https://doi.org/10.31925/farmacia.2025.2.5 **REVIEW**

PHARMACOLOGICAL INSIGHTS WITH IMPACT ON DEPRESSIVE SYMPTOMS

ANDREEA SĂLCUDEAN [1#], DORA-MIHAELA CÎMPIAN [1]*, RAMONA-AMINA POPOVICI [2#], ANCA MEDA VASIESIU [3], DANIELA LUCIA MUNTEAN [4]

[1]*Department of Ethics and Social Sciences, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureş, 540139, Târgu Mureş, Romania*
[2]*Department of Management and Communication in Dental Medicine, Department I, Faculty of Dental Medicine, "Victor Babes" University of Medicine and Pharmacy of Timisoara, 300041 Timisoara, Romania*
[3]*Department of Infectious Diseases, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Targu Mures, 540142 Târgu Mureş, Romania*
[4]*Department of Analytical Chemistry and Drug, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540139, Târgu-Mureș, Romania*

**corresponding author: dora.cimpian@umfst.ro*
[#]Authors with equal contribution.

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Abstract

Depression is a multifaceted mental health disorder characterised by a range of emotional and physical symptoms, including persistent sadness, loss of interest, and cognitive dysfunction. Recent research has increasingly focused on the role of neuroinflammation in the pathophysiology of depression, suggesting that inflammatory processes may significantly affect neurotransmitter systems, thereby contributing to the development and persistence of depressive symptoms. This comprehensive review aims to synthesise current findings on how neuroinflammation affects neurotransmitter systems in depression, highlighting brain regions affected by neuroinflammation and its impact on brain function. The relationship between neuroinflammation and depression is complex, involving multiple pathways and factors that contribute to the onset and maintenance of depressive symptoms. Moreover, the implications of neuroinflammation extend beyond the immediate effects on mood regulation; they also encompass broader neurobiological consequences, such as altered neurogenesis and synaptic plasticity. Understanding these mechanisms is essential for the development of targeted therapies that can mitigate the effects of neuroinflammation on mood disorders.

Rezumat

Depresia este o tulburare complexă de sănătate mintală, caracterizată printr-o varietate de simptome emoționale și fizice, printre care se numără tristețea persistentă, pierderea interesului față de activitățile cotidiene și disfuncțiile cognitive. În ultimii ani, cercetările s-au concentrat tot mai mult asupra rolului neuroinflamației în fiziopatologia depresiei, evidențiind faptul că procesele inflamatorii pot influența în mod semnificativ sistemele neurotransmițătorilor, contribuind astfel la apariția și menținerea simptomelor depresive. Această recenzie cuprinzătoare își propune să sintetizeze datele actuale privind modul în care neuroinflamația afectează sistemele neurotransmițătorilor în depresie, punând accent pe regiunile cerebrale implicate și pe impactul acestor procese asupra funcționării creierului. Relația dintre neuroinflamație și depresie este una complexă, implicând o multitudine de căi și factori care participă atât la declanșarea, cât și la perpetuarea simptomatologiei depresive. În plus, implicațiile neuroinflamației depășesc efectele imediate asupra reglării dispoziției, incluzând consecințe neurobiologice mai ample, precum alterarea neurogenezei și a plasticității sinaptice. Înțelegerea acestor mecanisme este esențială pentru dezvoltarea unor terapii țintite, capabile să reducă impactul neuroinflamației în tulburările afective.

Keywords: neuroinflammation, major depressive disorder, cytokines, microglia, astrocytes, neurotransmitters, neurotoxicity, hypothalamic-pituitary-adrenal axis

Introduction

In depressive disorders, and in particular in major depressive disorder (MDD), neuroinflammation is considered a significant therapeutic target because it is implicated in the aetiology and persistence of depression. Therefore, scientific research increasingly focuses on novel therapeutic strategies targeting inflammatory processes. Depression is a mental health disorder that is characterised by a polymorphism in the manifestation of symptoms. Data from the literature related to the most recent research has shown a link between inflammatory status and the development and maintenance of depressive symptoms. Microglial activation, a response to inflammatory stimuli (lipopolysaccharides (LPS) and other cytokines), leads to neuroinflammation. Activation of the brain's immune cells (microglia) leads to the release of proinflammatory cytokines (interleukin-1β (IL-1β), tumour necrosis factor-alpha (TNF-α) and interleukin-6

