Cytokines and Depression

How your immune system *causes* depression

by Ronald S. Smith

Chapter 7:

Immunological Evidence Supporting The Immune-Cytokine Model of Depression

The Immune-Cytokine Model of Depression (ICMD) is an entirely new concept for understanding the riddle of depression. This is the only model of depression to bridge the conceptual and diagnostic gap between physical and mental disorders.[1,2] ICMD views depression to be any number of chronic physical-biological disorders that have mental-emotional symptoms. From the perspective of ICMD, depression isn't really a disease, but rather a multifaceted sign of chronic immune system activation. During chronic immune system activation, greater than normal amounts of various cytokines are secreted. The cytokines produce the multifaceted signs and symptoms of depression. This chapter summarizes the extensive immunological evidence supporting ICMD. Chapter 7 reviews the evidence from biological psychiatry supporting ICMD.

Cytokines Cause The Symptoms Of Depression

Cytokines are at the heart of the immunological basis of depression since they provoke a wide spectrum of neuropsychiatric symptoms when given to human volunteers. The profound effects of cytokines on mood, thought and behavior were first discovered in the early 1980's. For the first time in history, physicians had found molecules made by the human body which, when given to humans, produced all the symptoms necessary for the diagnosis of depression.

These discoveries are of monumental importance. They should have dazzled every psychiatrist and psychologist in the world, but quite surprisingly, mental health professionals had meager interest in these discoveries. Most psychologists and psychiatrists were (and still seem to be) engrossed in their own theories of psychopathology and had little time or interest in psychiatric discoveries coming from other disciplines, especially when they came from something as seemingly unrelated as immunology.

Interferon-alpha Interferon-alpha (INFα) is a cytokine released by activated monocytes and macrophages. It has a number of beneficial effects on various immune cells[3], but it also has many very debilitating neuropsychiatric consequences.[4] Priestman[5] in 1980 was one of the first to report some of INFα's neuropsychiatric effects. A few year later Rohatiner et al.[6] published a more detailed study. They gave INFα intravenously for seven days to eleven volunteers and observed the effects. All volunteers became feverish, fatigued and lacked appetite. They were socially withdrawn, slow to answer questions, lost interest in their surroundings and slept most of the day. In one week, these volunteers developed nearly all the symptoms necessary for the diagnosis of major depressive episode. Their brain waves also became abnormal and were suggestive of a brain degenerative disease.

A year later, Adams et al.[7] did a longer term (four week, ten patient) study on the effects of INFα. For the first few days fever, headache, aching muscles and other flu like symptoms occurred, but they did not persist. They were replaced by symptoms of severe depression. From the end of the first week to the end the fourth week, eight of

So depression is an inflammatory disease, but where does the inflammation come from?

Michael Berk[1234*], **Lana J Williams**[12], **Felice N Jacka**[12], **Adrienne O'Neil**[15], **Julie A Pasco**[16], **Steven Moylan**[1], **Nicholas B Allen**[7], **Amanda L Stuart**[1], **Amie C Hayley**[1], **Michelle L Byrne**[7] and **Michael Maes**[18]

- *Corresponding author: Michael Berk mikebe@barwonhealth.org.au

BMC Medicine 2013, **11**:200 doi:10.1186/1741-7015-11-200
Published: 12 September 2013

Abstract

Background

We now know that depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. It is similarly accompanied by increased oxidative and nitrosative stress (O&NS), which contribute to neuroprogression in the disorder. The obvious question this poses is 'what is the source of this chronic low-grade inflammation?'

Discussion

This review explores the role of inflammation and oxidative and nitrosative stress as possible mediators of known environmental risk factors in depression, and discusses potential implications of these findings. A range of factors appear to increase the risk for the development of depression, and seem to be associated with systemic inflammation; these include psychosocial stressors, poor diet, physical inactivity, obesity, smoking, altered gut permeability, atopy, dental cares, sleep and vitamin D deficiency.

Summary

The identification of known sources of inflammation provides support for inflammation as a mediating pathway to both risk and neuroprogression in depression. Critically, most of these factors are plastic, and potentially amenable to therapeutic and preventative interventions. Most, but not all, of the above mentioned sources of inflammation may play a role in other psychiatric disorders, such as bipolar disorder, schizophrenia, autism and post-traumatic stress disorder.

