

# Depression has a Strong Relationship to Alterations in the Immune, Endocrine and Neural System

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**Abstract:** Epidemiological findings indicate a connection between depressive symptoms and changes in status of the immune system in depressed patients. This raises the possibility of causative connections. Theories on mechanisms for interactions between immune and affective systems – directly and via endocrine system – are evolving. Such hypothesized causative connections are supported by several findings. First, in depressed patients changes in the status of the immune system *in vivo* and *ex vivo* are seen. Also, depressive symptoms are seen in patients with altered immune status (physiologically, pathologically or chemically induced). Knowledge in this field may have implications regarding psychiatric follow up of physically ill people suffering from diseases caused by an altered immune system (long lasting infections, autoimmune diseases, hypersensitivity disorders) as well as disorders for which treatment and prognoses depends on the immune system (infections, cancer). Similarly, medical treatment of depressed patients may be adjusted by more specific knowledge about the interaction between neuroimmunology and depression. Important findings and the present knowledge and theories are reviewed.

**Keywords:** Depression, immunology, endocrinology, neurology, inflammation, brain, psychiatry.

## INTRODUCTION

Depression is a potentially devastating disorder that can have profound influences on both patient and surroundings. While Freud attributed depression to losses in ones life, modern biology introduced pharmacological treatment affecting the monoamine system (TCA, SSRI / SNRI, MAO-I), indicating that depression could be a disorder with major disturbances in the neurotransmitter system. It has also been suggested that endocrine disturbances, such as hypercortisolemia, may be linked to depression [1] as an increase in level of cortisol is found in 30 – 50% of depressed patients [2]. As cortisol affects inflammation, there may be an important link between inflammation and depression. However, as we will show in this review, recent research indicates that connections between the immune system and psychiatric symptoms may be more specific.

In depression, there is a changed emotional state, loss of interest and joy and loss of energy which results in fatigue and reduced activity. The patient is usually exhausted even after small efforts. These symptoms may also be seen in patients with persistent inflammation as well as in patients receiving treatment with cytokines or other immune modulators. In addition to these shared symptoms, epidemiological findings indicate connections between depression and immunological alterations. Several prominent somatic disorders have been connected to depression. Depression is shown to

be of importance in coronary artery disease (CAD) [3], and is a risk factor for both development and progression of such disease [4], and inflammation may be a common link. There has also been shown a high mortality rate in demented patients who have a co-morbid depression [5]. Similarly, several diseases characterized by a change in immune status (e.g. rheumatoid arthritis and inflammatory bowel disease) are found to be worsened by psychological stress. Another condition with changed status of the immune system and depression is the puerperal phase (post-partum depression). These phenomena all raise the question whether – and how – depression is connected to these major somatic diseases.

In this review we shall first briefly address depressive symptoms in patients with somatic disorders that may involve immunological and inflammatory mechanisms. We then turn to immune system alterations in depressed patients. Potential biological mechanisms will be addressed by discussing human and animal studies revealing potential basic mechanisms. At the end we summarize and discuss further questions.

## INCREASED DEPRESSION IN SOMATIC DISORDERS WITH INFLAMMATION? CARDIOVASCULAR DISORDER AND THE POST-PARTUM PERIOD

It is well known that severe illnesses like chronic infections [6, 7], autoimmune disorder, cancer, Alzheimer's disease, and multiple sclerosis (MS) [8, 9] are often associated with depression.

Depressed older patients have a high mortality [10-12] and cause of death usually is heart-, vascular – or lung re-

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lated diseases. Indeed, coronary artery disorder (CAD) is epidemiologically related to depression, and is a risk factor for both development and progression of such disease [4]. The incidence of depression is three times higher in CAD patients than in the general population [13], and 20 - 50% of patients who die from myocardial infarction (MI) are thought to be significantly depressed prior to MI [14-16]. Macrophages, lymphocytes, cytokines, acute phase proteins and adhesion molecules all are of importance in the immune response to MI. A main focus of investigation in these patients has been on C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) [3, 17]. These inflammatory mediators are - as we will show in this review - also increased in depression. Moreover, endothelial dysfunction has been reported in both depressed patients [18] and patients who have been treated successfully for their depression [19, 20], potentially further contributing to the link between depression and CAD. Finally, there are many hematological abnormalities in depression such as signs of platelet activation that may be of concern for patients with CAD [21]. In addition to posing a potential bidirectional causative link between inflammation and depression, this potential interaction should be taken into account when it comes to choosing medications for one or the other of these prominent disorders.

During pregnancy and post partum, there are changes both in immune status and occurrence of depressive symptoms. To protect the fetus against spontaneous abortion (miscarriage), the immune system of the mother has an immune tolerance for the "non-self" tissues of the developing baby [22, 23]. After labor, an increase in the pro-inflammatory immune response is noted [24, 25], involving activation of a T cell type 1 (Th1) response which include increased production of interferon (INF)  $\gamma$  and TNF $\alpha$  [24, 25]. This Th1-mediated "maternal immune rebalancing" is potentially associated with "post partum blues" [24], a condition that is found, to varying degrees, in 20-75% of the mothers post partum [25-27]. Post partum depression, a more severe form of mood change, is found in 10-15% of the mothers [28].

These two definitively somatic physiological conditions (i.e., CAD and post partum period) exemplify that there may be an increased occurrence of depression in somatic disorders and that there may be a link between immunity and depression. We will now turn to immunological findings in depressed individuals.

#### **DO DEPRESSED PATIENTS HAVE MORE INFLAMMATION THAN OTHERS?**

The earliest studies on connections between the immune system and depression focused on immune suppression rather than inflammation, with an impaired lymphocyte function *ex vivo* as a major finding [29]. Similarly, a reduced number of Natural killer cells (NK-cells) have been reported in many depressed patients [30]. However, methods for measuring immune activity have improved greatly the last 15 - 20 years. Over the last 10 years, focus has changed towards immune activation *in vivo* measured as levels of inflammatory cytokines and other inflammatory mediators. There are several reports of increased levels of inflammatory cytokines in depressed individuals [30-32]. These apparently

contradictory findings (suppression *vs* stimulation) probably are not mutually exclusive, as these *ex vivo* and *in vivo* findings may represent different aspects or phases of the same phenomena. Hence, sustained immune activation *in vivo* may result in an attenuated stimulation induced response when immune cells from these individuals are stimulated *ex vivo*, the distinct functions of different cytokines also must be kept in mind.

In summary, there seem to be strong indications that depression is linked to increased inflammatory activity. We will now discuss these findings in more detail and briefly discuss potential mechanisms for depressive effects of inflammation. We will look at findings in serum and then in cerebrospinal fluid (CSF) and CNS of depressed patients.

#### **SYSTEMIC TH1-DOMINATED CYTOKINE RESPONSE IN DEPRESSED INDIVIDUALS**

Several studies on depressed patients have shown increased serum- or plasma levels of inflammatory markers such as neopterin, a general marker of monocyte/macrophage activation, primarily reflecting Th1 activation and soluble IL-2 receptors (sIL-2R). There are also several reports of increased levels of acute phase proteins (APP) such as CRP and its "upstream" inducer IL-6. Activated monocytes or macrophages from these patients *ex vivo* produce increased levels of IL-1, IL-6, TNF $\alpha$  and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Activated T cells from depressed individuals *ex vivo* have been shown to produce increased levels of IFN $\gamma$  [33-40]. Increased serum levels of IFN $\gamma$  as well in increased INF- $\gamma$ /IL-4 and INF- $\gamma$ /transforming growth factor (TGF)- $\beta$  ratio are found. Taken together, these findings indicate a Th1 activation and an imbalance between Th1 and Th2. This imbalance may cause a net inflammatory effect in depressed individuals [41]. There are several reports that the severity of anxiety, depression and cognitive failure seems to be related to level of circulating inflammatory cytokines [42, 43].

