

The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression

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Submitted: 2008-03-09 *Accepted:* 2008-03-18 *Published online:* 2008-06-24

Key words: **depression; antidepressants; cytokines; interleukin; inflammation; oxidative; nitrosative stress; serotonin; tryptophan; indoleamine de-oxidase; leaky gut; translational medicine**

Neuroendocrinol Lett 2008; **29**(3):287-291 PMID: 18580840 NEL290308R02 © 2008 Neuroendocrinology Letters • www.nel.edu

Abstract

This paper hypothesizes that inflammatory, oxidative and nitrosative (IO&NS) pathways, and an increased translocation of LPS from gram-negative bacteria are causally related to depression following external (psychological) and internal (organic) stressors and that IO&NS pathways are novel targets for antidepressant development. We review that depression is accompanied by an inflammatory reaction as indicated by an increased production of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-6, tumour necrosis factor- α (TNF- α) and interferon- γ (IFN)- γ . These cytokines are stress-sensitive and may cause depressive behaviors. The latter may be induced by an increased catabolism of tryptophan, the precursor of serotonin, to neurotoxic TRYCATs (tryptophan catabolites along the indoleamine oxidase pathway). Inflammatory biomarkers are detected in animal models of depression. Newly developed animal models of depression are based on induced inflammation. Most if not all antidepressants have specific anti-inflammatory effects. Antiinflammatory compounds may augment the clinical efficacy of antidepressants. Depression is also accompanied by an IgM-related (auto)immune response directed against disrupted lipid membrane components, such as phosphatidyl-inositol, by-products of lipid peroxidation, e.g. azelaic acid and malondialdehyde, and NO-modified amino-acids, which are normally not detected by the immune system but due to damage caused by O&NS have become immunogenic. Increased translocation of lipopolysaccharide from gram-negative bacteria, which may be induced by internal and external stressors, may further aggravate the induced IO&NS pathways.

Abbreviations:

IO&NS	– inflammation, oxidative & nitrosative stress
TRYCATS	– tryptophan catabolites along the indoleamine oxidase pathway
IDO	– indoleamine-2,3-dioxygenase
5-HT	– serotonin
IL	– interleukin
INF	– tumor necrosis factor
NO	– nitric oxide
LPS	– lipopolysaccharide

The serotonin hypothesis of depression reviewed that depressed patients show decreased plasma levels of tryptophan; lowered brain 5-HT contents; and alterations in brain 5-HT receptors [1]. Tryptophan is the precursor of serotonin (5-HT) and its plasma concentrations are significantly related to the concentration of serotonin (5-HT) in the brain [1]. This is underscored by the findings that experimental tryptophan depletion in humans or depressed subjects (by means of the administration of large doses of amino-acids competing with tryptophan for blood-brain transport) may induce or aggravate depressive symptoms [2]. During decades, new drug development in depression targeted the serotonergic system, more specifically 5-HT reuptake. However, the current hypotheses on serotonergic dysfunctions in depression do not provide sufficient explanations for the nature of depression, while less than two thirds of the depressed patients achieve remission using the current available antidepressant drugs.

There is now evidence, that inflammatory pathways play an important role in the pathophysiology of depression [3]. Multiple inflammatory biomarkers have been detected in depression:

- increased plasma levels or production of pro-inflammatory cytokines, e.g. “monocytic” cytokines, such as interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF α), and Th-1-like cytokines, such as interferon- γ (IFN γ); and
- signs of an acute phase (AP) response, such as increased levels of AP proteins and lower serum zinc [3].
- indicators that lowered plasma tryptophan, an established inflammatory marker, bears a strong relationship with the inflammatory biomarkers of depression [3].

Therefore, we concluded that the lowered tryptophan in depression results from an induction of indoleamine-2,3 dioxygenase (IDO), the first and rate-limiting enzyme that induces the degradation of tryptophan into TRYCATs (tryptophan catabolites along the IDO pathway).³IDO is induced during inflammation mainly by IFN γ , but also by IL-1 β and TNF α , [3,4] cytokines that are increased in depression. This novel putative pathway related to depression is further underscored by recent findings that IDO activation may occur in postmortem anterior cingulate cortex [5] and in the plasma from

individuals with bipolar depression [6]. Based on the above findings we hypothesized that inflammation may underpin the development of depression not only by decreasing the availability of tryptophan, which may jeopardize 5-HT metabolism in the brain, but also because some TRYCATs have neurotoxic and behavioral effects [3,4,7]. For example: kynurenine, has anxiogenic effects while quinolinic acid is highly neurotoxic through different mechanisms including exacerbation of the neurotoxic effects of pro-inflammatory cytokines, oxidative effects resulting in lipid peroxidation, and agonistic activities at glutamate receptors, which induce neurotoxicity [4,7].