Keywords:

Depression; Inflammation; Cytokines; Diet; Obesity; Exercise; Smoking; Vitamin D; Dental cares; Sleep; Atopic; Gut; Oxidative stress

Abstract

Full text links

KARGER Final Version

Neuroimmunomodulation. 2014;21(2-3):123-30. doi: 10.1159/000356540. Epub 2014 Feb 14.

Immunology of major depression.

Müller N[1].

Author information

Abstract

High levels of several proinflammatory components of the immune system, such as interleukin-6, C-reactive protein, tumor necrosis factor (TNF)-α, or neopterin in patients suffering from major depression (MD) point to the involvement of an inflammatory process in the pathophysiology of MD. The direct and indirect effects of cytokines on neurotransmitter storage and release - mediated by microglia cells and astrocytes - are discussed. The tryptophan/kynurenine metabolism is one of the indirect mechanisms because the enzyme indoleamine 2,3-dioxygenase - a key enzyme of this metabolism in the central nervous system - is driven by pro- and anti-inflammatory cytokines and degrades serotonin. Moreover, neuroactive kynurenines such as kynurenic acid and quinolinic acid act on the glutamatergic neurotransmission as N-methyl-D-aspartate antagonists and agonists, respectively. Alterations of the serotonergic, noradrenergic and glutamatergic neurotransmission have been shown with low-level neuroinflammation and may be involved in symptom generation. Epidemiological and clinical studies show a role for inflammation as a risk factor for MD. A large-scale epidemiological study in MD clearly demonstrates that severe infections and autoimmune disorders are lifetime risk factors for MD. The vulnerability-stress-inflammation model matches with this view as stress may increase proinflammatory cytokines and even contribute to a lasting proinflammatory state. Further support comes from the therapeutic benefit of anti-inflammatory medications such as the cyclo-oxygenase-2 inhibitors, TNF-α antagonists and others, and the anti-inflammatory and immunomodulatory intrinsic effects of antidepressants.

PMID: 24557045 [PubMed - indexed for MEDLINE]

PubMed

Abstract

Full text links

ELSEVIER FULL-TEXT ARTICLE

Biol Psychiatry. 2010 Mar 1;67(5):446-57. doi: 10.1016/j.biopsych.2009.09.033. Epub 2009 Dec 16.

A meta-analysis of cytokines in major depression.

Dowlati Y[1], Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL.

Author information

Abstract

BACKGROUND: Major depression occurs in 4.4% to 20% of the general population. Studies suggest that major depression is accompanied by immune dysregulation and activation of the inflammatory response system (IRS). Our objective was to quantitatively summarize the data on concentrations of specific cytokines in patients diagnosed with a major depressive episode and controls.

METHODS: We performed a meta-analysis of studies measuring cytokine concentration in patients with major depression, with a database search of the English literature (to August 2009) and a manual search of references.

RESULTS: Twenty-four studies involving unstimulated measurements of cytokines in patients meeting DSM criteria for major depression were included in the meta-analysis; 13 for tumor necrosis factor (TNF)-alpha, 9 for interleukin (IL)-1beta, 16 for IL-6, 5 for IL-4, 5 for IL-2, 4 for IL-8, 6 for IL-10, and 4 for interferon (IFN)-gamma. There were significantly higher concentrations of TNF-alpha ($p < .00001$), weighted mean difference (WMD) (95% confidence interval) 3.97 pg/mL (2.24 to 5.71), in depressed subjects compared with control subjects (438 depressed/350 nondepressed). Also, IL-6 concentrations were significantly higher ($p < .00001$) in depressed subjects compared with control subjects (492 depressed/400 nondepressed) with an overall WMD of 1.78 pg/mL (1.23 to 2.33). There were no significant differences among depressed and nondepressed subjects for the other cytokines studied.

CONCLUSIONS: This meta-analysis reports significantly higher concentrations of the proinflammatory cytokines TNF-alpha and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the IRS.