In depressed patients, PGE<sub>2</sub>, a potent inflammatory mediator, is increased in plasma [44], saliva, serum and CSF [45, 46]. *Ex vivo* studies report increased PGE<sub>2</sub> secretion from lymphocytes of depressed patients compared to lymphocytes from healthy individuals. Also, both clinical [45, 47] and experimental (animal) studies of depression have shown an increase in tissue concentration of PGE<sub>2</sub> [44]. IL-6, which is also associated with depression, seems to play a crucial role in synthesizing this prostaglandin [48, 49], and PGE<sub>2</sub> is itself a potent stimulant for IL-6 production, potentially representing an inflammatory pathogenic loop that may be operating in depressed individuals. It has been shown that tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) attenuate the PGE<sub>2</sub>-synthesis, probably via inhibition of pro-inflammatory cytokines. Finally, Müller et al. (2006) [50], reported that treatment with a PGE<sub>2</sub> synthesis inhibitor (i.e., cyclooxygenase 2 inhibitor / COX2 inhibitor) showed beneficial effects on depression. All these findings indicate a potential causative link between PGE<sub>2</sub> and depression.

Another interesting finding in depressed patients are the increased serum titers of antibodies against serotonin [51] and gangliosides (a part of the serotonin receptor) [51]. The presence of such antibodies is associated with increased immune activation with increased levels of IL-6 and positive

acute phase protein (pAPP) [51]. Such reactions may indicate an autoimmune reaction towards certain components in the serotonin system in depressed patients [32], potentially, at least in part, driven by Th1 related cytokines such as IL-6.

### ENHANCED ENDOTHELIAL CELL ACTIVATION IN DEPRESSION

Enhanced endothelial activation is essential in immune responses, to direct immune cells to relevant tissue / body areas. Several findings indicate an inappropriate and enhanced activation of the endothelium in depression. Intercellular adhesion molecule-1 (ICAM-1), at least partly derived from endothelial cells, has been shown to be increased in prefrontal cortex in older depressed patients [52]. Raised systemic levels of the endothelial-derived E-selectin and vascular cell adhesion molecule-1 (VCAM-1) also have been reported in depression. Increased levels of nitric oxid (NO) may further suggest endothelial activation in these individuals. Endothelial activation is accompanied by increased levels of chemokines such as monocyte chemo attractant protein-1 (MCP-1) that attracts leukocytes into areas of inflammation. It is tempting to hypothesize that this enhanced activation of endothelial cells and chemokines could contribute to a disturbed blood-brain-barrier (BBB) during depression, potentially promoting some degree of invasion of immune cells into the CNS, and eventually leading to an inflammatory intra-CNS response [53].

To summarize, in serum from depressed patients increased levels of pro-inflammatory activity is suggested from the finding of increased levels of pro-inflammatory cytokines IL1, IL-6, TNF $\alpha$ , IFN $\gamma$  and PGE $_2$  in different *in vivo* studies measuring levels of serum cytokines as well as *ex vivo* studies on leucocytes from blood & serum of depressed individuals. The activity seems mainly to be Th $_1$  dominated. In addition, antibodies against central components traditionally thought to be important in depression (serotonin) may be found, further indicating inflammatory processes in depression. Finally, molecules indicating endothelial activation, indirectly suggesting inflammatory activation, are also increased in depressed individuals.

### INFLAMMATION IN CSF AND CNS IN DEPRESSED INDIVIDUALS

Published studies on levels of cytokines in CSF are sparse and to some degree contradictory. One study found that depressed patients had higher CSF concentrations of IL-1 $\beta$ , lower IL-6 and no change in TNF $\alpha$  compared to normal controls [54]. Stübner *et al.*, [55] confirmed the decreased level of IL-6 and also of soluble IL-6 receptor, this time in geriatric patients with major depression. There are also some reports of increased PGE $_2$  in CSF during depression [45]. In contrast to these significant findings, Carpenter *et al.* [56] found no difference in levels of IL-6 in CSF in patients with unipolar depression compared to healthy controls, and Blasko *et al.*, (2005) [57] found no elevation of TNF $\alpha$ , TGF- $\beta$ 1, or MCP-1 in CSF.

Interpretation of these findings is difficult, and because of limited data, no definitive conclusions can be drawn. One might possibly expect levels of IL-6 to be increased in CSF, as they are in serum of depressed patients, especially as the

increased levels of IL-6 seem to be associated with depressive symptoms; symptoms expected to be produced in CNS. Several non-mutually exclusive factors may explain these apparently discrepant results, such as unreliable methods of measuring IL-6 in CSF, compartmentalization or binding of IL-6 in CNS or increased metabolism and removal of IL-6 from CSF/CNS. Alternatively, depressive symptoms in response to – or associated with – IL-6 may reflect IL-6-inducing effects outside CNS, affecting production or release of other cytokines and neurotransmitters which are consequently transported into CSF/CNS, inducing depressive symptoms. It is tempting to hypothesize that the association between serum levels of IL-6 and depressive symptoms reflect an association between systemic inflammation and these symptoms, and not a direct pathogenic effect of IL-6 in the development of depression.

Glial abnormalities (in the frontal cortex) are apparent and consistent characteristics of major depressive disorders [58-61]. Miller and O'Callaghan (2005) [62] suggest that oligodendroglia in particular may play a part in the etiology of depression. They also point out that cytokines like TNF $\alpha$  and IL-2 have a suppressive or cytotoxic effect on oligodendroglia [62], again indicating an inflammatory effect on depression.

To summarize, in serum from depressed patients increased IL-6, IL-1 $\beta$  and TNF $\alpha$  cytokine levels are found, corresponding with a Th1-dominated pro-inflammatory response in serum. Increased levels of PGE $_2$  are also found. Antibodies against proteins related to depression have been shown, as well as signs of endothelial activation. Findings in CSF so far are less convincing, though not totally negative. A possibility of compartmentalization and degradation in CSF also has to be taken into account. Inflammation outside CNS modulating affective symptoms also must be explored. Known changes in glial cells may potentially be linked to inflammation.

### DOES INFLAMMATION LEAD TO DEPRESSIVE SYMPTOMS? FINDINGS IN HUMANS INDICATING A CAUSATIVE CONNECTION

We above have discussed evidence that depressed patients have alterations in their immune system. Whether depression causes these immune changes or *vice versa* is not obvious. It is possible that inflammation may actually cause the depressive symptoms [63]. There are studies showing that changes in immune regulation often can be detected before the clinical symptoms of depression [8, 9, 64, 65]. Also, several studies have shown that administration of certain cytokines may elicit depressive symptoms in people. Cytokines are used in the treatment of several infectious and malignant disorders; for example, IFN $\alpha$  in hepatitis C (HCV) and cancer, IFN $\beta$  in multiple sclerosis (MS), IFN $\gamma$  in Kaposi sarcoma, and IL-2 in certain forms of cancer. Therapy with these inflammatory cytokines has been shown to be followed by development of depressions, manias and bipolar syndromes [66-68]. Importantly, patients with no prior history of mental illness have - after treatment with cytokines - developed depressive symptoms such as sadness, increased worrying, cognitive impairment, lack of motivation and difficulties with flexible thinking [32]. In patients treated with IFN $\alpha$ , an increased level of soluble ICAM-1 - indicating

endothelial activation - has been observed to be associated with increased depressive symptoms [71]. Vaccination is known to enhance immune responses, and interestingly, vaccination against influenza virus in older adults has been shown to be associated with depressive symptoms in some sub-groups, and is accompanied by a rise in serum levels of IL-6 [77].

