

# Targeting the Inflammatory Pathway as a Therapeutic Tool for Major Depression

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## Key Words

Depression · Inflammation · Cytokines

## Abstract

In the last decades convergent findings from several lines of evidence has revealed a robust association between major depressive disorder (MDD) and inflammatory pathways. Despite this, the translation of these findings into new and better treatments for MDD has not occurred. The objective of this study is to comprehensively review what is already known with reasonable certainty on inflammatory pathways in MDD, to clarify some points that have been insufficiently studied and to discuss the implications of these findings for future studies targeting inflammatory pathways as a therapeutic tool for individuals with MDD. © 2014 S. Karger AG, Basel

## Introduction

Activation of inflammatory pathways is a characteristic of several chronic diseases and, in the last decades, convergent findings from several lines of evidence has revealed a robust association between major depressive disorder (MDD) and inflammation and immune activation [1–3].

More specifically, depression is accompanied by cell-mediated immune (CMI) activation and a chronic mild inflammatory response. In spite of this, we are far from the incorporation of these findings into new and better treatments for people living with MDD. Bridging the gaps of knowledge about inflammatory pathways and mood disorders requires knowledge in more detail on the causative, consequential and concurrent relation between these factors. The objective of this study is to comprehensively review what we already know, to clarify some points that have been insufficiently studied and to discuss the implications of these findings for future studies targeting inflammatory pathways as a therapeutic tool for individuals with MDD.

## What Do We Know about Inflammatory Pathways in MDD?

### *Individuals with MDD Present a Persistent and Low-Grade Inflammatory and CMI Activation*

The finding that individuals with MDD present activation of inflammatory pathways is a highly reproduced and convergent finding in case-control, postmortem [4], cross-sectional and longitudinal studies in humans and animal models [5, 6]. In cross-sectional studies, many pro-inflammatory cytokines, or their receptors or receptor an-

tagonists, are associated with MDD, including IL-1 $\beta$ , IL-2, IL-6, IFN- $\gamma$ , TNF- $\alpha$ , IL-6R and IL-1RA [7–10]. In addition to increased cytokine levels, depressed patients also show other signs of inflammation, such as an acute-phase response (increased haptoglobin, lower albumin) and activated complement cascades (increased C3 and C4) [2]. Other signs of cell-mediated immune activation include increased levels of neopterin, soluble CD8 molecule and lower levels of plasma tryptophan and increased tryptophan catabolites. Depression is also accompanied by lowered levels of plasma CC16, an endogenous anti-cytokine that inhibits the production of pro-inflammatory cytokines [11]. Lowered CC16, therefore, may contribute to the inflammatory response in MDD. Three recent meta-analyses show higher concentrations of TNF- $\alpha$ , IL-6, IL-1, sIL-2R and/or C-reactive protein (CRP) in patients with depression [7, 12, 13]. In studies with postmortem brain tissue samples from the prefrontal cortex, Dean et al. [4] found increased levels of TNF transmembrane and, more recently, Shelton et al. [14] found an upregulation of several pro- and anti-inflammatory cytokines, such as IL-1 $\alpha$ , IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, IFN- $\gamma$  and lymphotoxin- $\alpha$  in psychotropic drug-free individuals with a history of MDD.

In rodents, induction of a systemic inflammatory response through administration of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 and IFN- $\gamma$ , and lipopolysaccharide, LPS, provokes depressive-like behavior, including anhedonia [15–18]. More importantly, sustained production of IL-6 and IFN- $\gamma$  in transgenic mice is accompanied by the onset of depressive-like behavior [19, 20]. Chronic mild stress and learned helplessness in the rodent are accompanied by peripheral activation of immune-inflammatory pathways [21].

Although most works report immune activation in MDD, there is compelling data suggesting immune suppression. In a meta-analysis, Zorrilla et al. [10] considered this paradox – MDD seems to be accompanied by leukocytosis (mainly due to an increase in the percentage of neutrophils), elevation of B cells, CD4 and activation markers (HLA-DR and CD25) and pro-inflammatory cytokines. Despite the elevation of these markers of immune activation, leukocytosis occurs with shrinkage of the lymphocyte and monocyte population, and reduction of NK and T cells. Regarding cell function, low proliferation by lymphocytes in response to Con A, PWN and PHA, hindered neutrophil phagocytosis and lower NK cytotoxicity was associated with MDD. These data suggest that both adaptive and innate immunity may be impaired in MDD.