PMID: 20015486 [PubMed - indexed for MEDLINE]

BJPsych | The British Journal of Psychiatry (2010) 197, 372–377. doi: 10.1192/bjp.bp.109.076430

Association of high-sensitivity C-reactive protein with *de novo* major depression

Julie A. Pasco, Geoffrey C. Nicholson, Lana J. Williams, Felice N. Jacka, Margaret J. Henry, Mark A. Kotowicz, Hans G. Schneider, Brian E. Leonard and Michael Berk

Background
Although there is cross-sectional evidence that changes in the immune system contribute to the pathophysiology of depression, longitudinal data capable of elucidating cause and effect relationships are lacking.

Aims
We aimed to determine whether subclinical systemic inflammation, as measured by serum high-sensitivity C-reactive protein (hsCRP) concentration, is associated with an increased risk of *de novo* major depressive disorder.

Method
Major depressive disorder was diagnosed using a clinical interview (SCID–I/NP). This is a retrospective cohort study; from a population-based sample of 1494 randomly selected women recruited at baseline during the period 1994–7, 822 were followed for a decade and provided measures of both exposure and outcome. Of these women, 644 (aged 20–84 years) had no prior history of depression at baseline and were eligible for analysis.

Results
During 5827 person-years of follow-up, 48 cases of *de novo* major depressive disorder were identified. The hazard ratio (HR) for depression increased by 44% for each standard deviation increase in log-transformed hsCRP (ln-hsCRP) (HR = 1.44, 95% CI 1.04–1.99), after adjusting for weight, smoking and use of non-steroidal anti-inflammatory drugs. Further adjustment for other lifestyle factors, medications and comorbidity failed to explain the observed increased risk for depression.

Conclusions
Serum hsCRP is an independent risk marker for *de novo* major depressive disorder in women. This supports an aetiological role for inflammatory activity in the pathophysiology of depression.

Declaration of interest
M.B. has received grant/research support from the Stanley Medical Research Foundation, MBF, National Health and Medical Research Council, Beyond Blue, Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, Servier and AstraZeneca. He has been a paid consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Pfizer, and a paid speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth.

Psychoneuroendocrinology. 2014 Dec;50:210-9. doi: 10.1016/j.psyneuen.2014.08.016. Epub 2014 Sep 2.

Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood.

Grudet C[1], Malm J[2], Westrin A[3], Brundin L[4].

Author information

Abstract

BACKGROUND: Low levels of vitamin D may play a role in psychiatric disorders, as cross-sectional studies show an association between vitamin D deficiency and depression, schizophrenia and psychotic symptoms. The underlying mechanisms are not well understood, although vitamin D is known to influence the immune system to promote a T helper (Th)-2 phenotype. At the same time, increased inflammation might be of importance in the pathophysiology of depression and suicide. We therefore hypothesized that suicidal patients would be deficient in vitamin D, which could be responsible for the inflammatory changes observed in these patients.

METHODS: We compared vitamin D levels in suicide attempters (n=59), non-suicidal depressed patients (n=17) and healthy controls (n=14). Subjects were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, and went through a structured interview by a specialist in psychiatry. 25(OH)D2 and 25(OH)D3 were measured in plasma using liquid-chromatography-mass-spectrometry (LC-MS). We further explored vitamin D's association with plasma IL-1β, IL-6 and TNF-α.

RESULTS: Suicide attempters had significantly lower mean levels of vitamin D than depressed non-suicidal patients and healthy controls. 58 percent of the suicide attempters were vitamin D deficient according to clinical standard. Moreover, there was a significant negative association between vitamin D and pro-inflammatory cytokines in the psychiatric patients. Low vitamin D levels were associated with higher levels of the inflammatory cytokines IL-6 and IL-1β in the blood.

CONCLUSION: The suicide attempters in our study were deficient in vitamin D. Our data also suggest that vitamin D deficiency could be a contributing factor to the elevated pro-inflammatory cytokines previously reported in suicidal patients. We propose that routine clinical testing of vitamin D levels could be beneficial in patients with suicidal symptoms, with subsequent supplementation in patients found to be deficient.

