IMPLICATIONS OF THE INFLAMMATORY PROCESSES IN MAJOR DEPRESSIVE EPISODE

Traian Purnichi¹,², Ruxandra Grigoras³, Ileana Marinescu¹, Mihai C. Parlog⁴, Silvia Ristea³, George Paraschiv³, Ruxandra Banu⁴, Lavinia Duica⁴, Mihnea Manea¹, Valentin P. Matei⁴

Abstract There are an increasing number of evidences that suggests that the immune system and inflammatory processes can contribute to MDD pathogenesis in a significant proportion. In this article, we tried to review the current evidences that are suggesting that inflammatory processes contribute to the development of MDD by direct actions on the brain as well as by effects on secondary pathways that are linking the brain to other system of the organism. We consider that more and more evidences are linking the immunomodulatory interventions to mood variation and this may hold the promise of a new approach in MDD treatment, especially in patients with elevations of the inflammatory biomarkers. These interventions refer to cytokine and cyclooxygenase antagonists, but also to agents that impact inflammatory transcription factors or signaling cascades.

Keywords: major depressive episode, inflammation

Until now, the studies have only been able to establish a bidirectional interaction between the brain and body's immune system but these findings are more relevant in the way that an individual is more likely to develop an episode of Major Depressive Disorder (MDD) in response to both stress and inflammatory disease than other individual with normal immune response. Also, it has been established that the psychosocial stressors are among the most replicaded and reliable risk factors for MDD (1) most likely because the psychosocial stress activates the inflammatory response and this is the major link between stress and MDD. For example, the exposure to the Trier Social Stress Test (TSST - a public speaking and mental arithmetic stressor) was associated with a significant increase in DNA binding of the inflammatory transcription factor (NFκβ) in peripheral blood mononuclear cells (PBMCs), whereas merely watching others undergoing the TSST had no such effect (2). Others studies suggested that psychosocial stressors may result in enhanced inflammatory responses in individuals with early life adversity no matter if these people are currently depressed or not depressed in that moment (3, 4). It is possible that an early life stress like trauma or maltreatment can represent a powerful risk factor for adult MDD by inducing a long term increases in inflammatory signaling because the inflammatory biomarkers are elevated if these people are depressed, but this status is maintained even in the not depressed state (5).

Some articles indicate also that the parasympathetic nervous system is involved in immune regulation and has potent anti-inflammatory effects (6). The inhibitory effects on the inflammatory response, referred to as the ‘cholinergic anti-inflammatory pathway’, have been proved to be mediated by vagal release of acetylcholine that in turn activates the alpha7 subunit of the nicotinic acetylcholine receptor which can regulate both cytokine transcription and translation (6). Moreover, some studies suggest that T cells may contribute to this inhibitory cholinergic reflex (7). In addition, the reduced heart rate variability which is a reflection of reduced parasympathetic tone, has been associated with increased inflammatory biomarkers including IL—6 and CRP in medically healthy individuals as well as patients with MDD and heart disease (8, 9). On the other hand, the stress might activate the inflammatory response and the evidences most strongly support the role of the central autonomic nervous system (10).

The relationship between MDD and inflammation on an experimental pathophysiological model, was initially demonstrated by the fact that the cytokine administration induces depressive symptoms. For example, chronic administration of the inflammatory cytokine, interferon (IFN)-α, has also been found to induce depressive symptoms, with as many as 30—50% of IFNα-treated patients meeting symptom criteria for MDD (11). Moreover, supporting the similarity between the MDD associated with IFNα and depression in other populations is the fact that IFNα—induced MDD can be prevented and/or treated by conventional antidepressants therapy (12, 13, 14, 15).

Recent evidences suggest that the inflammatory response itself can contribute to the various measures of suppressed immunity observed in MDD, including direct effects of inflammatory cytokines on signaling through the T cell receptor (16, 17, 18, 19, 20). Many articles and meta-analyses confirm that peripheral blood elevations in the cytokines like IL-6, tumor necrosis factor (TNF-α), and the acute phase reactant, C reactive protein (CRP),

1. MD, Hospital of Psychiatry, „Prof Dr. Al. Obregia” , Bucharest
2. PhD student, University of Medicine and Pharmacy of Craiova.
3. MD, PhD, University of Medicine and Pharmacy of Craiova; Clinical Hospital of Neuropsychiatry Craiova.
4. PhD, University of Medicine and Pharmacy of Craiova; Clinical Hospital of Neuropsychiatry Craiova.
5. MD, National Institute of Geriatrics in Bucharest
6. MD, PhD, University of Lucian Blaga Sibiu, Faculty of Medicine; Hospital of Psychiatry in Sibiu

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Corresponding author:
Traian Purnichi

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chemokines and cellular adhesion molecules in peripheral blood as well as increased stress-induced nuclear factor-κB (NFκB) are among the most reliable biomarkers of increased inflammation in MDD patients (21, 22, 23, 24). Moreover, many studies have found significant associations between blood concentrations of inflammatory factors and the severity of depressive symptoms but the proofs are somehow inconsistent if we refer to the fact that increased inflammatory markers in MDD patients return to control levels after successful antidepressant treatment (25, 26, 27, 28).