(IL-6)) [20, 61, 92, 113]. Depressive symptoms are often associated with neurodegeneration and synaptic dysfunction due to chronic neuroinflammation [94, 112]. In the context of MDD, microglia activation leads to altered neurotransmitter dynamics (*e.g.* serotonin and dopamine), thus dysregulated mood [45].

Significant findings demonstrate that anti-inflammatory treatment can result in substantial improvements in depressive symptoms. For instance, infliximab, an anti-inflammatory drug, has been implicated in reducing neuroinflammation and improving mood in patients with bipolar depression [64]. In preclinical studies, eicosapentaenoic acid (EPA) demonstrated more robust anti-inflammatory effects compared to docosahexaenoic acid (DHA), effectively decreasing pro-inflammatory cytokine levels in models of chronic stress-induced depression [76]. Moreover, in animal studies, promising results in ameliorating depressive behaviours have also shown promising results with targeted therapies for the NLRP3 inflammasome, a key regulator of neuroinflammatory processes [115].

Neuroimaging studies have shown increased microglial activation and neuroinflammation in the brains of MDD patients. Therefore, neuroinflammation both leads to the onset of depressive states and potentiates the severity and duration of depressive episodes [42, 82]. Due to markers utilising translocator protein (TSPO), treatment resistance in some patients suffering from depressive episodes requires the targeting of neuroinflammatory therapies [22]. Moreover, certain therapeutic pathways intervene in the complex relationship between neuroinflammation and neurotransmitter metabolism, for example, the kynurenine pathway in tryptophan metabolism that consumes serotonin precursors and exacerbates depressive symptoms [105].

The most recent studies emphasise the link between cortisol, the production of proinflammatory cytokines, and their involvement in the patho-physiologic mechanism of depression through alterations in the HPA axis and secondary changes in adrenergic, dopaminergic, and serotonergic neurons [10, 15, 35, 106]. The cascade of proinflammatory cytokines, such as IL-6, IL-1, and TNF-α, can directly affect CNS regions regulating thymic and cognitive processes. These implicitly affected regions are the nucleus accumbens, hippocampus, amygdala, pons, locus coeruleus, and prefrontal cortex (PFC). Current research has also revealed pharmacological insights, and non-steroidal anti-inflammatory drugs (NSAIDS) have been shown to have a relieving effect on depressive symptoms in some patients [104, 110].

In general, neuroinflammation is a critical pathological process in depression, offering new and more effective avenues for therapeutic intervention focusing on inflammatory mechanisms to address the psychological and biological processes that occur in depressive disorders.

Neuroinflammation and Brain Function

Neurotrophic factors and neurotransmitter dysregulation

Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are essential for neuronal survival, growth, and differentiation. Neuroinflammation significantly affects the production and availability of these neurotrophic factors. Therefore, their reduction is extremely important in the pathophysiology of depression, with profound implications for brain function.

Proinflammatory cytokines released during neuro-inflammatory responses may inhibit the expression of neurotrophic factors, thereby affecting neurogenesis and neuroplasticity. For example, Chen *et al*. demonstrated that the administration of Neurod1, a transcription factor that promotes neurogenesis, significantly attenuated neuroinflammation and pre-suppressed the expression of neurotrophic factors such as pleiotrophin (PTN) in a mouse model of subarachnoid haemorrhage [18]. In depressed patients, BDNF levels are reduced, and when neuroinflammation is involved, these processes are exacerbated. For example, some research studies have shown that neuroinflammation induced by influenza infection led to decreased levels of BDNF in the hippocampus, thereby impairing cognitive function [49, 86]. In addition, other research studies have shown that inflammatory cytokines can reduce the expression of GDNF, leading to impaired survival and function of dopaminergic neurons, which is particularly important in patients suffering from degenerative diseases [7, 11].