Other pathways related to inflammation and CMI activation have been explored recently. Increased oxidative and nitrosative stress (O&NS) may be in part a consequence of elevated pro-inflammatory cytokines and CMI activation, leading to lipid peroxidation and DNA damage, deregulating the immune response [2, 22]. Moreover, many studies have demonstrated lower levels of antioxidants, such as coenzyme Q10, vitamin E and glutathione in depressed patients, predisposing towards increased O&NS and damage to fatty acids, proteins, DNA and mitochondria by O&NS [2, 22].

#### *Individuals with MDD Are a Heterogeneous Population and May Exhibit Differences in Inflammatory Patterns*

Recently, inter-individual differences in the severity of inflammatory changes have been explored. A comparison between individuals with MDD with melancholic characteristics and a group of patients with atypical characteristics indicated that inflammatory changes are more pronounced in the first group, showing more significant abnormalities in TNF- $\alpha$  levels, CRP and IL-6 [23]. In addition, the increased numbers of MDD patients examined in different studies permitted the analysis of subgroups in a meta-analysis and meta-regression. The effect of MDD on IL-6 and IL-10 levels was significantly larger in subgroups with the diagnosis of MDD compared with those with only depressive symptoms, and in subgroups where individuals were recruited from inpatient or outpatient settings compared to the community [24]. The effect was also larger in those participants who were not selected for a particular comorbidity compared to those selected for cardiovascular disease [24].

#### *The Link between MDD and Cardiovascular Conditions Is at Least Partially Mediated by Inflammatory Pathways*

The relation between acute myocardial infarction (AMI) and depression has long been explored. Nowadays, this association is well established, with a review demonstrating that patients who suffered an AMI have a prevalence of depression three times higher compared to the general community [25]. Remarkably, an MDD diagnosis is present in 15–20% of AMI patients [25]. On the other hand, depression increases the risk of cardiovascular events. A depressive mood alone is a predictor of coronary heart disease, with a relative risk (RR) of 1.49 (95% CI 1.16–1.92), wherein a full diagnosis of MD is an even stronger predictor, with an RR of 2.69 (95% CI 1.63–4.43) [26]. Several mechanisms are thought to underlie this in-

teraction, including stress, diet and lifestyle. Among these, various inflammatory processes have been considered to be of pivotal importance, including increased levels of pro-inflammatory and Th1-like cytokines, CRP, haptoglobin, oxidized LDL-cholesterol antibodies, oxidized phospholipids, and lowered levels of antioxidants, including glutathione, vitamin E and coenzyme Q10 [2, 27].

#### *The Effect of Stress on the Development of MDD Can Be Partially Mediated by Inflammatory Changes*

Stress has been associated with a pro-inflammatory profile [28, 29] and usually occurs in association with MDD and conflicting relationships, enhancing immune dysregulation [29, 30]. The general reaction to stress includes both activation of sympathetic tonus and activation of the hypothalamus-pituitary-adrenal (HPA) axis. Acutely, activation of the immune system in stressful situations is physiological, but intense and sustained persistence of stress is able to chronically activate the HPA axis, leading to reductions in cortisol levels by downregulation of hypothalamic cortisol receptors and, in the end, to loss of the regulatory effect of cortisol in the inflammatory system [31]. The well-known effect of stress in autoimmune and inflammatory conditions was the base for the investigation of the role of stress in increased severity of inflammatory imbalances in MDD. In fact, individuals with MDD who report childhood maltreatment present more severe inflammatory changes than those who report the absence of these experiences [32]. In rats exposed to chronic stress the levels of IL-1 were increased [33].