IL-1 mediates fever in inflammation, but at the same time it may lead to depressive symptoms like fatigue, sadness, pain, emotional changes, suicidal thoughts and anorexia [69]. IFN and IL-2 are other cytokines mediating both inflammation and depressive symptoms of sickness behavior. Antidepressant medications can prevent several of the depressive symptoms (e.g., sadness) induced by these cytokines, but not the fever, anorexia and fatigue [70].

Another interesting approach to the question of whether inflammation has a causative effect, or at least a contributing role, in the development of depression is studying the effect of anti depressive medications on inflammatory markers.

*In vitro*-studies have shown that anti depressive drugs such as clomipramine, imipramine and citalopram attenuate the production of IL-1 $\beta$ , TNF $\alpha$  and IL-6 [32, 72]. Drugs like clomipramine and sertraline may therefore have an anti-inflammatory effect [72]. A down regulation of IL-6 production was observed after amitriptyline treatment in depressive patients, and in medication responders, levels of TNF $\alpha$  were normalized [73]. In one *in vitro* study both tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI) impaired cytokine-induced production of PGE<sub>2</sub> and NO [74]. Hestad *et al.* (2003) [75] compared patients with severe depression who were given electroconvulsive therapy (ECT) with other severely depressed patients treated with other standard approaches. Compared to healthy blood donors, depressed patients had significantly elevated levels of TNF $\alpha$ . After ECT, as depressive symptoms improved, TNF $\alpha$  levels were normalized, suggesting an attenuation of TNF $\alpha$  production or release after ECT.

Based on the discussed findings regarding immune responses and depression, it may be that the immune system changes induced by both anti-depressant medications [76] and by ECT [75], represent a common, important aspect of their antidepressive effect. This again would indicate inflammation as a mediator or cause of depression.

## EXPERIMENTS IN HUMANS

### Microbial Stimulation of the Immune System and Depressive Symptoms

In line with the findings indicating a potential causative effect of inflammation on depression, experimental induction of inflammation in healthy humans has been performed. Injection of a vaccine containing *Salmonella (typhi or abortus)* into human healthy volunteers leads to activation of the immune system. Randomised groups injected with either *Salmonella* or placebos were monitored several times during the hours following injection. Monitoring consisted of psychological questionnaires, neuropsychological tests, measurement of rectal temperature and heart rate; blood samples were taken and analyzed for cortisol and several cytokines, such as IL-1, IL-6 and TNF $\alpha$ . The conclusion from several such experiments seems to be that, although there was a

slight increase in rectal temperature, there was no general feeling of physical illness related to the injection. However, in some of the studies depressive effects were seen in individuals already under long standing stress. Moreover, in those who developed depressive symptoms, anxiety or decreased memory, these symptoms corresponded to increased levels of cortisol and inflammatory cytokines TNF $\alpha$ , IL-1 and IL-6 [78-80].

### Animal Models

Though animals do not report feelings of depression or existential problems typical of depression, they can inhibit several signs typical of depression. This includes psychomotor retardation and anorexia. In addition, levels of cytokines can be measured, and levels and localization of neurotransmitters can be monitored more systematically. In an animal model such depression-like symptoms following an immune response have been shown to be reduced by pretreatment with cytokine synthesis inhibitors and cytokine antagonists, or with cytokine gene manipulation (e.g. gene knockout) [8, 81, 82]. In animal studies using antidepressive medications affecting the monoamine system there also are interesting findings. Proinflammatory cytokines are seen to be reduced upon administration of SSRI medications [83-85]. In animal experiments many antidepressants seem to contribute to the transition from a Th1 to a Th2 cytokine profile, that is, from a pro-inflammatory to an anti-inflammatory immune response. In line with this, sertraline, clomipramine and trazodone are *in vitro* observed to reduce INF- $\gamma$ /IL-10 ratio. The drugs induced both a decline in production of INF- $\gamma$  and a significantly increase in production of IL-10 [86]. These *in vitro* experiments on antidepressants are consistent with the hypothesis that depression is associated with, and potentially caused by, inflammatory activity.

### Conflicting Findings? Pro-Inflammatory Activity and Reduced Depressive Symptoms?

We have reviewed research indications that depressive symptoms are associated with – and potentially caused by – pro-inflammatory cytokines. Before we discuss potential mechanisms we must mention potentially conflicting findings. Depression is associated with change in dopaminergic (DA), noradrenergic (NA) and serotonergic (5-HT) activity in the brain. In an animal experimental system, intra-cerebroventricular (i.c.v.) administration of IL-1 $\beta$  was followed by increased hippocampal extracellular 5-HT concentrations [87]. In this experiment, systemic administration of cytokines (IL-1) or agents inducing production of cytokines (lipopolysaccharides [LPS]) showed similar effects. In rodents, IL-1 has been shown to induce increased DA, NA and 5-HT activity in hypothalamus, nucleus accumbens and limbic regions, including hippocampus [86;88-90]. Administration of LPS intraperitoneally (i.p.) has been shown to increase hippocampal NA and 5-HT concentrations [87, 91]. The LPS-induced increase in neurotransmitters was significantly reduced if IL-1 was blocked by i.c.v. pre-treatment with IL-1 receptor antagonist (IL-1Ra), supporting the indications that the effect is mediated by IL-1. These findings strongly support theories regarding connections between the immune system and affective symptoms generated in the limbic system, potentially mediated by inflammatory cytokines.

These findings may, however, be confusing as they indicate that proinflammatory cytokines (directly administered or induced by for example administered LPS) cause *increase* in intracerebral neurotransmitters NA, 5-HT and DA. This is not in line with other theories regarding depression, as pharmacological treatment of depression is mainly based on increasing the presence of 5-HT and NA and even dopamine (bupropionhydrochloride) in synapses, indicating that depressed patients have *too low levels* of these. One explanation of this contradiction may be that the measured levels of neurotransmitters reflect levels outside and not within synapses. Another explanation could be that there is an increased turnover of these neurotransmitters, which in the long term will result in a deficiency.

Inefficient re-uptake of neurotransmitters may result in increased secretion due to reduced effectiveness or reduced number of post-synaptic receptors.

Another apparently conflicting finding in humans is the suggestion that physical activity may have a positive effect on depressive symptoms, but at the same time enhance the production of the pro-inflammatory cytokine IL-6. For example IL-6 induce CRP and subsequent activation of the complement system with further inflammatory activity [92-94]. However, the increase of IL-6 may be very temporary and it is actually seen that it is followed by a raise in anti-inflammatory cytokine IL-1Ra, IL-10 and sTNFR [95, 96], and after repeated physical activity (for weeks or months) there is a decrease in levels of inflammatory cytokines.

## WHAT ARE THE POTENTIAL MECHANISMS MEDIATING THE CONNECTION BETWEEN DEPRESSION AND INFLAMMATION?

### How do Cytokines Communicate with the Brain?

Animal model studies have helped us to understand the communication between signals of systemic inflammation and the responses within CNS, as well as how the brain internally responds to cytokine activation. These interactions seem to be bidirectional, with redundant possible pathways, both neuronal and humoral [69].

Peripherally circulating cytokines may enter the brain and affect it by different routes. As part of an inflammatory process with potential upregulation of transporter molecules, cytokines can be transported actively across the BBB [97, 98]. Cytokines might also be passively transported via the circumventral organs, especially organum vasculosum, where the BBB is absent [99]. Additionally, cytokines in circulation may adhere outside the BBB to the cerebral vascular endothelium, that is activated due to inflammation, and induce second messenger systems such as prostaglandins and NO [30] inside the CNS.