In depressed patients, the reduction in neurotrophic factors leads to exacerbation of neurotransmitter dysregulation, which further leads to depressive symptoms [118]. For example, BDNF leads to serotonin enhancement, and a reduction in serotonin can impair serotonergic transmission [16]. Furthermore, excitotoxicity from neuroinflammation can further contribute to the decrease in neurotrophic factors, and excess glutamate release leads to neuronal damage and ultimately neuronal death, which also affects neurotrophic factor production [19]. Therefore, the selection of treatments with an impact on promoting the production of neurotrophic factors that also target neuroinflammation may offer new therapeutic strategies for treating depression. A good example of these strategies is compounds that enhance BDNF signalling or those that inhibit proinflammatory cytokines, thereby helping restore neuroplastic and neurogenic processes in the brain [96, 85, 90].

In neuroinflammation, proinflammatory cytokines influence the synthesis, release, and reuptake of

neurotransmitters (serotonin, dopamine, and norepinephrine), leading to mood dysregulation. Therefore, it can be said that the biological mechanisms underlying depression are involved in neurotransmitter dysregulation. Monoamine deficiency also contributes to the development of depression [3]. Research has shown that elevated levels of IL-6 lead to inhibition of tryptophan hydroxylase activity, reducing serotonin levels in the brain. TNF-α can reduce dopamine D2 receptor expression, causing the depressed patient to develop anhedonia and lose motivation. All these changes in serotonin and dopamine signalling caused by inflammation only exacerbate depressive symptoms and affect the patient's need to process rewards [67]. Cognitive impairment and fatigue occur when the norepinephrine system is impaired by an inflammatory process, especially in patients suffering from chronic stress [37].

The relationship between neuroinflammation and neurotransmitter dysregulation is reinforced by clinical studies that refer to the importance of inflammatory markers in patients with depression. It has been shown that patients with elevated levels of inflammatory cytokines are at increased risk of experiencing depressive symptoms and have poorer treatment outcomes [33]. Anti-inflammatory agents, such as cytokine inhibitors and NSAIDs, have shown promise in relieving depressive symptoms in people with elevated inflammatory markers [38, 74].

Excitotoxicity and neuronal damage

Excitotoxicity and neuronal damage are important components of the neuroinflammatory processes associated with depression and refer to the pathological process that involves excessive activation of excitatory neurotransmitter receptors (especially N-methyl-D-aspartate (NMDA) receptors), leading to neuronal damage and death. Glutamate is the main excitatory neurotransmitter in the brain, related to learning and memory, and plays an important role in synaptic transmission. In neuroinflammation, it can be released in excess. Glutamate release from astrocytes is enhanced by the proinflammatory cytokines IL-1β and TNF-α. The same cytokines also contribute to the uptake of glutamate by glial cells, leading to increased extracellular glutamate levels [57], which further overstimulate NMDA receptors, ultimately leading to increased intracellular calcium levels, oxidative stress, and neuronal damage [62]. Furthermore, neuronal damage is exacerbated in depressed patients with neuroinflammation due to the potentiation of excitotoxicity, leading to cognitive and emotional deficits. In the hippocampus, neuronal damage occurs following the release of proinflammatory cytokines and excitatory neurotransmitters by activated microglia [107]. Excitotoxicity can also impair neurogenesis and neuroplasticity by reducing neurotrophic factors, leading to degradation of neuronal health [23,62]. Still, at the same time, it can inhibit BDNF expression by affecting signalling pathways required for neuroplasticity, leading to cognitive impairment, similar to patients with depression [23]. In addition, excitotoxicity can lead to programmed cell death by activating apoptotic pathways and caspases and releasing pro-apoptotic factors following an excessive influx of calcium ions through NMDA receptors, especially in the hippocampus [41,52]. Patients with depression have been shown to have reduced hippocampal levels due to excitotoxicity and neuronal loss [87,97].