#### *Neuroprogression: Inflammatory Mediators Can Potentially Contribute to the Structural, Functional and Cognitive Changes Reported in MDD*

In MDD, some clinical features suggest neuroprogression, which is a progressive process of neurodegeneration, with reduced neurogenesis and neuroplasticity and increased neural apoptosis [34, 35], manifested by increased illness severity over time, longer and more frequent episodes, and more spontaneous episodes in later stages [36]. Inflammatory processes were associated with both structural and functional anomalies found in MDD patients. Depressed patients show evidence of both pro-inflammatory changes and neurophysiological abnormalities such as increased amygdala reactivity and volumetric decreases of the hippocampus and ventromedial prefrontal cortex. In addition, in individuals with MDD, there are some studies reporting a modulatory effect of inflammation in cognition, with increases in IL-6 being related to reduction in verbal memory [37].

Furthermore, increased pro-inflammatory cytokines may be associated with neuroprogression [36], as evidenced by the involvement of TNF- $\alpha$  in glutamate neurotoxicity process [38] and IL-2 enhancing the action of N-methyl-D-aspartate, resulting in astrogliosis, myelin damage and neuronal loss [39]. In the same line, inflammatory pathways may contribute to the staging of depression. TNF- $\alpha$  and IL-6 were associated with treatment resistance to antidepressants [34]; over time pro-inflammatory cytokines may mediate a sensitization in the inflammatory response to stressors, resulting in a higher susceptibility of new depressive episodes [34, 36].

#### *Traditional Antidepressants Modulate Immune Activity*

Antidepressants, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors, possess in vitro immunosuppressive or negative immunoregulatory effects by suppressing the production of pro-inflammatory cytokines and Th1-like cytokines, such as IFN- $\gamma$ , and increasing that of IL-10, a negative immunoregulatory cytokine [40–42].

In rodents, pre-administration of fluoxetine or paroxetine reduced LPS-induced inflammation and depressive-like behaviors [43]. In humans, a meta-analysis was performed exploring Alzheimer's disease (AD) effects on IL-1 $\beta$ , IL-6 and TNF- $\alpha$  in MDD patients. It was found that AD treatment reduces IL-1 $\beta$  and possibly IL-6 levels, but not TNF- $\alpha$  levels, despite symptom improvement. When different ADs were analyzed, a possible effect of SSRIs in IL-6 and TNF- $\alpha$  levels was found [44].

#### **What Do We Not Know about Inflammation in MDD?**

##### *Do Changes in Peripheral Inflammatory Mediators Predict Central Changes?*

The observation that a dye failed to penetrate the brain suggested to Ehrlich [45] in 1885 the existence of a blood-brain barrier (BBB), which was able to partially isolate the central nervous system (CNS). The structure of the BBB has systematically been studied since that time, revealing an organized composition of different cell types. The inner part of the physical barrier is composed by a specialized endothelium that acts like a moderator between blood and the brain. The brain microvascular endothelial cells have a homogenous thickness, with no transendothelial fenestrations and uninterrupted tight junctions. Paracellular flux is limited to essential molecules only by

specific transporters. BBB is also composed by astrocytic endfoot processes which cover almost the entire vasculature [46]. Although the BBB has an important role in maintaining the separation of the CNS from the immunological system, nowadays there are questions about whether the CNS is truly immune-privileged.

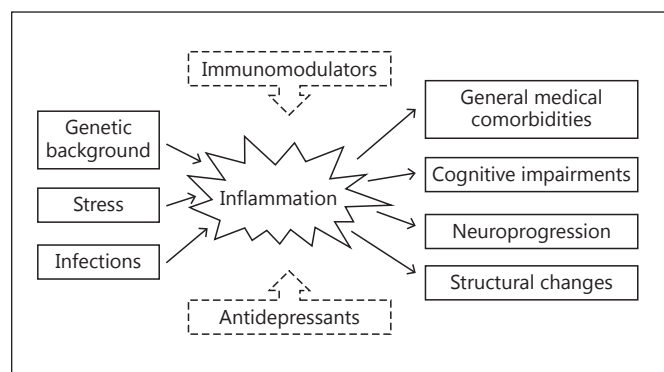
Cytokines are not small enough to cross the BBB. However, it has been demonstrated that the immune system and the CNS can interact in normal conditions by different pathways. Cytokines generated in the periphery can enter the CNS by leaky regions without a BBB-like choroid plexus and circumventricular organ regions [47, 48]. Also, cytokines can reach the CNS by saturable transporter systems, as has been reported for IL-1, IL-1 antagonist, TNF- $\alpha$  and IL-6 [49]. Furthermore, the vagus nerve can play a role in the immune system/brain communication. Vagus afferent fibers are activated by IL-1, and its integrity is necessary to induce hyperthermia [50]. Lymphocytes can also be found in the CNS, but the process by which they cross the intact BBB is still obscure [46, 51].