Another route for the effect of peripheral cytokines on CNS is via afferent peripheral nerves, stimulating them peripherally with subsequent responses in the brain. The cytokine effect on the vagus nerve system is an example of this mechanisms, as well as an example of the reciprocal interaction between cytokines and the nervous system. Cortex, hypothalamus and peripheral sites all project fibers to vagal nuclei. The vagus nerve will respond to either mechanical or chemical stimuli in these areas. Emotional and cognitive processes in cortex and subcortical structures may activate

the vagus and those cortical and subcortical areas themselves receive afferent nerve-fibers from vagal nuclei. ACTH affects vagal activity, and either directly or indirectly, factors like physical activity and fatty acids in diet may also affect vagal activity. In addition to fibers projecting into the CNS, a main effect of the vagus nerve is via neurons using acetylcholine (ACh) as transmitter, binding to postsynaptic nicotinic/muscarinic receptors. Medications or drugs stimulating or antagonizing ACh, as well as nicotine from tobacco, may mediate similar effects. Thus, stimulation of the vagus nerve by cytokines that bind to peripheral afferent fibers, may activate projections to hypothalamus and cortex, and thereby influence emotions and affect. On the other hand, the described ACh-receptors are present on macrophages and lymphocytes, so vagus activation may more directly modulate inflammation. Especially macrophages and lymphocytes in the spleen are reached by efferent vagal fibers. An  $\alpha 7$ -subunit of the AChR seems to be specially important in mediating suppression of cytokine synthesis. This suppression involves JAK2 and STAT3 resulting in suppression of NF- $\kappa$ B. In particular, the pro-inflammatory cytokines TNF $\alpha$ , IL-1, IL-6 and IL-8 are all suppressed by ACh stimulation. Thus, affective processes in cortex and subcortical areas can stimulate the vagus nerve and modulate inflammatory activity [100-113]. Interestingly, actual stimulation of the vagus nerve, mechanically or electrically, has shown some positive effect in the treatment of depression [114, 115] and it is conceivable that this could involve anti-inflammatory effects.

The vagus nerve also interacts with the HPA-axes, at least in part by influencing the corticotrophic release factor (CRF) and ACTH, both coordinating the production of cortisol. Activity in the vagus nerve may lead to increased release of CRF. The close relationship between vagal nuclei, central areas in HPA-axes and subcortical areas involved in depression and other emotional phenomena allows for extensive bidirectional communication among these structures. Moreover, the vagus nerve; potentially via HPA-axes, is affected by dietary fatty acids. This could also be a link partly explaining epidemiological connections between dietary fatty acids and depression.

### HPA-Axes

The HPA axes represent a system important in both depression and inflammation. Normally, inflammation, physical stress, and psychological stress all lead to increased production of CRH from hypothalamus. This again induces release of ACTH and Arginine vasopressin from the pituitary gland, stimulating the release of corticosteroids from the adrenal cortex. Normally, circulating corticosteroids will down-regulate production of CRH. In addition, there is a background diurnal pattern of secretion in this system, with lowest levels late at night. The system has well known effects on cell metabolism, anti-inflammatory effects, and also regulates sleep / awake cycles, food intake, and has effects on cognitive processes including attention and learning.

In depressed individuals, the background production of corticosteroids is increased, and diurnal variations are attenuated, resulting in a more constantly increased level. In addition, reflexive regulation of the HPA-axes, as measured by the Dexamethasone Suppression Test (DMT), is reduced

in depressed patients. It is well recognised that administration of steroids like prednisolone (particularly in high doses), can cause affective symptoms. These findings are not surprising as the brain areas involved in the HPA-axes project neurons to amygdala, raphe nucleus, nucleus ceruleus [116]-brain areas involved in affect and emotions, and where receptors for CRH and corticosteroids are found. Also, CRF acts on locus ceruleus and raphe nuclei and regulates production of NA, a transmitter thought to be of importance in depression [113]. Further supporting a link between depression and HPA-axes dysfunction are the findings that high circulating levels of cortisol reduce the number of post-synaptic 5-HT<sub>1A</sub>-receptors, consistent with increased depressive symptoms [117]. On the other hand, short pulses of increased corticosteroids may up-regulate somatodendritic levels of 5-HT<sub>1A</sub>-receptors in a way potentially protecting against depression [118-120], and short term infusion of high doses of corticosteroids may result in hypomania, not depression. Animal models have also supported theories of the involvement of the HPA-axes in depression. In rodents administration of pro-inflammatory cytokines (IL-1, IL-6 and TNF $\alpha$ ) causes activation of the HPA-axis [90, 121-123], and this communication between the immune system and HPA axis may indeed be an important pathway in the interaction between depression and the immune system.

It is well recognised, and widely used therapeutically, that the immune system is regulated by the HPA-system, with potent anti-inflammatory effects of corticosteroids involving down-regulation of neutrophil, macrophage and Th1 activity. Consistent with this the HPA-axes is a regulator of the immune system, the immune system itself may enhance HPA activity when appropriate. Potent inflammatory cytokines such as TNF $\alpha$ , IL-1 and IL-6 all bind to receptors in the hypothalamus, pituitary gland and adrenal glands, and up-regulate activity in the HPA-axes. In longstanding, ongoing inflammations, chronic infections and autoimmune reactions, the immune activity may finally result in a dysregulated HPA-axes, as has been reported in inflammatory bowel disease (IBD) [124] and infection with human immunodeficiency virus (HIV) [125].

Thus, the HPA-axes regulate both the affective and the immune systems, and may be an important candidate in delineating the mechanism for interaction between immune system and depression. Its role is further emphasized by the close connections to the cholinergic vagus nerve system. This can explain how affective disorders affect the immune system, and it could explain how inflammation, via cytokines, can activate – and potentially dysregulate – the HPA-axes, which can again cause affective symptoms such as depression.

### **IDO and TDO**

Another potential mechanism mediating immune effects on depression is via Indoleamin-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). IDO and TDO are enzymes that are induced by several inflammatory cytokines, such as IL-1, IL-2, IL-6 and IFN $\gamma$ . The substrate for IDO and TDO is tryptophan (TRP) and the metabolic product is kynurenin [126]. Thus, as inflammation leads to increased levels of IDO and TDO, more TRP is used by IDO and TDO to produce higher levels of kynurenin. Consequently, less

TRP is available for the tryptophan hydroxylase using TRP as a substrate for production of serotonin. Thus, increased activity in IDO and TDO, result in less production of serotonin [127, 128, 130, 131]. As depression is linked to monoamines (medications for treatment of depression affect monoamine systems) like serotonin and noradrenalin, there seems to be a lack of regulation in NA and 5-HT neurotransmission in depression [50, 132-140].

In addition to reducing levels of serotonin, it is proposed that IDO and TDO can mediate depression via their metabolic products. IDO and TDO turn TRP into kynurenin. Kynurenin metabolites 3-hydroxy-kynurenine (3OH-KYN) and quinoline acid (QUIN) are produced in astrocytes and glial cells [141, 142]. 3OH-KYN and QUIN both are neurotoxic and have been proposed as possibly involved in a number of neurodegenerative conditions, such as Parkinson's disease and HIV-related dementia [129, 137, 143]. 3OH-KYN may cause high production of reactive oxygen species (ROS), as well as an increase of monoamine oxidase (MAO) activity [144]. Too much ROS may negatively influence function or density of both serotonin and catecholamine receptors by inducing changes in membrane viscosity, as well as apoptosis [144]. Increased MAO activity is associated with depression, as increased MAO activity results in decreased concentrations of 5-HT and catecholamine. Inhibition of MAO is the physiological therapeutic effect of a group of efficient antidepressants - the MAO-inhibitors.

The other main IDO- / TDO byproduct, QUIN, - a potent NMDA-receptor agonist that may impair the physiological negative feedback regulation on HPA-axes - normally mediated by circulating corticosteroids. QUIN neurotoxicity is hypothesized to cause hippocampal atrophy and loss of corticosteroid-receptors [4, 137].