In turn, oxidative stress further complicates neuronal damage in patients with depression. The occurrence of an imbalance between reactive oxygen species (ROS) production and antioxidant defence leads to exacerbation of excitotoxicity, damaging cellular components and promoting inflammation [8]. Holton proposed in his study that the neurotoxic triad of excitotoxicity, oxidative stress, and neuroinflammation can perpetuate each other, leading to a cycle of neuronal damage and dysfunction [43]. Compounds that possess antioxidant properties may help alleviate oxidative stress and protect against excitotoxicity, potentially improving outcomes for people with depression [44,89].

Specific brain regions affected by neuroinflammation

The role of the nucleus accumbens in depression

The nucleus accumbens (NAc) is a critical brain region where stress-induced neuroinflammation can profoundly affect mood regulation, and neuro-inflammation due to excitotoxicity leads to neuronal damage in the NAc [5,50,80]. A high concentration of glutaminergic receptors contributes to reward processing and addiction, making the NAc vulnerable to excitotoxicity, thereby impairing neuronal health and function. Vulnerability of the NAc to excitotoxicity can occur through excessive activation of NMDA receptors, increased intracellular calcium levels, and subsequent neuronal damage [56, 78], exacerbating the development of addictions, which increase excitotoxic conditions [56, 77]. Certain subdivisions of the NAc (*e.g.* the nucleus and cortex) react differently to the onset of excitotoxic lesions, disrupting behavioural functions related to reward and learning [75, 78]. Moreover, the presence of GABAergic neurons in the NAc also contributes to its vulnerability to excitotoxicity, as these neurons influence excitatory neurotransmission and neuronal integrity [120]. To avoid increased glutamatergic activity and neurochemical interactions, thus avoiding excitotoxic lesions, BDNF is required to promote neurogenesis and maintain synaptic connections. Nevertheless, BDNF expression and signalling in the NAc can be inhibited by proinflammatory cytokines, thus leading to reduced neuroplasticity and mood dysregulation. This reduction in neurotrophic support

may contribute to the cognitive and emotional deficits observed in people with depression [120].

Hippocampal neuroinflammation

Research indicates that neuroinflammation in the hippocampus is characterised by activation of microglia, which release proinflammatory cytokines such as IL-1β and TNF-α and other mediators that can alter neurotransmitter systems and neuroplasticity, ultimately leading to mood disturbances [81, 111, 117]. Xiao *et al*. demonstrated that chronic unpredictable stress induced significant microglial activation in the hippocampus, correlated with increased levels of inflammatory markers [110]. This microglial activation contributes to inflammation and disrupts neurogenesis [48, 58]. One of the primary consequences of neuroinflammation in the hippocampus is the reduction of neurotrophic factors. Low levels of BDNF, especially in people with MDD, lead to cognitive-emotional deficits and hippocampal atrophy, disorders characteristic of depression [114]. The relationship between neuroinflammation and neurotransmitter systems, in particular serotonin, which is essential for mood regulation, is quite complex, due to proinflammatory cytokines that interfere with the signalling of this neurotransmitter by modulating the 5-HT pathway, thus exacerbating depressive symptoms [6]. Furthermore, in people depressed due to stress, the cyclooxygenase-2 (COX-2) pathway in the hippocampus is overexpressed following neuroinflammation, contributing to the production of prostaglandins, which activate the HPA axis, exacerbating depressive symptoms [4, 98]. In the hippocampus, in contrast to microglia, astrocytes become reactive following inflammation, leading to neuronal dysfunction [58]. The interaction between microglia and astrocytes is important, as these cell types can influence neuroinflammation in the hippocampus, thereby affecting neuroplasticity and neurotransmitter dynamics [58]. Following the activation of astrocytes, these cells release the inflammatory mediators, thereby influencing the onset of synaptic dysfunction and enhancing the long-term process essential for learning and memory [12, 14, 32, 119].