These findings suggest that failure to respond to antidepressant treatment should be associated with ongoing elevations in inflammatory biomarkers, and indeed several studies support this theory (29, 30). Out of these data we can appreciate that an elevation in inflammatory markers prior to treatment might predict poor response, suggesting a relationship between inflammation and treatment resistance (29, 30, 31, 32). This can be explained by the fact that the administration of cytokines modifies the serotonin and dopamine level but also the glutamate level (28). Moreover, the serotonin reuptake inhibitors (SSRI) can prevent or treat depressive symptoms during chronic exposure to IFNα patients with infectious diseases and cancer provides strong evidence that serotonin pathways are involved in cytokine effects on behavior (12, 33). Further implicating of the alterations in serotonin metabolism in cytokine induced behavioral changes, are studies showing that IFNα associated increases in cerebrospinal fluid (CSF) concentrations of IL-6 are inversely correlated with the serotonin metabolite, 5-hydroxyindoleacetic acid (5—HIAA), which, in turn, negatively correlate with IFNα that induced depression severity (34). Also, cytokines were proved to have a significant impact on dopamine pathways. Studies have found altered blood flow and metabolic activity in basal ganglia nuclei during exposure to inflammatory stimuli (35, 36, 37), and in studies in non-human primates, reduced CSF concentrations of the dopamine metabolite, homovanillic acid (HVA), were associated with depressive-like huddling behavior secondary to chronic IFNα administration (38). This is happening because the enzyme indoleamine 2,3—dioxygenase (IDO) is activated by various cytokines alone or in combination (39, 40). IDO catalyzes tryptophan, the primary amino acid precursor of serotonin, into kynurenine. Depletion of tryptophan provides protection against a variety of pathogens, but also inhibits effector T cell responses and thereby contributes to immune tolerance (41). IDO increases the production of kynurenine and its metabolites for immune-induced depression (42, 43).

Another pathway that can influence monoamine metabolism is the cytokine signaling pathway mitogen—activated protein kinase (MAPK). It was demonstrated that stimulation of p38 MAPK pathways increases the expression and function of the serotonin transporter (SERT), which in animal studies has been shown to increase depressive-like behavior in response to inflammatory stimuli (44). In humans, increased phosphorylation of p38 MAPK following the first injection of IFNα was associated with the subsequent development of IFNα-induced depression and fatigue (45). In addition to effects on serotonin metabolism, MAPK pathways have also been found to influence the dopamine transporter (DAT) (46). Moreover, the inflammatory mediators are known to profoundly impact glutamergic functioning in the CNS because cytokines have been shown to decrease the expression of glutamate transporters on glial cells and to increase the release of glutamate from astrocytes (47, 48, 49). This astrocyte-derived glutamate has preferential access to extra synaptic NMDA receptors, which can mediate excitotoxicity and lead to decreased production of trophic factors including brain—derived neurotrophic factor (BDNF) (50, 51).