To summarize, IDO and TDO, induced by inflammatory cytokines, may induce reduced monoamine neurotransmitters levels by reducing bioavailability of its precursor TRP, by increasing degradation by MAO in response to increased 3OH-KYN levels, and by altering the density of monoamine surface receptors. Products of IDO / TDO (i.e., 3OH-KYN and QUIN) may also have neurotoxic neurodegenerative effects. Activation of IDO may impair the physiological regulation of HPA-axes, as seen in depression. Other routes than IDO / TDO proinflammatory cytokines may also be involved in changes in NA and 5-HT. Inflammatory cytokines may directly affect 5-HT turnover (reuptake and degradation) as well as receptor distribution and sensitivity in brain regions presumed to be involved in depression such as hypothalamus, hippocampus, amygdala and prefrontal cortex [123, 145-149], reinforcing the IDO / TDO mediated effect on serotonin.

### **CONCLUDING REMARKS**

This paper summarises evidence supporting basic associations and potential causative mechanisms for inflammation to induce or modulate depressive symptoms. Future research should more precisely define the most important factors - as well as their mechanism of action - in this pathogenic loop between neurotransmitters, HPA axis and the immune system. Studies should also address how psychological stress affects inflammation and the potential role of this interaction in inflammatory disorders; and whether there

is a role for anti-inflammatory or immunomodulating drugs in the pharmacological management of depressed individuals.

Can depressive symptoms be treated by immune modulating medications? As reviewed by Watson and Young [116], at least inflammation suppression by ketoconazole or mifepristone, as well as CRH-antagonists, can treat depressive symptoms. As a basis for these additional studies, research must address the primary question: can inflammation – caused by infection, autoimmunity or other stimulus – cause depression? If so, it will have major influence on prophylaxis and treatment of these disorders.

The use of anti-inflammatory drugs in the treatment of depression is still only in the experimental stage [150-152]. Tying *et al.* [153] found that etanercept (inhibiting / blocking binding of TNF to its receptor) treatment might relieve fatigue and symptoms of depression associated with in psoriasis. Müller *et al.* [154] found that celecoxib (COX-2 inhibitor, inhibiting production of PGE<sub>2</sub>), as an add-on medication, had therapeutic effects on major depression. Infliximab (blocking TNF) in the treatment of Chrons disease, has been reported to increase quality of life, the patient's ability to work and involvement in leisure activities, and reduce feeling of fatigue, anger and depression [155]. However, animal research has shown that many types of anti-inflammatory drugs may have unfortunate side effects [152]. Side effects, unfortunately, remain a big issue in most medications for treatment of depression. Through this review we have shown that depression is related to inflammation, but there is still a lot to learn before the relationship is totally understood. The immune system has been conceptualized as a "sixth sense" [156] where it may internally sense and detect things the body cannot otherwise hear, see, smell, taste or touch. The body may react to both physical and psychological stress, but in which way the immune system is activated as a sense is poorly understood in other contexts than inflammation. New research may enlighten our understanding and way of thinking about psychological reactions, and how psychological reactions intervene with illnesses and diseases.

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#### ABBREVIATIONS

|      |   |                                |
|------|---|--------------------------------|
| Ach  | = | Acetylcholine                  |
| APP  | = | Acute phase proteins           |
| ACTH | = | Adrenocorticotrophic hormone   |
| ANS  | = | Autonomic nervous system       |
| BBB  | = | Blood brain barrier            |
| CNS  | = | Central nervous system         |
| CVO  | = | Circumventricular organs       |
| CAAs | = | Competing amino acids          |
| CAD  | = | Coronar artery disease         |
| CRF  | = | Corticotropin-releasing-faktor |

|          |   |   |
|----------|---|---|
| CS       | = | Cortisol  |
| CRP      | = | C-reactive protein  |
| DMT      | = | Dexametasone suppression test   |
| DA       | = | Dopamine  |
| ECT      | = | Electroconvulsive treatment   |
| GnRH     | = | Gonadotropin-releasing hormone  |
| HPA-axes | = | Hypothalamic, pituitary, adrenal axis   |
| IDO      | = | Indoleamin-2,3-dioxygenase  |
| ICAM     | = | Intercellular adhesion molecule   |
| IFN      | = | Interferon  |
| IL       | = | Interleukin   |
| LNAAs    | = | Large Neutral amino acids   |
| LPS      | = | Lipopolysaccharide  |
| MAO      | = | Monoamine oxidase   |
| MCP      | = | Monocyte chemo attractant protein   |
| MS       | = | Multiple sclerosis  |
| MI       | = | Myocardial infarction   |
| NK-cells | = | Natural killer cells  |
| NO       | = | Nitric oxide  |
| NMDA     | = | N-methyl-D-asparate   |
| NA       | = | Noradrenalin  |
| PAMP     | = | Pathogen associated molecules   |
| PGE      | = | Prostaglandin E   |
| ROS      | = | Reactive oxygen species   |
| RA       | = | Rheumatoid arthritis  |
| SSRI     | = | Selective serotonin reuptake inhibitor  |
| 5-HT     | = | Serotonin   |
| SNRI     | = | Serotonin noradrenaline reuptake inhibitor /- Selective serotonin and noradrenalin reuptake inhibitor |
| Th-cells | = | T-helper cells  |
| TLRs     | = | Toll-like receptors   |
| TGF      | = | Transforming growth factor  |
| TCA      | = | Tricyclic antidepressants   |
| TRP      | = | Tryptophan  |
| TDO      | = | Tryptophan-2,3-dioxygenase  |
| TNF      | = | Tumor necrosis factor   |
| VCAM-1   | = | Vascular cell adhesion molecule-1   |

#### REFERENCES

- [1] Hellhammer DH, Wade S. Endocrine correlates of stress vulnerability. *Psychother Psychosom* 1993; 60: 8-17.
- [2] de Beaupaire R. Questions raised by the cytokine hypothesis of depression. *Brain Behav Immun* 2002; 16: 610-7.
- [3] Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. *Psychosom Med* 2005; 67 Suppl 1:S37-S41.