Neuroinflammation and neuronal connectivity

Neuronal connectivity is particularly impaired following neuroinflammation in certain regions of the brain, especially the hippocampus and nucleus accumbens. Research in animal models has shown that systemic administration of LPS impaired discrimination memory in rats, indicating that neuroinflammation may selectively disrupt specific hippocampus-dependent memory functions. As a consequence of the neuroinflammatory process, the integrity of neuronal connectivity in the hippocampus is compromised, leading to cognitive dysfunction in patients with depression [27].

The mechanisms involved in impaired neuronal connectivity following hippocampal inflammation are related to the dysregulation of synaptic transmission and neurotrophic factor expression [26].

The interaction between the excitotoxic environment and neuroinflammation further impairs neuronal connectivity, as NMDA receptors are overstimulated due to excessive glutamate release. Cognitive deficits are exacerbated because the excitotoxic environment affects synaptic connections in the hippocampus and NAc. Furthermore, excitotoxicity may reduce dendritic spine density in the hippocampus and NAc, exacerbating cognitive dysfunction, and neuro-inflammation may alter the timing of neuronal oscillations, disrupting efficient communication between brain regions [63].

Neuroinflammation has been shown to alter neuronal activity patterns in the hippocampus and prefrontal cortex, essential for cognitive processes and mood regulation. This disruption of functional connectivity may contribute to the cognitive and emotional deficits seen in people with depression [25]. Anti-inflammatory agents that inhibit microglial activation and reduce levels of pro-inflammatory cytokines have shown promise in preclinical models of depression [29, 40, 91, 100].

Impact of the hypothalamus on stress regulation

The hypothalamus is a critical brain region that plays a major role in stress regulation and is significantly affected by neuroinflammation. This region also integrates the body's responses to various stressors (*e.g.* hormonal and autonomic) by activating the HPA axis. Neuroinflammation can also be triggered in the hypothalamus by other factors, such as chronic stress, systemic inflammation, and metabolic disorders. Metabolism can be disrupted following the inflammatory process due to visceral adipose tissue, which induces macrophages into the hypothalamus [17]. Neuroinflammation leads to chronic activation of the HPA axis, which leads to hypercortisolism, a process commonly seen in people with depression [83]. Normal functioning of the HPA axis is also influenced by hypothalamic inflammation, and this process leads to increased vulnerability to stress, with depressive symptoms more easily developing [83]. These vulnerabilities can be countered by controlling the relationship between neuroinflammation and neurotransmitter dysregulation in the hypothalamus. Neuropeptide Y (NPY) and CRH, two neuropeptides produced by neurons in the hypothalamus, are essential for regulating stress and mood [24]. Furthermore, cognitive function is also impaired due to the development of neuroinflammation in the hypothalamus, expressed by elevated inflammatory markers, thus affecting learning and memory processes [59].

The role of pons and locus coeruleus in mood regulation

Other brain regions, such as the pons and locus coeruleus (LC), also play an important role in the

stress response and inflammatory processes. The locus coeruleus is a small nucleus in the pons responsible for arousal modulation, attention, and emotional responses. It influences various brain regions involved in mood regulation (such as the prefrontal cortex, amygdala, and hippocampus), due to its projections extending throughout the brain [65]. As the main source of norepinephrine (NE) in the brain, activation of the locus coeruleus releases norepinephrine, which prepares the brain for the stress response, thereby increasing the brain's alertness. Although they release a large amount of norepinephrine upon activation, chronic stress and neuroinflammation can lead to deregulation of the locus coeruleus, thereby altering norepinephrine signalling and exacerbating mood disorders [103]. Depressive symptoms also occur due to increased levels of proinflammatory cytokines, which affect the function of locus coeruleus neurons, leading to reduced norepinephrine release [108].

