HYPOTHESIS OF NEUROINFLAMMATION IN DEPRESSION

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Abstract:
Numerous clinical and experimental studies show that neuroinflammation hypothesis became a foundation pillar in the etiopathogenesis of depression alongside the monoamine hypothesis, given the fact that the existence of a pro-inflammatory status was repeatedly proven both in human subjects and laboratory animals. Depression induced by cytokine treatment in cancer and by interferon treatment in viral chronic hepatitis became a frequent therapeutic entity in the later years, on the opposite pole being important proofs of amelioration in psychic and neurovegetative depressive symptoms with anti-cytokine and anti-inflammatory treatment.

Key words: pro-inflammatory cytokines, neurodevelopment, neuro-inflammation, depression.

BACKGROUND
Pro-inflammatory cytokines play an important role in the etiopathogenesis of depression, fact sustained by many experimental data and clinical trials. Experimental data show that an increased prenatal and early age level of pro-inflammatory cytokines favors the apparition of neurodevelopmental abnormalities which determine symptoms similar to depression in lab rats: social withdrawal, cognitive dysfunctions, anhedonia, increased hypothalamic-pituitary-adrenal axis activity, psychomotor retardation, sleep disturbances and the alteration of neural transmission. There are numerous clinical proofs regarding the risk of depression in patients who receive recombinant cytokines in the treatment of cancer and viral infections. The apparition of depression in these patients was linked with a decreased tryptophan level due to the induction of indoleamine 2-3 dioxygenase, the enzyme that metabolizes this amino acid. The degradation of tryptophan by this enzyme and the proliferation of T-lymphocytes is induced by interferon and other inflammatory cytokines. (1) For a long time it was thought that depression was associated with immunosuppression, but this theory was subsequently infirmed, being considered that the etiopathogenic factor was not immunosuppression, but a lack of balance in the immune system functioning, with the activation of monocyte and macrophage activity, associated with the diminishing lymphocyte activity. (2) The antidepressants that exist now on the market have the target of increasing in monoamine transmission, the monoamine theory of depression being the main etiopathogenic theory studied. (3,4) Nevertheless, there are many non-responsive patients, which suggests that the etiopathogenesis of depression is much more complex, as there are more factors that have not been considered regarding the therapeutic alternatives. Numerous studies suggest that depression, especially the major type, is associated with a deregulation of the immune system and the production of pro-inflammatory cytokines, the most frequently encountered being (IL)-1β, IL-2, IL-6, interferon γ (IFN-γ), tumor necrosis factor α (TNF α), the soluble receptor for IL-6 (IL-6R), and the antagonist of IL-1 receptor (IL-1RA). Many studies have also reported a low level of anti-inflammatory cytokines in depression (IL-4 and IL-10) (5,6).

SHORT HISTORY
The first information regarding the possible involvement of cytokines in depression was taken from gastroenterology and oncology. The oncologic patients and those with hepatitis B and C with cytokine treatment for immune system stimulation presented psychosis and/or major depressive symptoms a few weeks after the treatment was initiated. (7) Then Smith's macrophage theory of depression appeared in 1991, stating that a high level of interleukine-1 associated with the presence of macrophage degradation products produces cerebral abnormalities that are the base of depression pathogenesis. It was further experimentally demonstrated that pro-inflammatory cytokines determine the activation of hypothalamic-pituitary axis, fact associated with major depressive symptoms in laboratory animals. It was initially considered that patients with major depression

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are immunosuppressed due to low activity of natural killer cells and lymphocyte proliferation. It was further demonstrated that depression is not associated with immunosuppression, but with a malfunction and a lack of balance in the immune system functioning. This was associated with monocyte and macrophage hyperactivity, which activates the apoptosis and leads to apparition of toxic cerebral degradation products. In 1995, Maes was the one who showed increased pro-inflammatory cytokines and acute phase proteins in the plasma of patients with major depression. (8) In 1996 Yirmiya demonstrated that antidepressant treatment administered for a long time in laboratory mice ameliorates anhedonia and social withdrawal, confirming the theory stating that anti-cytokine treatment and antidepressants decrease cytokine production and diminish depression symptoms. (9) Numerous clinical studies were performed later, but they didn't show such a pronounced lack of equilibrium in the immune system as experimental data showed. But new data appeared, and according to these, a high level of pro-inflammatory cytokines and the activation of hypothalamic-pituitary system are not only etiopathogenic factors in depression but also in schizophrenia, and the increased level of pro-inflammatory cytokines and acute phase proteins in a first psychotic episode is positively correlated with a low response to treatment in subsequent episodes.