- [4] Frasura-Smith N, Lesperance F. Reflections on depression as a cardiac risk factor. *Psychosom Med* 2005; 67 Suppl 1: 19-S25.
- [5] Forsell Y, Jorm AF, Winblad B. Association of age, sex, cognitive dysfunction, and disability with major depressive symptoms in an elderly sample. *Am J Psychiatry* 1994; 151: 1600-4.
- [6] Meijer A, Zakay-Rones Z, Morag A. Post-influenzal psychiatric disorder in adolescents. *Acta Psychiatr Scand* 1988; 78: 176-81.
- [7] Hall S, Smith A. Investigation of the effects and aftereffects of naturally occurring upper respiratory tract illnesses on mood and performance. *Physiol Behav* 1996; 59(3): 569-77.
- [8] Yirmiya R, Weidenfeld J, Pollak Y, *et al.* Cytokines, "depression due to a general medical condition," and antidepressant drugs. *Adv Exp Med Biol* 1999; 461: 283-316.
- [9] Pollak Y, Ovadia H, Goshen I, *et al.* Behavioral aspects of experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2000; 104(1): 31-6.
- [10] Burvill JD, Hall WD. Predictors of increased mortality in elderly depressed patients. *Int J Geriatric Psychiatry* 1994; 9: 219-227.
- [11] Engedal K. Mortality in the elderly: A 3-year follow-up of an elderly community sample. *Int J Geriatr Psychiatry* 1996; 11: 467-71.
- [12] O'Brien JT, Ames D. Why do the depressed elderly die? *Int J Geriatr Psychiatry* 1994; 9: 689-93.
- [13] Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 27: 99: 2192-217.
- [14] Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry* 1998; 155: 4-11.
- [15] Greene WA, Goldstein S, Moss AJ. Psychosocial aspects of sudden death. A preliminary report. *Arch Intern Med* 1972; 129: 725-31.
- [16] Lebovits BZ, Shekelle RB, Ostfeld AM, Paul O. Prospective and retrospective psychological studies of coronary heart disease. *Psychosom Med* 1967; 29: 265-72.
- [17] Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? *Lancet* 1997; 9: 350(9075):430-6.
- [18] Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol* 2004; 88: 196-8.
- [19] Broadley AJ, Korszun A, Jones CJ, Frenneaux MP. Arterial endothelial function is impaired in treated depression. *Heart* 2002; 88: 521-3.
- [20] Broadley AJ, Korszun A, Jones CJ, Frenneaux MP. Arterial endothelial function is impaired in treated depression. *Heart* 2002; 88: 521-3.
- [21] Strike PC, Steptoe A. Depression, stress, and the heart. *Heart* 2002; 88: 441-3.
- [22] Marzi M, Viganò A, Trabattini D, *et al.* Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clin Exp Immunol* 1996; 106: 127-33.
- [23] Saito S, Sakai M, Sasaki Y, Tanebe K, Tsuda H, Michimata T. Quantitative analysis of peripheral blood Th0, Th1, Th2 and the Th1:Th2 cell ratio during normal human pregnancy and preeclampsia. *Clin Exp Immunol* 1999; 117: 550-5.
- [24] Maes M, Verkerk R, Bonaccorso S, Ombelet W, Bosmans E, Scharpe S. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. *Life Sci* 2002; 71: 1837-48.
- [25] Østensen M, Förger F, Nelson JL, Schuhmacher A, Hebisch G, Villiger PM. Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis* 2005; 64: 801-3.
- [26] Stein GS. The pattern of mental change and body weight change in the first post-partum week. *J Psychosom Res* 1980; 24(3-4):165-71.
- [27] Josefsson A, Berg G, Nordin C, Sydsjo G. Prevalence of depressive symptoms in late pregnancy and postpartum. *Acta Obstet Gynecol Scand* 2001; 80: 251-5.
- [28] O'Hara MW, Swain AM. Rates and risk of postpartum depression-A meta-analysis. *Int Rev Psychiatry* 1996; 8: 37-54.
- [29] Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. *Psychol Bull* 1993; 113: 472-86.
- [30] Kronfol Z, Remick DG. Cytokines and the brain: Implications for clinical psychiatry. *Am J Psychiatry* 2000; 157: 683-94.
- [31] Dantzer R, Wollman EE, Vitkovic L, Yirmiya R. Cytokines, stress, and depression. Conclusions and perspectives. *Adv Exper Med Biol* 1999; 461: 317-29.
- [32] Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci* 1998; 62: 583-606.
- [33] Muller N, Hofschuster E, Ackenheil M, Mempel W, Eckstein R. Investigations of the cellular immunity during depression and the free interval: evidence for an immune activation in affective psychosis. *Prog Neuropsychopharmacol Biol Psychiatry* 1993; 17: 713-30.
- [34] Maes M, Meltzer HY, Bosmans E, *et al.* Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord* 1995; 34: 301-9.
- [35] Maes M. Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry* 1995; 19: 11-38.
- [36] Maes M, Meltzer HY, Buckley P, Bosmans E. Plasma-soluble interleukin-2 and transferrin receptor in schizophrenia and major depression. *Eur Arch Psychiatry Clin Neurosci* 1995; 244: 325-9.
- [37] Irwin M. Immune correlates of depression. *Adv Exp Med Biol* 1999; 461: 1-24.
- [38] Nunes SO, Reiche EM, Morimoto HK, *et al.* Immune and hormonal activity in adults suffering from depression. *Braz J Med Biol Res* 2002; 35: 581-7.
- [39] Müller N, Schwarz MJ. Immunology in anxiety and depression. In: Kasper S, den Boer JA, Sitsen JMA, editor. *Handbook of depression and anxiety*. NY, USA: Marcel Dekker 2002. p. 267-88.
- [40] Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *Eur Neuropsychopharmacol* 2001; 11: 203-8.
- [41] Myint AM, Leonard BE, Steinbusch HWM, Kim YK. Th1, Th2, and Th3 cytokine alterations in major depression. *J Affect Disord* 2005; 88:167-73.
- [42] Reichenberg A, Kraus T, Haack M, Schuld A, Pollmacher T, Yirmiya R. Endotoxin-induced changes in food consumption in healthy volunteers are associated with TNF-alpha and IL-6 secretion. *Psychoneuroendocrinology* 2002; 27: 945-56.
- [43] Maes M, Bosmans E, Meltzer HY, Scharpe S, Suy E. Interleukin-1 beta: a putative mediator of HPA axis hyperactivity in major depression? *Am J Psychiatry* 1993; 150: 1189-93.
- [44] Song C, Lin A, Bonaccorso S, *et al.* The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Disord* 1998; 49: 211-9.
- [45] Linnoila M, Whorton AR, Rubinow DR, Cowdry RW, Ninan PT, Waters RN. CSF prostaglandin levels in depressed and schizophrenic patients. *Arch Gen Psychiatry* 1983; 40: 405-6.
- [46] Ohishi K, Ueno R, Nishino S, Sakai T, Hayaishi O. Increased level of salivary prostaglandins in patients with major depression. *Biol Psychiatry* 2002; 27: 945-56.
- [47] Calabrese JR, Skwerer RG, Barna B, *et al.* Depression, immunocompetence, and prostaglandins of the E series. *Psychiatry Research* 1986; 17: 41-7.
- [48] Akarasereonont P, Techatrak K, Chotewuttabor S, Thaworn A. The induction cyclooxygenase-2 in IL-1 beta treated endothelial cells is inhibited by Prostaglandin E<sub>2</sub> through cAMP. *Mediat Inflamm* 1999; 8: 287-94.
- [49] Schmidlin F, Loeffler S, Bertrand C, Landry Y, Gies JP. PLA2 phosphorylation and cyclooxygenase-2 induction, through p38 MAP kinase pathway, is involved in the IL-1beta-induced bradykinin B2 receptor gene transcription. *Naunyn Schmiedeberg Arch Pharmacol* 2000; 361: 247-54.
- [50] Müller N, Schwarz MJ. Neuroimmune-endocrine crosstalk in schizophrenia and mood disorders. *Expert Rev* 2006; 6: 1017-38.
- [51] Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology* 1997; 35: 123-7.
- [52] Thomas AJ, Ferrier IN, Kalaria RN, *et al.* Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. *Am J Psychiatry* 2000; 157: 1682-4.
- [53] Rieckmann P, Nunke K, Burchhardt M, *et al.* Soluble intercellular adhesion molecule-1 in cerebrospinal fluid: an indicator for the inflammatory impairment of the blood-cerebrospinal fluid barrier. *J Neuroimmunol* 1993; 47: 133-40.
- [54] Levine J, Barak Y, Chengappa KN, Rapoport A, Rebec M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. *Neuropsychobiology* 1999; 40: 171-6.