The hypothalamic—pituitary—adrenal (HPA) axis anomalies and their relationship with mood are one of the most reproducible findings in patients with MDD because these patients have been found to exhibit increased concentrations of the HPA axis hormones (like ACTH and cortisol) and an increase in CSF measures of the HPA axis regulatory neuropeptide, corticotrophin—releasing hormone (CRH) (52, 53). Moreover, the studies in patients have proven that the acute ACTH and cortisol response to the first injection of IFNα (presumably due to activation of CRH pathways) is powerful and relates with the subsequent development of depressive symptoms during IFNα therapy in patients with cancer but the acute administration of IFNα, chronic IFNα administration is associated with flattening of the diurnal curve and increased evening cortisol concentrations, both of which correlate with the development of depression and fatigue (54, 55). This finding is important because the flattening of the diurnal cortisol rhythm has been seen in many medical disorders associated with inflammation including cardiovascular disease and cancer, where it has been associated with a worse outcome in these diseases (55). For example, previous studies have shown that the flattened cortisol rhythm is associated with non-suppression of cortisol by dexamethasone (DEX) in the DEX suppression test (DST) (56). DST non-suppression is a common finding in major depression both in vivo and in vitro in peripheral blood mononuclear cells (PBMCs) (52, 53, 57). DEX non-suppression, also referred to as glucocorticoid resistance, has additionally been correlated with stimulated production of IL-18 by PBMCs of patients with MDD (58). The inflammatory cytokines can disrupt glucocorticoid receptor (GR) function while decreasing GR expression (59). A similar protein—protein interaction between the GR and NFκB in the nucleus has also been described (60). On the other hand, IL-1α and IL-1β have been shown both in vitro and in Vivo to inhibit GR translocation from the cytoplasm to the nucleus through activation of p38 MAPK (61, 62). Moreover, the stress induced alterations in GR translocation leading to glucocorticoid resistance in laboratory mice has been found to be mediated by Ile1 (using IL-1 KO mice), who fail to exhibit impaired GR translocation following social disruption stress (61). So, chronic exposure to inflammatory glucocorticoids can lead to decreased GR expression as well as increased expression of GRB (GRB expression has been proven to be increased in patients with inflammatory disorders including patients with bronchial asthma and rheumatoid arthritis), a GR isoform which has a distinct hormone binding domain (that is unable to bind known glucocorticoids) and a unique pattern of gene regulation (59, 63).
Neurogenesis is stimulated by many antidepressant medications (by increasing the BDNF level) and it is important in the MDD recovery and in the relapses prevention (64). The data have showed that the stress induces a decrease in neurogenesis and on the expression of relevant nerve growth factors, including BDNF (which support neurogenesis). This can be reversed by administration of the IL-1 receptor antagonist or transplantation of IL-1—IRa secreting neural precursor cells into the hippocampus or the use of IL-1 receptor knock—out (KO) mice (65, 66, 67). In patients, the treatment with IFNα has been associated with reduced levels of peripheral BDNF, which are known to correlate well with BDNF availability in the CNS (68).

In patients under IFNα therapy for cancer or C hepatitis (by using positron emission tomography (PET SCAN)), was found a marked increase in glucose metabolic activity in the basal ganglia which correlated with symptoms of fatigue (69, 70). These increases were found also in patients with Parkinson's disease and they are believed to reflect increased oscillatory burst activity in relevant basal ganglia nuclei secondary to DA depletion (71,72).

Another brain region that has been found to be influenced by cytokine administration and inflammatory stimuli is the dACC that plays an important role in error detection and conflict monitoring (73). Patients with hepatitis C treated with IFNα were found to have significantly higher activation of the dACC using fMRI and a task of visuospatial attention (12, 74). A strong correlation was found in this study between activation of the dACC in IFNα-treated patients and the number of errors made during the task. The error rate was quite low for the task, and no such correlation was found in control subjects. In this context, the patients with high-trait anxiety have also been shown to exhibit increased dACC activation during fMRI in the context of low error rates (75). Moreover, increased activation of the dACC after a psychosocial stressor (TST) was correlated with the degree of activation of peripheral blood IL—6, suggesting a role for stress-induced inflammation in the findings (76). Moreover, the dACC plays a role in processing the social pain, also (77). Given the connection of the dACC with downstream autonomic nervous system arousal pathways, these investigators have further hypothesized that the dACC may serve as a “neural alarm system” that can both detect and respond (with arousal and distress) to threatening environmental stimuli in the social domain (77). In this context, the cytokines may sensitize the responsivity of the dACC, thereby contributing to the anxiety, arousal and alarm that often accompany chronic exposure to inflammatory stimuli such as IFNα. From an evolutionary perspective, this heightened dACC activity (and heightened sensitivity to social threat) may sub serve the survival priority of vigilance against attack in an animal that is otherwise vulnerable due to infection or wounding (78). In conclusion, the administration of an inflammatory stimulus has been associated with activation of the sub-genual ACC, the target of deep brain stimulation strategies in patients with treatment resistant depression (79).