The pathways linking the immunological system and CNS are not yet completely understood. However, there are several pathways by which the low-grade inflammation and CMI activation can be translated into neuroinflammation and microglial activation, and consequently may drive behavioral changes.

#### *What Is the Primary Source of Abnormalities in Inflammation in MDD?*

The primary source of abnormalities in inflammatory mediators has not been completely elucidated, although there are some plausible hypotheses (fig. 1). The first is genetics. There have been some association studies exploring polymorphisms in cytokine genes, including IL-1 [52]. Initiatives to map the genome of individuals with MDD in genome-wide association studies found that TNF- $\alpha$  was identified as the only gene for which the association with MDD remained significant after correction for multiple testing [53].

The second possible source is environmental. Epigenetic changes produced in early life and provoked by environment adversities have been considered as a potentially pivotal factor in the determination of permanent reprogramming of the HPA axis and inflammatory system [23]. Only very recently, epigenetic aspects of the regulation of cytokines has begun to be explored in MDD, with methylation microarrays to assess genome-wide methylation profiles, but without conclusive results [54]. In addition, interaction with pathogens and other antigens during the development of the immune system has also been considered relevant.



**Fig. 1.** Trigger factors of depression, the inflammatory pathway and its consequences.

It cannot be dismissed that the influences of both genetic and environmental factors interact during development to produce vulnerability to MDD. One example of this interaction is the study of Haastруп et al. [55], where the major C allele of the IL-18 rs187238 and the major G allele of rs1946518 had a significantly higher prevalence among the patients with a stressful life event prior to the onset of MDD than both patients without a stressful life event and healthy controls.

#### *Do Inflammatory Pathways Predict Treatment Response to Antidepressants?*

A possible application of inflammatory biomarkers in MDD is their use as predictors of response to antidepressants. TNF- $\alpha$  plasmatic concentrations are significantly reduced in responders to treatment with amitriptyline [56]. In another study, early responders and early nonresponders showed opposite trends in cytokine levels during duloxetine treatment. Nonresponders showed a baseline Th2 shift compared to controls (decreased IL-1, IFN- $\gamma$  and TNF- $\alpha$ ), with an increase in Th1 cytokine levels during treatment (increased IL-1, IL-12, IFN- $\gamma$  and decreased IL-10) [57]. In spite of this interesting result this subject remains largely unexplored, albeit with the same promising biomarkers, such as lowered zinc as a marker of treatment-resistant depression [58].

#### *Are Alterations in Inflammatory Mediators in MDD Cause, Consequential or Epiphenomena?*

Despite the evidence of the association between inflammation and CMI activation and MDD, the pathological mechanism remains elusive. It is unknown if immune deregulation is a cause or a consequence of MDD, or just an epiphenomenon. Animal studies show that administration



of pro-inflammatory cytokines and Th1-like cytokines induce depressive-like behavior in the rodent, indicating that inflammatory mediators can directly cause depression or at least some features of it [2]. From a neurobiological point of view this effect may be subserved by the influence of inflammatory markers in neuroplasticity processes, in monoamine metabolism and in the glutamate-kynurenine pathway, which could lead to an increase in vulnerability to the development of depression [59]. This hypothesis is supported by the well-known induction of depressive symptoms by exogenous cytokine administrations, such as treatment with IFN- $\alpha$  [60]. On the other hand, some pathophysiological processes of depression have been recognized to affect inflammatory activity. Psychosocial stress, both acute and chronic, is one of the main risk factors for the development of MDD [61] and has also been shown to deregulate inflammatory response, an effect likely mediated by the HPA axis and the sympathetic nervous system (SNS) function [62]. Therefore, the dysfunction of the stress-response system observed in depression could, consequentially, lead to inflammatory abnormalities. Finally, other factors related to MDD that also impact on inflammation may explain this association. Obesity and depression have been shown to be connected. Studies have documented a correlation between increased body mass index and a higher probability of developing MDD, and also that depression can be a risk factor for the development of obesity [63, 64]. Adipose tissue and adipocytes have been linked to an increased production of several inflammatory markers, including IL-1 $\beta$ , IL-6 and TNF- $\alpha$  [65, 66], which can be thought of as a mediator of the depression-obesity relation, but it also could be considered an unrelated factor. Gut microbiota has recently been attracting some attention as it was shown to interact with stress-response systems, as well as with inflammatory pathways, and could also be implicated in MDD pathophysiology [59].