- [55] Stubner S, Schon T, Padberg F, *et al.* Interleukin-6 and the soluble IL-6 receptor are decreased in cerebrospinal fluid of geriatric patients with major depression: no alteration of soluble gp130. *Neurosci Lett* 1999; 259: 145-8.
- [56] Carpenter LL, Heninger GR, Malison RT, Tyrka AR, Price LH. Cerebrospinal fluid interleukin (IL)-6 in unipolar major depression. *J Affect Disord* 2004; 79: 285-9.
- [57] Blasko I, Lederer W, Oberbauer H, *et al.* Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dement Geriatr Cogn Disord* 2006; 21: 9-15.
- [58] Rajkowska G, Miguel-Hidalgo JJ, Wei J, *et al.* Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 1999; 45: 1085-98.
- [59] Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry* 2000; 48: 766-77.
- [60] Stockmeier CA, Mahajan GJ, Konick LC, *et al.* Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiatry* 2004; 56: 640-50.
- [61] Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proc Natl Acad Sci USA* 1998; 95:13290-5.
- [62] Miller DB, O'Callaghan JP. Depression, cytokines, and glial function. *Metabolism* 2005; 54 (Suppl 1): 33-8.
- [63] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. [Review] [106 refs]. *Nat Rev Neurosci* 2008; 9: 46-56.
- [64] Sakic B, Denburg JA, Denburg SD, Szechtman H. Blunted sensitivity to sucrose in autoimmune MRL-lpr mice: a curve-shift study. *Brain Res Bull* 1996; 41: 305-11.
- [65] Yirmiya R. Depression in medical illness: the role of the immune system. *West J Med* 2000; 173: 333-6.
- [66] Renault WF, Hoofnagle JH, Park Y, *et al.* Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987; 147:1577-80.
- [67] Janssen HL, Brouwer JT, van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994; 21: 241-3.
- [68] Denicoff KD, Rubinow DR, Papa MZ, *et al.* The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. *Ann Int Med* 1987; 107:293-300.
- [69] Dantzer R. Cytokine, sickness behavior, and depression. *Neurol Clin* 2006; 24: 441-60.
- [70] Capuron L, Gummnick JF, Musselman DL, *et al.* Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 2002; 26: 643-52.
- [71] Schaefer M, Horn M, Schmidt F, *et al.* Correlation between sICAM-1 and depressive symptoms during adjuvant treatment of melanoma with interferon-alpha. *Brain Behav Immun* 2004; 18: 555-62.
- [72] Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J Clin Psychopharmacol* 2001; 21: 199-206.
- [73] Lanquillon S, Krieg JC, ing-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology* 2000; 22: 370-9.
- [74] Yaron I, Shirazi I, Judovich R, Levartovsky D, Caspi D, Yaron M. Fluoxetine and amitriptyline inhibit nitric oxide, prostaglandin E2, and hyaluronic acid production in human synovial cells and synovial tissue cultures. *Arthritis Rheum* 1999; 42: 2561-8.
- [75] Hestad KA, Tonseth S, Stoen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. *J ECT* 2003; 19:183-8.
- [76] Kenis G, Maes M. Effects of antidepressants on the production of cytokines. *Int J Neuropsychopharmacol* 2002; 5: 401-12.
- [77] Glaser R, Robles TF, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. *Arch Gen Psychiatry* 2003;60: 1009-14.
- [78] Reichenberg A, Yirmiya R, Schuld A, *et al.* Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001; 58: 445-52.
- [79] Strike PC, Wardle J, Steptoe A. Mild acute inflammatory stimulation induces transient negative mood. *J Psychosom Res* 2004; 57:189-94.
- [80] Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. *Brain Behav Immun* 2005;19: 345-50.
- [81] Dantzer R, Gheusi G, Johnson RW, Kelley KW. Central administration of insulin-like growth factor-1 inhibits lipopolysaccharide-induced sickness behavior in mice. *Neuroreport* 1999; 10: 289-92.
- [82] Meyers CA. Mood and cognitive disorders in cancer patients receiving cytokine therapy. *Adv Exp Med Biol* 1999; 461:75-81.
- [83] Bengtsson BO, Zhu J, Thorell LH, Olsson T, Link H, Walinder J. Effects of zimeldine and its metabolites, clomipramine, imipramine and maprotiline in experimental allergic neuritis in Lewis rats. *J Neuroimmunol* 1992; 39: 109-22.
- [84] Song C, Killeen AA, Leonard BE. Catalase, superoxide dismutase and glutathione peroxidase activity in neutrophils of sham-operated and olfactory-bulbectomised rats following chronic treatment with desipramine and lithium chloride. *Neuropsychobiology* 1994; 30: 24-8.
- [85] Zhu J, Bengtsson BO, Mix E, Thorell LH, Olsson T, Link H. Effect of monoamine reuptake inhibiting antidepressants on major histocompatibility complex expression on macrophages in normal rats and rats with experimental allergic neuritis (EAN). *Immunopharmacology* 1994; 27: 225-44.
- [86] Maes M, Song C, Lin AH, *et al.* Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* 1999; 20: 370-9.
- [87] Linthorst AC, Flachskamm C, Muller-Preuss P, Holsboer F, Reul JM. Effect of bacterial endotoxin and interleukin-1 beta on hippocampal serotonergic neurotransmission, behavioral activity, and free corticosterone levels: an *in vivo* microdialysis study. *J Neurosci* 1995; 15: 2920-34.
- [88] Merali Z, Lacosta S, Anisman H. Effects of interleukin-1beta and mild stress on alterations of norepinephrine, dopamine and serotonin neurotransmission: a regional microdialysis study. *Brain Res* 1997; 761: 225-35.
- [89] Anisman H, Merali Z. Anhedonic and anxiogenic effects of cytokine exposure. [Review] [153 refs]. *Adv Exper Med Biol* 1999; 461: 199-233.
- [90] Dunn AJ. The role of interleukin-1 and tumor necrosis factor alpha in the neurochemical and neuroendocrine responses to endotoxin. *Brain Res Bull* 1992; 29: 807-12.
- [91] Linthorst AC, Reul JM. Brain neurotransmission during peripheral inflammation. *Ann N Y Acad Sci* 1998; 840: 139-52.
- [92] Pedersen BK, Febbraio M. Muscle-derived interleukin-6--a possible link between skeletal muscle, adipose tissue, liver, and brain. *Brain Behav Immun* 2005; 19: 371-6.
- [93] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005 ; 98: 1154-62.
- [94] Febbraio MA, Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J* 2002; 16: 1335-47.
- [95] Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans--effect of intensity of exercise. *Eur J Appl Physiol* 2000; 83: 512-5.
- [96] Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol* 1999; 515: 287-91.
- [97] Banks WA, Kastin AJ, Durham DA. Bidirectional transport of interleukin-1 alpha across the blood-brain barrier. *Brain Res Bulletin* 1989; 23: 433-7.
- [98] Gutierrez EG, Banks WA, Kastin AJ. Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *J Neuroimmunol* 1993; 47: 169-76.
- [99] Hopkins SJ, Rothwell NJ. Cytokines and the nervous system. *Trends Neurosci* 1995; 18 : 83-8.
- [100] Tracey KJ. The inflammatory reflex. *Nature* 2002; 420: 853-9.
- [101] Oke SL, Tracey KJ. From CNI-1493 to the immunological homunculus: physiology of the inflammatory reflex. *J Leukoc Biol* 2008; 83: 512-7.
- [102] Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* 1987; 238: 522-4.