Concerning the amygdala, research studies have indicated that its increased reactivity is due to the process of inflammation, which subsequently exacerbates increased anxiety and depressive symptoms. For example, Mehta *et al*. showed that, in patients with depression, inflammatory markers are negatively correlated with functional connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC), suggesting that the inflammatory process disrupts the regulatory influence of vmPFC on amygdala activity, thus leading to an exacerbation of emotional dysregulation [66]. These claims were also supported by the Davies *et al*. study, which showed that treatments targeting inflammation (*e.g.* anti-TNF therapies) led to changes in amygdala reactivity, thereby modifying depressive symptoms. These findings emphasise the amygdala's role in mediating inflammation-related mood changes [28]. Furthermore, the amygdala's involvement in emotional processing is further illustrated by its response to facial expressions. A systematic review reported by Stuhrmann *et al*. emphasised the important role of the amygdala in the perception and processing of emotional salience, particularly in the recognition of facial emotions, which is often impaired in people with MDD [99]. For example, patients with MDD have been shown to show altered activation patterns in the amygdala following exposure to negative emotional stimuli [21]. Therefore, the sustained activity of the amygdala in response to negative emotional stimuli can be considered a feature of depression [21]. Various neurobiological mechanisms are thought to be involved in the changes that occur in amygdala function. Some studies have stated a bidirectional relationship between emotional processing and neuroinflammation, as the increase in amygdala activity during stress is due to an increase in the inflammatory response [70]. Following the onset of neuroinflammation in the locus coeruleus, adrenergic neurons are degenerated, thus affecting their structural integrity. This phenomenon can also be observed in patients suffering from various neuro-degenerative diseases, such as Alzheimer's and Parkinson's disease [116].

Prefrontal cortex

Various mechanisms (*e.g.* glial cell activation, changes in neurotransmitter levels, and changes in neuroplasticity) are responsible for mediating the inflammatory response that emerges as a physiological factor in patients with depression, affecting in particular the prefrontal cortex (PFC). The PFC is characterised by a rich network of neurons and glial cells, which play an important role in maintaining homeostasis and responding to inflammatory stimuli. Neuroinflammation in this region is often marked by the activation of microglia and astrocytes, which release proinflammatory cytokines. Multiple studies in the literature on animal models have shown that elevated levels of proinflammatory cytokines in the PFC lead to neuronal dysfunction and subsequent cell death, thus worsening depressive behaviours [73, 101, 104, 108]. These animal model studies suggest a direct link between mood disorders and non-inflammatory processes. As regards the impact of neuroinflammation on neurotransmitters (such as serotonin-5-HT and norepinephrine-NE), their dysregulation is common in depression; therefore, keeping them within normal parameters is particularly important for mood regulation. It has been shown that neuroinflammation leads to low levels of 5-HT and NE in the PFC, resulting in depressive symptoms [46, 47, 60]. For example, activation of IL-6 leads to impairment of serotonin, a neurotransmitter involved in maintaining mood and emotional state [72, 102, 104]. Furthermore, receptor sensitivity and glutamate release from the glutamatergic system of the PFC are affected by neuroinflammation, which further complicates the depressed state due to neurochemical processes [68].

Chronic neuroinflammation also affects the processes of neurogenesis and synaptic neuroplasticity in the PFC, responsible for learning and emotional resilience, due to inflammatory mediators that disrupt the long-term potentiation of the two cellular mechanisms (learning and memory) in the PFC [47, 104]. This, in turn, leads to cognitive deficits (*e.g.* poor decision-making) and reduced cognitive flexibility, particularly seen in patients with depression. Furthermore, neuroinflammation leads to loss of dendritic spines in the PFC, and subsequently to cognitive deficits in depressed patients [68, 72].

Deregulation of the HPA axis is commonly seen in people with depression, and neuroinflammation can exacerbate this condition by increasing cortisol levels, which in turn can further impair PFC function [104, 108]. Furthermore, the impact of neuro-

inflammation on the PFC is not uniform across different populations. Women are more prone to an increased inflammatory response, which is often associated with an increased prevalence of depressive symptoms. In addition to sex differences, early-life stress has also been shown to induce long-lasting neuroinflammatory changes in the PFC, leading to depression later in life [36]. Early interventions targeting neuroinflammation are therefore particularly important in preventing the onset of depressive disorders, especially in women. Anti-inflammatory treatments (NSAIDs) and cytokine inhibitors have shown promise in alleviating depressive symptoms in some depressed patients [104, 110].