Because the immune system interacts with nearly every system in the brain and body, many therapeutically strategies can be putatively work for MDD treatment. Probably the best studied anti-inflammatory strategy for the treatment of depression is the targeting of inflammatory signaling pathways. The simplest approach in this regard can be the administration of pharmacologic agents that inhibit cyclo-oxygenase (COX - the enzyme that converts arachidonic acid into prostaglandin) because the prostaglandins have been demonstrated to be increased in depression and are known to play an important role in the inflammatory response including the mediation of fever and sensitivity to pain. Moreover, inhibition of COX—1 and COX—2 selectively and in combination have been shown in laboratory animals to inhibit depressive like behavior following administration of the inflammatory stimulus without influencing cytokine responses (80, 81). Still, there are some controversy as to whether COX—1 versus COX-2 is the most relevant target. Generally, the indomethacin and ibuprofen (nonselective COX inhibitors), have some proofs that showed an efficacy in animal models (81). In patient's studies, the add-on of the acetylsalicylic acid (which blocks COX-1 and COXeZ) to fluoxetine has increased remission rates in an open-label study of 24 depressed patients previously nonresponsive to fluoxetine alone (82). Another study of 20 medically healthy depressed patients who received the COXeZ inhibitor, celecoxib, in combination with reboxetine showed greater symptomatic improvement compared to patients randomized to reboxetine plus placebo (83). But, both studies involved small sample sizes, and in the celecoxib study, 50% or more of the sample in each group dropped out before conclusion of the study (83).

Another therapeutically add-on strategy could target the cytokine because they are probably one of the most obvious targets for treating the impact of peripheral inflammation on the brain. Some case reports indicated that several of the currently available biologics therapies (monoclonal antibodies, soluble cytokine receptors or other antagonists which combine cytokine receptors with other fusion proteins that target cytokines were effective in reducing symptoms of depression and fatigue as well as quality of life (84).

Another possible therapeutically strategy could include indoleamine 2,3—dioxygenase (IDO) as a potential target for the unique contributions of the immune system to depression is evidenced by studies that have administered an IDO antagonist or used IDO KO mice in the context of immune activation or infection. Thus, there are great hopes regarding the development of more potent IDO inhibitors (85). In some studies of the mice treatment with the IDO antagonist, 1—methyl tryptophan (I—MT), abrogates the impact of LPS as well as infection with bacillus Calmette Guerin (BCG), an attenuated form of mycobacterium bovis, on depressive like behavior including increased immobility in the PST and TST (86, 87). Targeted deletion of KAT II (the enzyme that converts KYN to KA) has also been shown to increase cognitive performance in association with an increase in the amplitude of long—term potentiation in vitro, while reducing extracellular KA as measured by hippocampal in vivo micro dialysis (88). Moreover, given the elaboration of the kynurenic pathway as well as data indicating the role of kynurenic acid and quinolinic acid in neuropsychiatric disease, especially neurodegenerative disorders, few compounds which interfere with multiple
steps in the kynurenine pathway have been identified in
clouding inhibitors of 3-hydroxyanthranilic acid
oxygenase which converts 3-hydroxyanthranilic acid to
quinolinic acid (42, 89).

Also, we must mention as a possible therapeutically target the NFκB because it plays a big role in
the inflammatory response by transmitting inflammatory signals from the periphery to the brain,
where it has been proven to mediate inflammation induced
inhibition of neurogenesis (90, 91). Out of all the
compounds that have been shown to inhibit NFκB, a
special interest has been recently paid to natural
compounds such as curcumin (a derivative of the curry
spice, turmeric), which has been shown to decrease NFκB
activation in PBMCs of patients with pancreatic cancer
(92). Another natural compound is d-tocopherol (a form of vitamin E) which has been shown to block NFκB and the
associated neuro-inflammatory and behavioral response to
LPS (93), and resveratrol (found in the skin of red
grapes) which has been shown to inhibit LPS-induced
induction of inflammatory cytokines, chemokines and
inducible nitric oxide synthase (iNOS) in murine microglia and astrocytes in association with inhibition of
NFκB (94).

In the end, we must not forget to mention that the
activation of the parasympathetic nervous system is
involved in immune regulation and has potent anti-
inflammatory effects (95) and because of that most
behavioral interventions that have shown antidepressant properties, including psychotherapy, exercise and weight
loss, also tend to reduce peripheral inflammatory
biomarkers. Recently, meditation practices have also
shown evidence of anti-inflammatory activity. The
practice of a secularized compassion meditation
technique has been reported to reduce inflammatory
responses (i.e. plasma IL-6) to a standardized laboratory
stress or in healthy young adults and to reduce resting state
levels of CRP in highly traumatized adolescents in state
custody (96, 97, 98). These studies also observed
behavioral effects of the training that might be expected to
either reduce or prevent depressive pathology. Also, the
mindfulness based stress reduction has been reported to
reduce feelings of loneliness in older individuals and to
down-regulate NFκB associated gene expression profiles
(99). Similar changes in the balance of pro to anti-
inflammatory transcription activity as assessed by gene
expression analyses have been observed in caregivers
of dementia patients trained in yoga meditation (100).

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