Taken together, the evidence indicates that the most likely scenario is of a multifaceted, bidirectional relationship between depression and inflammatory pathways, which is also influenced by different factors, through a network of multiple interacting networks. In this case, activation of the inflammatory pathway would not be the cause, consequence or epiphenomenon of MDD, but, instead, a combination of all three.

### The Future of Research on Inflammation in MDD

In spite of the considerable advance in understanding of the cross-talk between the brain and the immune system, our current belief is that it is time to investigate how

these findings can be translated into therapeutic interventions for MDD targeting inflammation. This would be realized by investigating two avenues.

#### *Antidepressant Effects of Anti-Inflammatory and Antioxidant Agents*

As the role of inflammatory pathways in the pathophysiology of depression has become increasingly understood, the use of anti-inflammatory agents in treatment is seen as the logical next step. Several agents have been tested so far, including celecoxib, naproxen, aspirin and TNF- $\alpha$  antagonists. Celecoxib was used as an adjuvant to reboxetine in a 6-week placebo double-blind, randomized controlled trial (RCT) for 40 individuals diagnosed with MDD [67]. Subjects that used celecoxib at a dose of 400 mg/day presented a significant improvement in depressive symptoms compared to the placebo group [67]. Another RCT tested celecoxib as an add-on to fluoxetine, showing the superiority of the association [68]. Celecoxib has also shown promising results as an adjuvant in the treatment of bipolar depression and schizophrenia [69–71], but has negative results in improving depressive symptomatology in cognitively normal volunteers aged 70 years and older with a family history of Alzheimer-like dementia [72].

The efficacy of aspirin was evaluated by an open-label study that employed 160 mg/day of aspirin as an adjuvant in 24 MDD patients with no response to SSRIs [73]. In this study, aspirin appeared to accelerate the response to antidepressants, as individuals presented a significant improvement of depressive symptoms in the first week of the trial [73]. One study did not report any additional clinical improvement with the combination of aspirin and fluoxetine compared to fluoxetine alone [74].

TNF- $\alpha$  antagonists have also been shown to exert positive effects on mood. In a large RCT involving individuals with psoriasis and without any diagnosed mental disorder, treatment with etanercept was associated with a significant reduction in depressive symptoms [75, 76]. Infliximab, a monoclonal antibody directed at TNF- $\alpha$ , was tested in a recent RCT for treatment-resistant MDD. Interestingly, infliximab was demonstrated to be more effective than placebo, but only in individuals with high baseline levels of a pro-inflammatory biomarker, the high-sensitivity CRP (defined as levels higher than 5 mg/l) [77].

Other substances with known anti-inflammatory properties have also been explored in the treatment of depression. This group includes minocycline and antioxidants, such as curcumin, and N-acetyl-cysteine (NAC) and zinc. Minocycline is an antibiotic with anti-inflammatory, antioxidant, antiglutamatergic and neuroprotective

tive effects [78]. Curcumin is a compound extracted from turmeric (*Curcuma longa*) and is commonly used as a culinary seasoning in different regions of Asia. Curcumin is believed to act in inflammatory, oxidative and apoptotic pathways [79]. To our knowledge, curcumin has not been used in clinical trials for depression so far. NAC is a glutathione precursor that has been shown to be involved in oxidative homeostasis, dopamine modulations and to interact with several inflammatory markers [80]. Preclinical studies with these agents have yielded promising results so far, with evidence supporting an antidepressant-like effect in animal studies [81–85].

Minocycline was tested in an open-label trial as an adjunctive therapy for patients with unipolar psychotic depression and demonstrated efficacy in both depressive and psychotic symptoms [86]. NAC use has been more extensively explored in bipolar depression. A 6-month double-blind RCT of add-on NAC to standard treatment showed a significant positive effect for depressive symptoms and functional outcome [87, 88]. However, a study using NAC for the maintenance of bipolar disorder observed no result in recurrence or symptomatic outcomes [89].