Further evidence that inflammation plays a role in depression comes from animal and human models,

- In animal models of depression, e.g. the chronic mild stress (CMS) model, multiple inflammatory markers are detected [3,8].
- Novel animal models of depression have been developed based on induced inflammation, e.g. administration of lipopolysaccharide (LPS) [9] and sustained administration of IL-6 [10].
- Systemic inflammation is known to cause a central neuroinflammation with activation of brain microglia and chronically elevated pro-inflammatory reactions [11].
- Peripheral and central administration of cytokines, such as IL-1 β and IL-6, to animals may induce sickness behavioral symptoms, such as anorexia, weight loss, soporific effects, disturbances of locomotor activity and exploration, or anhedonia [12]. Interestingly, the latter symptoms are similar to the vegetative symptoms of depression, while in depressed patients the occurrence of those symptoms is significantly related to inflammatory biomarkers [3,13]. This suggests that the vegetative symptoms in depression are induced by inflammation [3,13].
- In humans, cytokine-based immunotherapy for hepatitis-C was reported to be accompanied by depressive symptoms and full blown depression in a considerable number of patients [7].

For example, the severity of IFN α -induced depression is strongly related to the magnitude of the inflammatory response, e.g. increases in IL-6 [7,14]. Moreover, in IFN α -treated individuals, cytokine-induced depression is strongly related to the induction of the IDO pathway, rather than to decreases in tryptophan [7,15]. Therefore, we have proposed a shift in the serotonin hypothesis of depression from tryptophan and serotonin depletion [1,2] to inflammation-induced tryptophan degradation with consequent formation of neurotoxic TRYCATs. [3,7,14,15].

The knowledge that depression may occur following external stressors (psychological stressors) and internal stressors (during medical illness or conditions, such as the puerperium) has gained the status of a text-

book truism. Early life experiences increase the vulnerability to develop depression, while negative life events often precede depression. In experimental animals, it has been shown that early life stress, e.g. social isolation, and late-life stress models, e.g. CMS, induce inflammation with increased IL-1 β and IL-6 in the peripheral blood and in the brain as well [3,16]. Also, in humans it has been shown that external stressors induce the production of pro-inflammatory cytokines, such as IFN γ and TNF α , and that stress-induced depression/anxiety is related to an increased IFN γ response [3,16].

The cytokine hypothesis is also fueled by the increased incidence of depression in the postpartum period and by the high comorbidity of depression with inflammatory disorders, such as multiple sclerosis (MS), coronary-heart disorder, dementia Alzheimer's type, HIV-infection, inflammatory bowel disease and rheumatoid arthritis [3]. Significant inflammatory responses, characterized by increases in IL-6 and the IL-1-receptor antagonist (IL-1RA), both reflecting "monocytic" cytokine activation, occur in the post-partum period [17]. In the early puerperium, there are significant correlations between the magnitude of inflammation, on the one hand, and depressive and anxiety symptoms, lower plasma tryptophan and IDO activation, on the other [17].

In medical inflammatory disorders there is a correlation between inflammation and the incidence of depression. For example, in MS increases in IFN γ production precede the development of depressive episodes [18].

The cytokine hypothesis is further corroborated by the findings that antidepressants have anti-inflammatory effects. Thus, most if not all antidepressants have anti-inflammatory effects since they decrease the production of IFN γ and / or increase that of IL-10, a major negative immunoregulatory cytokine [19]. There are published data on selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine; tricyclic antidepressants, such as imipramine; reversible inhibitors of monoamine-oxidase, such as moclobemide; "noradrenergic" antidepressants, such as reboxetine; and lithium [19]. The clinical efficacy of antidepressant treatments may be enhanced by concurrent administration of agents with anti-inflammatory effects, such as celecoxib, a cyclooxygenase-2 inhibitor [20]. Also, omega-3 poly-unsaturated fatty acids, which have strong anti-inflammatory effects [3] may be useful in the treatment of depression, either as monotherapy or as adjunctive therapy [21]. In depression and MS, successful treatment of depression with SSRIs is accompanied by decreases in the production of IFN γ and other inflammatory biomarkers [3,18]. In animal models, antidepressants attenuate inflammation-induced depressive-like conditions and ameliorate depressive behavior through their anti-inflammatory effects, either by decreasing proinflammatory cytokines or increasing the production of IL-10 [3,8].

