

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Psychiatry

ESPS manuscript NO: 27055

Title: Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?

Reviewer's code: 01205020

Reviewer's country: Taiwan

Science editor: Jin-Xin Kong

Date sent for review: 2016-05-09 04:00

Date reviewed: 2016-05-09 16:45

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|-------------------------|---|---------------------------|-----------------------------------|
| [Y] Grade A: Excellent | [Y] Grade A: Priority publishing | Google Search: | [] Accept |
| [] Grade B: Very good | [] Grade B: Minor language polishing | [] The same title | [] High priority for publication |
| [] Grade C: Good | [] Grade C: A great deal of language polishing | [] Duplicate publication | [] Rejection |
| [] Grade D: Fair | [] Grade D: Rejected | [Y] No | [Y] Minor revision |
| [] Grade E: Poor | | BPG Search: | [] Major revision |
| | | [] The same title | |
| | | [] Duplicate publication | |
| | | [] Plagiarism | |
| | | [Y] No | |

COMMENTS TO AUTHORS

This review paper describes the etiology and the pathogenesis of depression regarding cytokine network. They suggested that depression may be caused by neuroinflammation and cytokine imbalances. The authors have summarized the reports nicely and have provided critical overview of the findings. The figures are informative. However, there are some issues which should be clarified. 1. P 10, "Peripheral and central injections of IL-1 β , IFN- γ , and TNF- α increase the levels of 5-HT in the hypothalamus, hippocampus, and cortex". Please check "increase the levels of 5-HT" or "increase the levels of 5-HIAA". Does IFN- γ also have this effect? 2. P 13, "Stress induces cytokine oversecretion.." Should it be "Stress induces proinflammatory cytokine oversecretion.."? 3. P 15, "TNF- α has most recently drawn attention as a treatment that can change the course of bipolar disorder". Do the authors mean to use TNF- α to treat bipolar disorder? 4. Figures must be cited in the text.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Psychiatry

ESPS manuscript NO: 27055

Title: Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?

Reviewer's code: 00551176

Reviewer's country: Hungary

Science editor: Jin-Xin Kong

Date sent for review: 2016-05-09 04:00

Date reviewed: 2016-05-20 16:50

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|--|--|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input checked="" type="checkbox"/> Grade A: Priority publishing | Google Search: | <input type="checkbox"/> Accept |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> No | <input checked="" type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | | BPG Search: | <input type="checkbox"/> Major revision |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | <input checked="" type="checkbox"/> No | |

COMMENTS TO AUTHORS

Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness? This is an interesting review of the existing knowledge about the role of cytokines and neuroinflammation in the development and treatment of depression. As we do not clearly know the underlying mechanism of depression, to summarize the existing knowledge helps to identify further directions of research. The text is well written and clear. Minor comments to authors: 1) Page 7, in 'Stress-cytokine-inflammation-depression' subchapter, second sentence authors state that 'nearly 90% of patients who undergo IFN treatments due to hepatitis C or cancer experience fatigue and depressive symptoms, and over 50% of patients who are treated with high-dose IFN- α satisfy the diagnostic criteria for major depressive disorders...' and cite a study from Musselman et al. From one hand this reference is inadequate here as the Musselman study is about the prevention of IFN induced depressive symptoms and not about the prevalence of these symptoms. From the other hand the Musselman's study reflects lower depression rates than authors cited. As there are a number of studies that aimed to survey prevalence of depression in IFN treated patients, it is advised to find a

better fitting citation here and correct the above mentioned sentence according to the newly cited publication. 2) On page 14 authors write: 'The anti-inflammatory effects of riluzole and ketamine, which are glutamatergic modulators, are also drawing attention. They increase the activities of the inflammatory microglial cells and induce astroglial loss, which consequently induces glutamate release and an upregulation of NMDA receptors[59]. Riluzole and ketamine prevent neurotoxicity and relieve inflammation by inhibiting glutamate secretion and NMDA receptors[60].' These statements seems to be contradictory to me. Please clarify the function of riluzole and ketamine. Do they induce, or inhibit glutamate secretion and NMDA receptors? 3) There are two Figures attached, but places of these figures in the text are not indicated.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Psychiatry

ESPS manuscript NO: 27055

Title: Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?