Reports that depression is associated with low blood zinc levels, which were increased by antidepressants, supports the idea that zinc homeostasis is involved in depression pathophysiology [90]. One placebo-controlled, double-blind pilot study of zinc supplementation to standard antidepressant therapy has been conducted [91]. In this study, patients who received zinc displayed a significant improvement after 6 and 12 weeks when compared to placebo controls [91].

#### *Exploration of Antidepressant Properties of Nonpharmacological Approaches That Modulate Inflammation*

Exercise is an efficacious treatment for MDD and has independently been shown to have anti-inflammatory effects in nondepressed subjects. In the Treatment with Exercise Augmentation for Depression (TREAD) study, participants who were partial responders to a selective serotonin reuptake inhibitor were randomized to receive one of two doses of exercise: 16 kilocalories per kilogram of body weight per week, KKW, or 4 KKW for 12 weeks. Higher baseline levels of TNF- $\alpha$  were associated with a greater decrease in depressive symptoms over the 12-week exercise period. In addition, a significant positive correlation between change in IL-1 and reduction in depression symptom scores was observed [92].

Acupuncture is another alternative treatment that has shown some benefit in MDD. An RCT with individuals

with mild-to-moderate depression demonstrated an improvement significantly higher than the placebo group [93], while a study using add-on acupuncture to paroxetine treatment obtained similar results [94]. Acupuncture has long been recognized to possess anti-inflammatory properties. Studies have shown that acupuncture can downregulate pro-inflammatory cytokines, including IL-1, IL-6 and TNF- $\alpha$ , and pro-inflammatory neuropeptides [95]. This suggests that modulation of the inflammatory response can be one of the paths by which acupuncture ameliorates depressive symptomatology.

#### **Future Direction**

Overall, these results support the idea that targeting inflammatory pathways can be effective in the treatment of depression [95]. However, most clinical studies present important limitations in design, time or sample size. This fact hinders the drawing of definitive conclusions, as well as the translation to clinical practice. Nonetheless, what does the evidences gathered so far tell us about the future in this field of research? Firstly, the delimitation of subgroups can be a promising path. The clinical trial with infliximab obtained a positive result, but only for a 'highly inflamed' subgroup of patients [77]. The characterization of this group, using biomarkers (i.e. dosage of cytokines) and/or risk factor (i.e. childhood trauma) strategies, could lead to clinical trials with more refined designs. Secondly, the stage of illness should also be more carefully considered. Inflammation acts differently according to phase (acute vs. chronic) and duration (early vs. late stages) of the disease. Acute and severe states most likely represent the peak of pathological inflammatory activity and can indicate a moment when the introduction of anti-inflammatory agents would be more beneficial. The experience of NAC in bipolar disorder, which presented effective results in depressive episodes but not on maintenance [89], reinforces this concept. Moreover, many of the behavioral effects of inflammatory dysfunction, such as cognitive deficits, can be thought of as late consequences of it, which is probably the case in patients with longer-duration, multi-episodic illnesses [2]. As a consequence, they may not be as susceptible to interventions targeting inflammatory pathways. Therefore, these interventions may be better suited to individuals in the earliest stages of depression, before most of the damage has already been done. Finally, this last point can also be extrapolated for primary prevention strategies. Although this field of psychiatry is only in its infancy and its discussion is beyond the scope of this

article, it is worth mentioning that anti-inflammatory interventions, especially the nonpharmacological ones, are ideal candidates for prevention studies. These interventions can have a disease-modifier effect, without the risk and side effects associated with psychotropic medications, and are therefore well-suited to use in groups with a high risk of developing depression, such as individuals with chronic diseases, history of childhood trauma or presence of subthreshold symptoms [96, 97].

## Conclusions

There is ample evidence that MDD is accompanied by activation of inflammatory pathways, suggesting that these pathways are new drug targets in depression. Translation of these findings into new clinical trials with negative immunoregulatory or antioxidant drugs in MDD should be part of the scientific agenda for the coming years.

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