Inflammation is also accompanied by increased oxidative and nitrosative stress (O&NS). Likewise, depres-

sion is accompanied by increased levels of malondialdehyde (MDA), a byproduct of polyunsaturated fatty acid peroxidation and arachidonic acid, as well as 8-hydroxy-2-deoxyguanosine, indicating damage to DNA by oxygen radicals [22,23]. Moreover, we found that the prevalences and mean values for the serum IgM levels directed against phosphatidyl-inositol (Pi), oleic, palmitic and myristic acid, azelaic acid, and the N-oxide derivatives, nitro-arginine, nitro-tryptophan, nitro-cysteinyl and bovine serum albumine were significantly greater in depressed patients than in normal controls [24-26]. These results show that depression is characterized by an IgM-related immune response directed against disrupted lipid membrane components, by-products of lipid peroxidation, and NO-modified amino-acids, which are normally not detected by the immune system but due to damage caused by O&NS have become immunogenic. This type of damage caused by O&NS is also observed in severe autoimmune disorders, such as acute multiple sclerosis, and in cancerous conditions [27]. Some of the damages caused by inflammation and O&NS (IO&NS) may have functional consequences and may interfere with intracellular signalling processes. For example, anti-Pi antibodies may change inositol 1,4,5-triphosphate (IP3), phosphatidylinositol-4,5-bisphosphate (PIP2), diacylglycerol and phosphatidylinositol-3,4,5-triphosphate (PIP3) production.

Recently, we found an increased translocation of LPS from gram negative bacteria in depression: the serum IgM and IgA levels directed against LPS of gram-negative enterobacteria were significantly higher in depressed patients than in controls [28]. Various trigger factors for depression may compromise the intestinal barrier and, thus, induce LPS translocation, e.g. external stressors and internal stressors, characterized by increased IFN γ and IL-6 production [29,30]. Increased blood LPS not only causes a systemic inflammation but also a central neuroinflammation and a long-standing activation of brain cytokines and microglia [29]. Thus, the LPS translocation may induce the sickness behavior complex or the vegetative or somatic symptoms of depression [12,31,32] since LPS may induce peripheral and central activation of the cytokine network. These findings show that increased LPS translocation is another pathway involved in the pathophysiology of depression.

Thus, the cytokine theory of depression hypothesizes that

- a) depression results from an increased production of pro-inflammatory cytokines, which may be triggered by external or internal stressors;
- b) inflammation may induce depressive symptoms through different pathways, such as central neuroinflammation, tryptophan degradation and an increased synthesis of neurotoxic TRYCATs;

- c) increased IO&NS may disrupt lipid membrane components and may modify protein structures thereby mounting an autoimmune response and interfere with functional proteins;
- d) the clinical efficacy of antidepressants is at least in part related to their anti-inflammatory activity, for example, through their interactions with the inflammatory - serotonin pathway; and
- d) antiinflammatory compounds including natural anti-IO&NS substances (NAIOSs) may augment the efficacy of antidepressants or may have antidepressive efficacy.

Future research to further examine the cytokine hypothesis calls for a powerful paradigm shift. Clearly, the testing of this complex hypothesis cannot be performed by one principal investigator which directs relatively small pharmacological or animal studies focusing on selected inflammatory biomarkers. Future research should make use of a high throughput screening according to the translational medicine methodology. Firstly, functional genomics should be used to examine inflammatory gene expression profiling; and genotyping microarrays to examine the genetic inflammatory predisposition towards depression. Secondly, external (early life stress models, e.g. social isolation, prenatal stress, and maternal deprivation; and late-life stress models, e.g. CMS) and internal (e.g. IL-6 and IFN γ administration) stress models in animals should focus on brain inflammatory pathways, such as the IDO pathway, cytokine signaling, and intracellular inflammatory mediators. Thirdly, new animal models should be generated to define the specific inflammatory pathways that determine depressive behavior, e.g. transgenic (TG) mouse models over-expressing inflammatory biomarkers, e.g. IDO and TNF α , or with conditional knock-out of anti-inflammatory markers, eg. IL-10. Fourthly, the same pathways should be examined in new *ex vivo* / *in vitro* models, such as organotypic brain slice culture models; knock-down functional screens on neural stem cells; and brain-specific promoter-induction based indicator cell lines with promoter sequences of various inflammatory substances. The above animal and *ex vivo* models should be examined to identify new IO&NS targets for antidepressive drug development and existing anti-inflammatory drugs and NAIOSs that may be used as adjunctive therapy to antidepressants. Candidates are: the IL-1RA, tocilizumab (a monoclonal antibody against IL-6), fontolizumab (a humanized anti-IFN γ antibody), IDO inhibitors, and curcumin. Only a large-scaled study which integrates clinical research and the application of translational medicine in human, animal, and *ex vivo* models of depression will be able to define the IO&NS pathways underpinning depression and to identify new drug targets in the IO&NS pathways and new anti-IO&NS treatments for depression.

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