**CLINICAL AND EXPERIMENTAL STUDIES**

In 1999, Levine et al. developed a clinical trial that included 23 patients, 13 with non-treated major depression and 10 controls, in order to confirm Smith's macrophage theory of depression. It was shown that the level of pro-inflammatory IL-1β in the cerebrospinal fluid and serum was higher in hospitalized patients with major depression compared to controls, being positively correlated with the severity of depression. In spite of this, IL-6 and TNFα levels were not significantly modified in patients versus controls. (10) Also in 1999, Hack et al. tried to include risk factors for depression like advanced age, smoking, increased BMI and personal history of infection into a similar study. The results were disappointing, as no evidence of alteration in serum interleukins and pro-inflammatory proteins for 361 depressed patients versus 61 controls was shown. (11) This study was contradicted later in the same year when Anisman demonstrated an increased interleukin-1β level in dysthymia and unipolar depression, statistically correlated with onset and disease duration. (12) But in 2001, a study on patients with melancholic depression didn't show an increased production of IL-1β compared to healthy controls, the only pro-inflammatory increased cytokine being the α-2-macroglobulin with a high monocyte level, but in patients with depression without melancholic features. (13) Experimental studies were much more prolific regarding the confirmation of macrophage and neuroinflammatory theory in depression. It was observed that antidepressant treatment, regardless of pharmacologic class, determines the amelioration of behavioral characteristics and neuroendocrine effects associated to immune activation. A better response was obtained for tricyclic antidepressants and tianeptine compared to selective serotonin reuptake inhibitors. (14) Antidepressants also ameliorate the lack of equilibrium between the lymphocyte arm and the macrophage arm of the immune system, and between the secretion of anti-inflammatory and pro-inflammatory cytokines in the brain. (15) In spite of this, clinical studies didn't show such good results regarding the decrease of pro-inflammatory cytokine level during antidepressant treatment compared to experimental studies, further investigations being necessary. Animal models for depression were created, a modification of the cytokine equilibrium in the brain being proved. In mice, medium intensity chronic stress was associated with the increased production of IL-1α and IL-6 and the decreasing activity of natural killer cells. (16) Connor et al demonstrated an attenuated cytokine pro-inflammatory response to lipopolysaccharides in bullectomized rats, effect accentuated during chronic treatment with desipramine. (17) Schmidt et al. showed that exposure to IL-1 induced the increased sensitivity of adrenocorticotropic hormone secretion through increasing the number of secreting neurons in the paraventricular nucleus of hypothalamus, which determines the activation of hypothalamic-pituitary axis. This process causes the persistence of hormonal stress response in the organism for many weeks after the stressor factors disappeared. (18) In conclusion, the hypothalamic-pituitary feedback system is also affected in depression.