Cytokine Inhibitors as Mediators of Depression

Cytokine inhibitors are increasingly being investigated because of their role as potential mediators of antidepressant effects. It is known that TNF-α, IL-1β, and IL-6 have been implicated in triggering neuroendocrine dysfunction, altering monoamine metabolism, and activating microglia, processes that underlie the pathophysiology of depression [1, 84, 93]. Therefore, cytokine inhibitors have been proposed not only as biomarkers in depressive symptoms but also as therapeutic agents that could attenuate neuroinflammation and restore homeostatic brain function [53, 93]. Compared to anti-inflammatory agents, the efficacy of cytokine inhibitors is supported by the limited number of randomised clinical trials, which are based on heterogeneity of patient profiles [53, 93].

The preliminary evidence highlighting the antidepressant properties of cytokine inhibitors has been obtained from preclinical studies in experimental animal models and clinical trials [33]. For example, in one research study, chronic infliximab (TNF-α inhibitor) administration was shown to significantly reduce the behaviours of chronically stressed rats, depression-like and anxiety-like behaviours [51]. This preclinical study was supported by another clinical trial investigating the use of the same inhibitor (infliximab) in treatment-resistant depressed patients. This study also revealed that elevated inflammatory biomarkers predicted a positive response to cytokine blockade [79].

Multiple systems are modulated to exert the antidepressant effects of cytokine inhibitors. For example, limiting the action of pro-inflammatory cytokines contributes to reduced activity of neuroendocrine pathways involved in the stress response and neurotransmitter modification, thus leading to the normalisation of synaptic plasticity and mood regulation [1, 84, 88].

Although the use of cytokine inhibitors as mediators of depression looks quite promising, this therapy is not without its challenges, particularly in terms of serious side effects. These serious side effects have not yet been fully elucidated and quantified. Therefore, rigorous randomised controlled trials need to be conducted to validate these inhibitors' efficacy and safety profiles [53, 93]. The clinical application of this therapy in depressed patients with heterogeneity of inflammatory state represents a significant hurdle, as only patients with a high inflammatory profile can benefit from the advantages of cytokine blockade following a personalised treatment [1, 79].

NSAIDs as Mediators of Depression

Recent data from the current literature highlight a significant connection between depressive symptomatology and inflammatory processes - a bidirectional connection. In the last decade, numerous clinical studies on humans and rodents have demonstrated a beneficial effect of anti-inflammatory agents in improving depressive symptoms [30, 71, 53]. Particularly, non-steroidal anti-inflammatory drugs (NSAIDs) have evidenced an improvement in depressive symptoms compared to placebo [54]. The antidepressant effect of NSAIDs is mediated through an anti-inflammatory mechanism. As a result, NSAIDs inhibit the synthesis of prostaglandin-E2, causing the suppression of indoleamine 2,3-dioxygenase (IDO) activation, ultimately reducing the conversion of tryptophan into kynurenine [13]. Since tryptophan is a precursor of serotonin, this mechanism demonstrates an increased probability of antidepressant results in affected patients. Recent literature data has evidenced that selective COX-2 inhibitors exert a more pronounced anti-inflammatory effect than other NSAIDs. Therefore, NSAIDs may be organised based on their mechanism of action into selective and non-selective COX inhibitors [54, 71].