Reviewer's code: 00646324

Reviewer's country: Canada

Science editor: Jin-Xin Kong

Date sent for review: 2016-05-09 04:00

Date reviewed: 2016-05-23 08:28

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|--|---|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input type="checkbox"/> Grade A: Priority publishing | Google Search: | <input type="checkbox"/> Accept |
| <input checked="" type="checkbox"/> Grade B: Very good | <input checked="" type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good | | <input type="checkbox"/> Duplicate publication | |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Plagiarism | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade E: Poor | | <input checked="" type="checkbox"/> No | <input checked="" type="checkbox"/> Minor revision |
| | <input type="checkbox"/> Grade D: Rejected | BPG Search: | <input type="checkbox"/> Major revision |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | <input checked="" type="checkbox"/> No | |

COMMENTS TO AUTHORS

This is a comprehensive review of the neuroinflammation hypothesis of depression. It will contribute to literature and I recommend its publication. There are minor clarifications or typos. Examples; Page 17, 2nd line "...but rather inhibition of the effects of peripheral-released cytokines on the CNS regardless (change on....to in the CNS) Page 17, Thus, can low-dose cytokines act on the CNS and affect the pathophysiology of depression? This question is rather vague Also, Page17, the comment " However, in some cases, childhood stress sustains CRF hyperactivity and increases stress responses in adulthood, which then results in the oversecretion of cerebral CRF and eventually leads to depression" was this confirmed or demonstrated in clinical research? Page 18, first paragraph: What is meant by "The sickness behavior"? Please define sickness behaviors? are these laboratory observations or actual patient's behavior? e.g. adopting the sickness role

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Psychiatry

ESPS manuscript NO: 27055

Title: Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?

Reviewer's code: 02445242

Reviewer's country: India

Science editor: Jin-Xin Kong

Date sent for review: 2016-05-09 04:00

Date reviewed: 2016-05-24 23:47

| CLASSIFICATION | LANGUAGE EVALUATION | SCIENTIFIC MISCONDUCT | CONCLUSION |
|--|--|--|--|
| <input type="checkbox"/> Grade A: Excellent | <input checked="" type="checkbox"/> Grade A: Priority publishing | Google Search: | <input type="checkbox"/> Accept |
| <input checked="" type="checkbox"/> Grade B: Very good | <input type="checkbox"/> Grade B: Minor language polishing | <input type="checkbox"/> The same title | <input type="checkbox"/> High priority for publication |
| <input type="checkbox"/> Grade C: Good | <input type="checkbox"/> Grade C: A great deal of language polishing | <input type="checkbox"/> Duplicate publication | <input type="checkbox"/> Rejection |
| <input type="checkbox"/> Grade D: Fair | <input type="checkbox"/> Grade D: Rejected | <input checked="" type="checkbox"/> No | <input checked="" type="checkbox"/> Minor revision |
| <input type="checkbox"/> Grade E: Poor | | BPG Search: | <input type="checkbox"/> Major revision |
| | | <input type="checkbox"/> The same title | |
| | | <input type="checkbox"/> Duplicate publication | |
| | | <input type="checkbox"/> Plagiarism | |
| | | <input checked="" type="checkbox"/> No | |

COMMENTS TO AUTHORS

I found this to be a lucid and comprehensive review on the subject. However, the authors may consider including certain other aspects of the cytokine hypothesis of depression. These include genetic aspects, role of early life stress and trauma, information on modulators of cytokine activity in depression such as diet, obesity, gut health, physical activity, sleep deprivation and vitamin D3 deficiency, more details on cytokine abnormalities and depression in medical illnesses, animal models of the cytokine activity in depression, inflammatory markers in suicide, and the influence of treatments such as ECT on inflammation. Since the heading was whether cytokine abnormalities are a cause or consequence of depression it would be useful to know the authors' final conclusions on this matter.