**NEUROINFLAMMATORY HYPOTHESIS OF DEPRESSION**

Exogenous administration of pro-inflammatory cytokines in laboratory animals determines a disease-modified behavior (neurovegetative basis): asthenia, fatigability, muscle weakness, malaise, food refusal and somnolence, associated with depression symptoms like anhedonia and social withdrawal. Neurovegetative symptoms predominate, leading to disease modified behavior (19) while administration of IL-1 in human subjects leads to similar symptoms, the ones that are common both clinically and experimentally being food refusal and nyctohemeral rhythm alteration. (20) All of these symptoms are due to excess activation of some branches in the immune system, which leads to a lack of immune equilibrium in the organism. Administration of α-interferon in patients with chronic hepatitis leads to fatigability as the main symptom. Fatigability was also associated with increased pro-inflammatory markers in patients with ischemic heart disease. (1) In animals, anhedonia is only induced by administration of IL-2, no results being obtained for IL-6 and IL-1β. (21) So, a new type of depression needs to be added as diagnostic formulation: the one induced by cytokine treatment, which is more obvious in treatment for cancer, chronic hepatitis and autoimmune diseases. Pro-inflammatory cytokines do not only induce somatic and psychiatric symptoms characteristic to depression, but also cognitive disturbances. This fact was demonstrated in patients treated with IL-2 and α-interferon in cancer, nyctohemeral rhythm alteration being added to the lack of concentration capacity and decreasing memory. The chronology of symptom apparition differs according to treatment modality, but cognitive and neurovegetative symptoms appear very early (generally from the first week) for IL-2 treatment and later, after 4-8 weeks for interferon treatment. Delaying of symptom apparition during interferon treatment led to a promising study:
administration of paroxetine for depression prophylaxis in patients treated with α-interferon prevented the apparition of depressive symptoms. In spite of this, paroxetine wasn't efficient in in the amelioration of neurovegetative symptoms, the most persistent being fatigability. (22) Alongside IL-2 and 2, IL-6 is a very well studied cytokine, as it represents a predictor factor for cardiovascular diseases and osteoporosis, its level being also high in depressed patients. Secretion of IL-6 is activated by the sympathetic neurovegetative system through β-adrenergic receptors, which makes it an important activator for the sympathetic vegetative system but also for the hypothalamic-pituitary axis. This cytokine is also a stimulator of the acute phase hepatic inflammatory response, increasing the pro-coagulating factors and platelets expression and endothelial cells activation, which makes it an important cardiovascular risk factor. IL-6 and IL-1β are activators of modified disease behavior (lack of motivation, social withdrawal, somnolence, fatigability an diffuse somatic manifestations- muscle and articular pains, headache). The peak of IL-6 secretion is between 1 and 5 am, the lowest secretory activity being registered also in the morning, between 8 and 10 am. (1,2) Alesci et al. show that the pattern of IL-6 secretion is modified in depressive patients, a new peak appearing in the afternoon, with persistent increased IL-6 levels during the day. Also, the morning level of IL-6 was increased in depressive patients compared to controls, while no circadian cortisol rhythms modifications were registered. The peak of IL-6 secretion in depressive patients was detected in the morning, with the lowest level during sleep hours, this pattern being completely different from the normal secretion pattern of this interleukin. The same modifications were demonstrated for chronic insomnia and sleep deprived healthy individuals. The morning secretion peak of IL-6 in depressive patients predisposes them to a 2-3 fold higher risk of cardiovascular premature pathology, compared to the non-depressive patients because it maintains an inflammatory pro-thrombotic status in the organism. (26) The most extensive and cited meta-analysis was published in 2010 and it included 24 clinical trials, studies that measured the following markers in both serum of patients and controls: TNF-α (n=13 studies), IL-1β (n=9), IL-6 (n=16), anti-inflammatory IL-4 (n=5), IL-2 (n=5), IL-8 (n=4), anti-inflammatory IL-10 (n=6), IFN-γ (n=4). High levels of TNF-α and IL-6 were obtained. For the other markers, no significant high values were recorded compared to controls, neither for IL-1β, a very high studied cytokine in experimental trials, with major increases in laboratory mice with similar symptoms to major depression. (27) TNF-α and IL-6 are acute phase proteins which are secreted when the organism is confronted with an