Effects of selective cyclooxygenase-2 inhibitors on depression

Several clinical studies have investigated the effect of selective COX-2 inhibitors in antidepressant therapy. Research conducted in the recent decade has focused on the role of celecoxib on depressive symptomatology [109]. Celecoxib is one of the COX-2 inhibitors with a major anti-inflammatory effect [109]. According to preclinical studies, the prostaglandin E-2 (PGE2) level significantly decreased after the Celecoxib administration [35]. Moreover, the treatment improved brain levels of IL-1β, TNF-α, and interferon γ (INFγ) [35]. It has also been found to inhibit the reduction of nerve growth factor (NGF) in the hippocampus [35]. During clinical trial research, patients were administered either 200 mg or 400 mg of Celecoxib daily for up to 12 months, in monotherapy or along with other antidepressant agents [39, 109]. The results indicated an enhanced antidepressant effect for the combination of celecoxib and antidepressants

compared to antidepressants and placebo [39]. Other clinical trials evidenced the efficacy of celecoxib as monotherapy in improving depressive symptoms among patients diagnosed with osteoarthritis, independent of its secondary analgesic effect [2, 69].

Esalatmanesh and Kashani reported a beneficial effect of celecoxib in improving symptoms in patients diagnosed with postpartum depression [31]. The results demonstrated statistically and clinically significant improvement in patients who received celecoxib compared to placebo after six weeks of treatment. Moreover, plasma levels of inflammatory markers (IL-1, IL-6, TNF-α) were significantly lower in the celecoxib group, while BDNF levels were significantly higher compared to the placebo group [31].

A systematic review of scientific literature evaluating the antidepressant effects of NSAIDs in rodents highlighted that selective COX-2 inhibitors produced more stable and long-lasting effects in comparison to other non-selective NSAIDs [9].

Effects of non-selective cyclooxygenase inhibitors on depression

Studies on the effects of non-selective cyclooxygenase inhibitors reveal several aspects beyond the improvement of symptoms in the context of major depressive disorder. One study demonstrated the efficacy of acetylsalicylic acid at a dose of 160 mg daily as an adjuvant antidepressant treatment in patients who had not shown an improvement in depressive symptomatology to selective serotonin reuptake inhibitors (SSRIs) [53]. Another study demonstrated the antidepressant efficacy of Naproxen and Ibuprofen as monotherapy over six weeks in a cohort of 890 patients diagnosed with osteoarthritis [53]. However, a comprehensive meta-analysis of clinical trials conducted by Köhler and Lydholm highlighted that the antidepressant effects of non-steroidal anti-inflammatory drugs remain incompletely understood [55]. There is an increased possibility, based on current literature, that the improvement in depressive symptoms due to NSAIDs may be correlated with the clinical improvement of underlying somatic pathologies [55].

A study evaluated the effects of citalopram and ibuprofen on stress-induced depressive phenotypes in rats. The results showed a stress reduction correlated with decreased plasma corticosterone levels [95]. These improving effects were supported by the administration of citalopram and ibuprofen, either as monotherapy or in combination. Moreover, both treatments increased BDNF levels and had a significant antidepressant effect in rodents [95].

Conclusions

In this study, we have shown that neuroinflammation affects different regions of the brain, a process implicated in many neurodegenerative disorders, including Alzheimer's disease. The activation of microglia and astrocytes, along with the release of proinflammatory cytokines, plays a crucial role in these processes, underscoring the importance of understanding regional neuroinflammatory dynamics in the development and progression of neuro-degenerative diseases.

The serotonergic system is one of the most studied neurotransmitter systems in depression and neuro-inflammation, being affected by neuroinflammation and the dopaminergic and glutamatergic systems. As a result, large amounts of serotonin and dopamine are released, leading to changes in mood and behaviour. Excitotoxicity occurs due to increased levels of proinflammatory cytokines, as glutamate receptors are over-activated, leading to neuronal damage and, subsequently, to depressive symptoms. Mood disturbances occur when the balance between excitatory and inhibitory neurotransmitters is disrupted, impairing mood stability. The onset of depressive symptoms persists when neurotransmitter synthesis and signalling are disrupted, leading to increased levels of proinflammatory cytokines. Therefore, to understand the aetiology of depression, it is imperative to understand the mechanisms of action involved in these pathological processes and to develop new therapeutic strategies aimed at treating neuroinflammation. Therefore, future research should focus on the complex relationships between non-inflammatory processes and neurotransmitter dysregulation so that more effective treatments for depression can be developed.

Conflict of interest

The authors declare no conflict of interest.

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