- [103] Sapolsky RM, Plotsky PM. Hypercortisolism and its possible neural bases. *Biol Psychiatry* 1990; 27(9): 937-52.
- [104] Baumann H, Gauldie J. The acute phase response. *Immunol Today* 1994; 15: 74-80.
- [105] Young EA, Haskett RF, Murphy-Weinberg V, Watson SJ, Akil H. Loss of glucocorticoid fast feedback in depression. *Arch Gen Psychiatry* 1991; 48: 693-9.
- [106] Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. *Adv Exp Med Biol* 1999; 461: 107-16.
- [107] Berkenbosch F, van O, del R, Tilders F, Besedovsky H. Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science* 1987; 238: 524-6.
- [108] Ericsson A, Kovacs KJ, Sawchenko PE. A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. *J Neurosci* 1994; 14: 897-913.
- [109] Breder CD, Dinarello CA, Saper CB. Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* 1988; 240: 321-4.
- [110] Goehler LE, Gaykema RP, Hammack SE, Maier SF, Watkins LR. Interleukin-1 induces c-Fos immunoreactivity in primary afferent neurons of the vagus nerve. *Brain Res* 1998; 804: 306-10.
- [111] Maier SF, Goehler LE, Fleshner M, Watkins LR. The role of the vagus nerve in cytokine-to-brain communication. *Ann NY Acad Sci* 1998; 840: 289-300.
- [112] Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 1998; 105: 83-107.
- [113] Gold PW, Chrousos G, Kellner C, et al. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am J Psychiatry* 1984; 141: 619-27.
- [114] George MS, Sackeim HA, Rush AJ, et al. Vagus nerve stimulation: a new tool for brain research and therapy. *Biol Psychiatry* 2000; 47(4): 287-95.
- [115] Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology* 2001; 25: 713-28.
- [116] Watson S, Young AH. Hypothalamic-pituitary-adrenal-axes Function in Bipolar disorders. *Clinical approaches in bipolar disorders* 2002; 1: 57-64.
- [117] Porter RJ, Ister-Williams RH, Lunn BS, Young AH. 5-Hydroxytryptamine receptor function in humans is reduced by acute administration of hydrocortisone. *Psychopharmacology (Berl)* 1998; 139: 243-50.
- [118] Young AH, Goodwin GM, Dick H, Fink G. Effects of glucocorticoids on 5-HT<sub>1A</sub> presynaptic function in the mouse. *Psychopharmacology (Berl)* 1994; 114: 360-4.
- [119] Young AH, Sharpley AL, Campling GM, Hockney RA, Cowen PJ. Effects of hydrocortisone on brain 5-HT function and sleep. *J Affect Disord* 1994; 32: 139-46.
- [120] Laaris N, Le PE, Laporte AM, Hamon M, Lanfumey L. Differential effects of stress on presynaptic and postsynaptic 5-hydroxytryptamine-1A receptors in the rat brain: an *in vitro* electrophysiological study. *Neuroscience* 1999; 91: 947-58.
- [121] Butler LD, Layman NK, Riedl PE, et al. Neuroendocrine regulation of *in vivo* cytokine production and effects: I. *In vivo* regulatory networks involving the neuroendocrine system, interleukin-1 and tumor necrosis factor-alpha. *J Neuroimmunol* 1989; 24: 143-53.
- [122] Wang J, Dunn AJ. The role of interleukin-6 in the activation of the hypothalamo-pituitary-adrenocortical axis and brain indoleamines by endotoxin and interleukin-1 beta. *Brain Res* 1999; 815: 337-48.
- [123] Dunn AJ, Wang J, Ando T. Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. *Adv Exp Med Biol* 1999; 461: 117-27.
- [124] Straub RH, Herfarth H, Falk W, Andus T, Scholmerich J. Uncoupling of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis in inflammatory bowel disease? *J Neuroimmunology* 2002; 126: 116-125.
- [125] Chittiprol S, Kumar AM, Satischandra P, et al. Progressive dysregulation of autonomic and HPA axis functions in HIV-1 clade C infection in South India. *Psychoneuroendocrinology* 2008; 33: 30-40.
- [126] Guillemin GJ, Kerr SJ, Smythe GA, et al. Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. *J Neurochem* 2001; 78: 842-53.
- [127] Wirleitner B, Neurauder G, Schrocksnadel K, Frick B, Fuchs D. Interferon-gamma-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. *Curr Med Chem* 2003; 10: 1581-1591.
- [128] Hayaishi O. Utilization of superoxide anion by indoleamine oxygenase-catalyzed tryptophan and indoleamine oxidation. *Adv Exp Med Biol* 1996; 398: 285-9.
- [129] Heyes MP, Saito K, Crowley JS, et al. Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. *Brain* 1992; 115: 1249-73.
- [130] Stone TW, Darlington LG. Endogenous kynurenines as targets for drug discovery and development. *Nat Rev* 2002; 1: 609-20.
- [131] Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; 29: 201-17.
- [132] Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* 1965; 122: 509-22.
- [133] Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress Anxiety* 2000; 12 Suppl 1: 2-19.
- [134] Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biol Psychiatry* 1999; 46: 1219-33.
- [135] Dursun SM, Blackburn JR, Kutcher SP. An exploratory approach to the serotonergic hypothesis of depression: bridging the synaptic gap. *Med Hypotheses* 2001; 56: 235-43.
- [136] Castanon N, Leonard BE, Neveu PJ, Yirmiya R. Effects of antidepressants on cytokine production and actions. *Brain Behav Immun* 2002; 16: 569-74.
- [137] Wichers MC, Maes M. The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon-alpha-induced depression. *J Psychiatry Neurosci* 2004; 29: 11-7.
- [138] Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol* 2002; 22: 86-90.
- [139] Capuron L, Ravaut A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry* 2002; 7: 468-73.
- [140] Capuron L, Neurauder G, Musselman DL, et al. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biol Psychiatry* 2003; 54(9): 906-14.
- [141] Heyes MP, Achim CL, Wiley CA, Major EO, Saito K, Markey SP. Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. *Biochem J* 1996; 320: 595-7.
- [142] Guillemin GJ, Smythe G, Takikawa O, Brew BJ. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia* 2005; 49: 15-23.
- [143] Stone TW. Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. *Prog Neurobiol* 2001; 64(2): 185-218.
- [144] Van d V, Bast A. Effect of oxidative stress on receptors and signal transmission. *Chem Biol Interact* 1992; 85: 95-116.
- [145] Muller N, Schwarz MJ. A psychoneuroimmunological perspective to Emil Kraepelin's dichotomy: schizophrenia and major depression as inflammatory CNS disorders. *Eur Arch Psychiatry Clin Neurosci* 2008; 258 Suppl-2: 97-106.
- [146] Muller N, Schwarz MJ. COX-2 inhibition in schizophrenia and major depression. *Curr Pharm* 2008; 14: 1452-65.
- [147] Kubera M, Maes M, Kenis G, Kim YK, Lason W. Effects of serotonin and serotonergic agonists and antagonists on the production of tumor necrosis factor alpha and interleukin-6. *Psychiatry Res* 2005; 134: 251-8.
- [148] Kubera M, Kenis G, Bosmans E, Scharpe S, Maes M. Effects of serotonin and serotonergic agonists and antagonists on the production of interferon-gamma and interleukin-10. *Neuropsychopharmacology* 2000; 23(1): 89-98.
- [149] Maes M. Major depression and activation of the inflammatory response system. *Adv Exp Med Biol* 1999; 461: 25-46.
- [150] Bosker FJ, Westerink BH, Cremers TI, et al. Future antidepressants: what is in the pipeline and what is missing? *CNS Drugs* 2004; 18: 705-32.
- [151] Tsai SJ. Glatiramer acetate could be a potential antidepressant through its neuroprotective and anti-inflammatory effects. *Med Hypotheses* 2007; 69(1): 145-8.

- [152] Dairam A, Antunes EM, Saravanan KS, Daya S. Non-steroidal anti-inflammatory agents, tolmetin and sulindac, inhibit liver tryptophan 2,3-dioxygenase activity and alter brain neurotransmitter levels. *Life Sci* 2006 79; 2269-74.
- [153] Tying S, Gottlieb A, Papp K, *et al.* Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; 367: 29-35.
- [154] Muller N, Schwarz MJ, Dehning S, *et al.* The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. *Mol Psychiatry* 2006; 11: 680-4.
- [155] Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis* 2002; 8 :237-43.
- [156] Blalock JE, Smith EM. Conceptual development of the immune system as a sixth sense. *Brain Behav Immun* 2007; 21: 23-33.

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