immunological aggression, their high level outside an inflammatory status, infectious or traumatic being considered abnormal. (28) IL-6 is secreted in the periphery by macrophages and natural killer cells and it stimulates the macrophages’ pro-inflammatory cytokines and prostaglandin release. (29) It is stated that an increasing of pro-inflammatory cytokines has pathologic effects on the brain, affecting the neurogenesis, fact observed in laboratory animals not only in depression but also in schizophrenia. The most affected structure in depression is the hippocampus, whose volume is reduced, being proved that an increased IL-6 at this level activates the microglial cells, which promote an anti-neurogenic signal. (29) An anti-proliferation activity upon progenitor neuronal cells was also proved for TNF-α and it's activity on the TNF 1 receptor. (30) Therapeutically, it was demonstrated that selective reuptake serotonin inhibitors might have a neurogenic effect by increasing the expression of BDNF, which maintains the proliferation and survival of progenitor neuronal cells. (31) IFN-γ, TNF-α and IL-6 determine the increased expression of indoleamine 2-3 dioxygenase (IDO), both in the central and peripheral nervous system. This enzyme degrades tryptophan, a precursor of synthesis for serotonin and melatonin, which can lead to depressive symptoms and circadian rhythm alterations. Kynurenin, a metabolite of tryptophan, and quinolinic acid, a metabolite of kynurenin, also have a negative effect upon hippocampal neurogenesis. Quinolinic acid is a NMDA receptor agonist, which perturbs the glutamate neurotransmission, increasing excitotoxicity in hippocampal neurons, which leads to apoptosis and decrease of hippocampal volume, leading in the end to major depression. (33) Given the numerous proofs of neuroinflammation in depression, more studies were made regarding the effect of anti-inflammatory agents in depression, preliminary studies having good results for patients treated with rofecoxib. (34) Another double blind, placebo-controlled randomized study, made on major depressive patients treated with reboxetine and celecoxib obtained a more important amelioration of symptoms compared to patients treated only with reboxetine. (35) MECHANISMS OF CYTOKINE- INDUCED DEPRESSION
The fact that the apparition of depressive and neurovegetative symptoms differs according to the type of cytokine administered and also the fact that some symptoms respond to antidepressants while others don't, suggest that the action mechanisms of pro-inflammatory cytokines are different according to the type of cytokine but also to the cerebral structure vulnerability and personality of the individual. A first hypothesis for depressive symptoms is linked to hypothalamic-pituitary axis modulation by pro-inflammatory cytokines. These cytokines lead to the increased activation of this axis and suppression of negative feedback for glucocorticoids with decreasing of cortisol-releasing hormone (CRH) secretion. (18) It is proven that IL-1 affects translocation on glucocorticoids receptor, which leads to increased resistance for this hormone in some cells. (23) This process affects organism's response to stressor factors by inadequate glucocorticoid secretion, mechanism also involved in neuroinflammation hypothesis in schizophrenia. A second neuroinflammation hypothesis of depression is linked to the chemical neurotransmission in the brain, as it is considered that pro-inflammatory cytokines lead to symptoms similar to depression by decreasing serotonin synthesis. Psychomotor retardation and anhedonia were associated with a perturbed function of basal ganglia due to dopamine synthesis alteration. The decrease in serotonin synthesis is due to it’s precursor alteration, tryptophan, it's metabolism being modified by the induction of an enzyme named indoleamine-2,3-dioxygenase which degrades tryptophan to kynurenine and quinolinic acid, in detriment of serotonin synthesis. (24) Tryptophan metabolism, according to the activity of
the enzymes involved, can take place in two directions: serotonin synthesis or active metabolites synthesis (quinolinic acid and kynurenic acid). Alteration of tryptophan metabolism with increased kynurenic acid synthesis in detriment of serotonin synthesis is considered a critical element in depression etiopathogenesis. The equilibrium between serotonin synthesis and kynurenin synthesis from the same element, tryptophan, is controlled by three enzymes: indoleamine-2,3-dioxigenase 1, indoleamine-2,3-dioxigenase 2 (IDO 1 and IDO 2) and tryptophan-2,3-dioxigenase (TDO2). The expression of these three enzymes is regulated by the innate immune system. (42) Alteration in tryptophan metabolism with production of kynurenes in detriment of serotonin was demonstrated both cerebral and peripheral, in laboratory animals treated with cytokines. (24)

