vivo* and morphological changes in the brain are still largely unknown. Although there is a long way to go before inflammation can be applied to the development of treatments and drug targets, it is clear that inflammation is a phenomenon that needs attention in psychiatric disorders.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Huang CY, Daniels R, Lembo A, et al., 2019, Life After Sepsis: An International Survey of Survivors to Understand the Post-Sepsis Syndrome. Int J Qual Health Care, 31(3): 191–198.

[2] Valentine AD, Meyers CA, Kling MA, et al., 1998, Mood and Cognitive Side Effects of Interferon-Alpha Therapy. Semin Oncol, 25(1 Suppl 1): 39–47.

[3] O'Connor JC, Lawson MA, André C, et al., 2009, Lipopolysaccharide-Induced Depressive-Like Behavior is Mediated by Indoleamine 2,3-Dioxygenase Activation in Mice. Mol Psychiatry, 14(5): 511–522.

[4] Song H, Fang F, Tomasson G, et al., 2018, Association of Stress-Related Disorders With Subsequent Autoimmune Disease. JAMA, 319(23): 2388–2400.