KEYWORDS: Cytokines; Depression; IL-1β; IL-6; Inflammation; Suicidality; TNF-α; Th-1; Th-2

Nutrition Journal

BioMed Central

Research

Open Access

Randomized comparison of the effects of the vitamin D_3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients

Reinhold Vieth*[1], Samantha Kimball[1], Amanda Hu[1] and Paul G Walfish[2,3]

Address: [1]Department of Laboratory Medicine and Pathology, University of Toronto, Canada, [2]Department of Medicine, Pediatrics, and Otolaryngology, University of Toronto, Canada and [3]Medicine and Endocrine Oncology Program, Mount Sinai Hospital, Toronto, Canada

Email: Reinhold Vieth* - rvieth@mtsinai.on.ca; Samantha Kimball - skimball@uoguelph.ca; Amanda Hu - amanda.hu@utoronto.ca; Paul G Walfish - walfish@mshri.on.ca

* Corresponding author

Published: 19 July 2004

Nutrition Journal 2004, **3**:8 doi:10.1186/1475-2891-3-8

Received: 23 March 2004
Accepted: 19 July 2004

This article is available from: http://www.nutritionj.com/content/3/1/8

Abstract

Background: For adults, vitamin D intake of 100 mcg (4000 IU)/day is physiologic and safe. The adequate intake (AI) for older adults is 15 mcg (600 IU)/day, but there has been no report focusing on use of this dose.

Methods: We compared effects of these doses on biochemical responses and sense of wellbeing in a blinded, randomized trial. In Study 1, 64 outpatients (recruited if summer 2001 25(OH)D <61 nmol/L) were given 15 or 100 mcg/day vitamin D in December 2001. Biochemical responses were followed at subsequent visits that were part of clinical care; 37 patients completed a wellbeing questionnaire in December 2001 and February 2002. Subjects for Study 2 were recruited if their 25(OH)D was <51 nmol/L in summer 2001. 66 outpatients were given vitamin D; 51 completed a wellbeing questionnaire in both December 2002 and February 2003.

Results: In Study 1, basal summer 25-hydroxyvitamin D [25(OH)D] averaged 48 ± 9 (SD) nmol/L. Supplementation for more than 6 months produced mean 25(OH)D levels of 79 ± 30 nmol/L for the 15 mcg/day group, and 112 ± 41 nmol/L for the 100 mcg/day group. Both doses lowered plasma parathyroid hormone with no effect on plasma calcium. Between December and February, wellbeing score improved more for the 100-mcg/day group than for the lower-dosed group (1-tail Mann-Whitney $p = 0.036$). In Study 2, 25(OH)D averaged 39 ± 9 nmol/L, and winter wellbeing scores improved with both doses of vitamin D (two-tail $p < 0.001$).

Conclusion: The highest AI for vitamin D brought summertime 25(OH)D to >40 nmol/L, lowered PTH, and its use was associated with improved wellbeing. The 100 mcg/day dose produced greater responses. Since it was ethically necessary to provide a meaningful dose of vitamin D to these insufficient patients, we cannot rule out a placebo wellbeing response, particularly for those on the lower dose. This work confirms the safety and efficacy of both 15 and 100 mcg/day vitamin D_3 in patients who needed additional vitamin D.

Study finds vitamin D improves feelings of well being in subjects with frequent respiratory tract infections

A reanalysis of a double-blind, randomized controlled trial of the effects of supplementation [Vitamin D_3 Supplementation in patients with frequent respiratory tract infections. Bergman et al.] found that those patients who significantly increased their vitamin D blood serum levels also reported their wellbeing to be 'better than before'. Vitamin D supplementation also have an effect on anti-depressant use.

Read the full news article at www.vitamindcouncil.org/

Read the original study at www.bmjopen.bmj.com

Mil Med. 2014 Nov;179(11 Suppl):192-8. doi: 10.7205/MILMED-D-14-00189.

The response of an expert panel to Nutritional armor for the warfighter: can omega-3 fatty acids enhance stress resilience, wellness, and military performance?

Coulter ID[1].

An expert panel unanimously agreed that omega-3 fatty acids should have a Daily Recommended Intake for military members. The panel concluded that evidence for cardiovascular, immunological, and surgical benefits was strong, as was the evidence for a reduction in depressive symptoms and suicide.

The final conclusion was that based on the studies, it would be unethical to not attempt to elevate omega-3 levels.

Abstract available at: www.ncbi.nlm.nih.gov/pubmed