This theory was confirmed by studies made on cancer patients on cytokine treatment, these presenting low serum tryptophan levels, correlated with the severity of depressive symptoms and behavior disturbances. The same results were obtained on patients with chronic hepatitis C in treatment with interferon. (25,7) In conclusion, we consider that future clinical studies for neuroinflammation in depression must consider numerous factors like somatic comorbidities and external stressors, both having a major influence upon the immune system but also upon cerebral synthesis of neurotransmitters. Inflammation has to be viewed globally, as it is a pathological state associated with numerous somatic and neurovegetative symptoms (cachexia, muscle weakness, fatigability), representing an important risk factor for cardiovascular diseases.

**METABOLIC SYNDROME AND DEPRESSION**

Metabolic syndrome is an affection that has a high pro-inflammatory status, associated with a very high risk for cardiovascular diseases. This disease caught the attention of researchers given that 12-36% of patients with depression present an associated metabolic syndrome. Depression influences glucose metabolism and the risk for metabolic syndrome and diabetes in patients with abdominal adiposity, first hypothesis in this direction being launched by Capuron et al. in 2008. (40) Depressive patients present alterations in vegetative system function, which lead to increased pulse, decreased cardiac adaptation to effort and stress, modification in circadian secretion of glucocorticoids and pro-inflammatory cytokines, and hypothalamic-pituitary axis hyperactivity. All these factors prepare the organism for insulin resistance and abdominal obesity, which favor the development of metabolic syndrome. Many pro-inflammatory markers associated with the metabolic syndrome (C reactive protein, TNF-α, IL-6, fibrinogen, leptin, resistin and adiponectin) are increased in patients with major depression (mostly TNF-α and IL-6). A study published in 2010 shows that adiponectin had low levels in patients with depression and metabolic syndrome. A high increase of IL-6 was demonstrated for patients with metabolic syndrome, similar to patients with depression. Increased acute phase proteins were observed in patients with metabolic syndrome but positive variations of C-reactive protein and fibrinogen appeared in depressed patients. (41) So patients associating depression and metabolic syndrome have an important pro-inflammatory status and a high risk for cardiovascular disease. This study comes to confirm the neuroinflammatory hypothesis in depression, showing that a similar inflammatory status is found in depression and a somatic disease, the metabolic syndrome.

**THERAPEUTIC CONSIDERATIONS**

In 2009, Yoshimura et al published a study that followed the IL-6, TNF-α and BDNF in patients with major depression treated with SSRI (one group) and SNRI (a second group), versus a control group, giving the fact that SSRI and SNRI are the reference antidepressant classes in depression treatment. The starting hypothesis was that patient’s response to treatment could be predicted according to the plasmatic level of pro-inflammatory cytokines. The study included 51 patients with major depression and 30 controls. SSRI group received paroxetine (n=16), sertraline (n=15) and fluvoxamine (n=10). Treatment for both groups was administered for 8 weeks, pro-inflammatory cytokine dosing being made before and after treatment. High plasma levels were shown for IL-6 and TNF-α in patients with depression, compared to control group and treated group, associated with low BDNF level in depressive patients. IL-6 levels dropped during treatment, TNF-α dropping being less significant than that of IL-6. In patients that did not respond to treatment (regardless the pharmacologic class), IL-6 level was more increased than in the responsive ones, with TNF-α level remaining constant. No difference in BDNF level was observed in patients treated with SSRI versus SNRI. A positive correlation was found between plasmatic IL-6 level and HAM-D score. No correlation between HAM-D and TNF-α was found. IL-6 level was maintained low after 8 weeks of treatment in both treated groups, TNF-α level remaining unmodified. A temporary conclusion would be that plasma IL-6 level could be a predictor for resistance to antidepressant treatment and could reflect the severity of depression. (36) Anti-inflammatory therapy represents an important starting point, numerous studies stating it’s efficiency in amelioration of depressive symptoms and fatigability in treated patients. Etanercept and infliximab, both TNF-α inhibitors, had a positive effect upon depressive symptoms in patients treated with monoclonal antibodies for Crohn disease and psoriasis. (37) At this moment there are many studies that follow their efficacy in subjects without autoimmune diseases, but suffering from major depression resistant to treatment. Association of cyclooxygenase inhibitors to antidepressant treatment increases the symptom response, while promising results were obtained with aspirin associated with antidepressants in patients nonresponsive to SSRI. (38) There are also some studies that show other therapies benefits (psychotherapy and physical exercise therapy) in decreasing inflammatory markers. (39)

**CONCLUSIONS**

Numerous clinical and experimental studies show that neuroinflammation hypothesis became a foundation pillar in the etiopathogenesis of depression alongside the monoamine hypothesis, given the fact that the existence of a pro-inflammatory status was repeatedly proven both is human subjects and laboratory animals. Depression induced by cytokine treatment in cancer and by interferon...
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