BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

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Thank you for your editorial decision and constructive criticisms. They allowed us to improve our manuscript. We are grateful for the opportunity to resubmit the manuscript, revised in accordance with the reviewer's comments and suggestions. Our replies are presented subsequently.

Responses to Reviewer (#1)

Reviewer's code: 01205020

Comment 1

P 10, "Peripheral and central injections of IL-1β, 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?

REPLY 1: As the reviewer suggested, we checked the results of the cited article

(Clement HW, Buschmann J, Rex S, Grote C, Opper C, Gemsa D, Wesemann W. Effects of interferon-gamma, interleukin-1 beta, and tumor necrosis factor-alpha on the serotonin metabolism in the nucleus raphe dorsalis of the rat. Journal of neural transmission 1997; 104: 981-991). We found our mistakes. The suggestions the reviewer pointed out were correct. The sentence has been corrected.

REVISION 1

Page 11. Peripheral injections of IL-1β and TNF-α increase the extracellular levels of 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus raphe dorsalis, and central injection (intracerebroventricular application) of IL-1β, IFN-γ, and TNF-α stimulates the 5-HT transmission in the nucleus raphe dorsalis[42].

Comment 2

P 13, "Stress induces cytokine oversecretion.." Should it be "Stress induces proinflammatory cytokine oversecretion.."?

REPLY 2: The sentence has been corrected..

REVISION 2

Page 14. Stress induces proinflammatory cytokine oversecretion, which results in depressive symptoms.

Comment 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?

REPLY 3: As the reviewer suggested, we rechecked the sentence and found that the citation was wrong. The citation has been corrected and more detail has been provided concerning the mechanisms of TNF-α treatment in bipolar disorder, including the study of TNF-α as a disease-modifying treatment in bipolar disorder in clinical trials.

REVISION 3

Page 16. TNF-α has most recently drawn attention as a treatment that can change the course of bipolar disorder (disease-modifying treatment)[64]. Current evidence suggests that TNF-α regulates apoptotic cascades that may be associated with neuronal and glial loss in bipolar disorder. TNF-α antagonists, such as adalimumab, etanercept, and infliximab, have been used as therapeutic agents for rheumatic diseases, and are currently being used in clinical trials to treat the depressive episodes of patients with bipolar disorder[64].

[Reference]

64 Brietzke E, Kapczinski F. TNF-alpha as a molecular target in bipolar disorder. Progress in neuro-psychopharmacology and biological psychiatry 2008; 32: 1355-1361 [PMID: 18316149, DOI: 10.1016/j.pnpbp.2008.01.006]

Comment 4

Figures must be cited in the text.

REPLY 4: Done

Responses to Reviewer (#2)

Reviewer's code: 00551176

Comment 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.

REPLY 1: The reviewer's points are correct. We have cited another article describing the study of the prevalence of depression in IFN-treated patients.

REVISION 1

Page 7. First, the injection of cytokines into animals and humans induces depression-like symptoms. Depression occurs frequently in patients with hepatitis C undergoing INF treatment. Of note in one study, 23% of patients during INF treatment satisfied the diagnostic criteria for major depressive disorders; in 74% of them depression occurred within 2 months after the start of INF treatment[20].

[Reference]

20 Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoinginterferon-alpha therapy: a prospective study. General hospital psychiatry 2003; 25: 34-38 [PMID: 12583926, DOI: 10.1016/S0163-8343(02)00239-6]

Comment 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?

REPLY 2: The points that reviewer made are correct. The sentence has been corrected.

REVSION 2

Page 15-16. Inflammation increases the activities of the microglial cells and induce astroglial loss, which consequently induces glutamate release and an upregulation of NMDA receptors[59]. The anti-inflammatory effects of riluzole and ketamine, which are glutamatergic modulators, are being studied. Riluzole and ketamine prevent neurotoxicity and relieve inflammation by inhibiting glutamate secretion and modulating NMDA receptors[60].

Comment 3

There are two Figures attached, but places of these figures in the text are not indicated

REPLY 3: Done

Responses to Reviewer (#3)

Reviewer's code: 00646324

Comment 1

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.

REPLY 1: The passage has been revised to provide clarity.

REVISION 1

Page 18-19. Second, the effects of antidepressant treatments are not always associated with decreased levels of proinflammatory cytokines[73, 74]. The effects of antidepressant treatment may not be caused by decreased cytokine release or synthesis but rather by disturbance of the actions of peripheral-released cytokines on the CNS regardless of the concentration of released cytokines. Thus, antidepressants may not directly inhibit immune activation but, rather, indirectly regulate immune functions.

Third, previous studies have shown that the increased levels of cytokines in depression are within a low range compared with those in systemic infection and inflammation. In acute infection, the huge amounts of cytokines are produced act on the brain functions, which often results in the progression of depression. However, in most clinical conditions, such as chronic infection and inflammation, only low amounts of cytokines circulate. Thus, there is a question whether and how low amounts of peripheral cytokines act on the brain and develop depression, even under baseline conditions. The difference in brain function affected by low and high

levels of cytokines is another issue. Low levels of peripheral cytokines have a similar effect on sleep-awake behaviors compared with a high dose of peripheral cytokines[75]. On the other hand, low levels of cytokines promote non-REM sleep, but this stage of sleep is suppressed by high level of cytokines[75]. It is still unclear, if the doses have similar effects on depression[75]. Because insufficient research for depression and brain functions in various levels of cytokines, the answer to these questions depend on further experimental studies.

Comment 2

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?

REPLY 2: We have now cited clinical trials that confirmed CRF hyperactivity in the subjects who had suffered childhood stress and oversecretion of cerebral CRF in adults during stress.

REVISION2

Page 19. 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[76, 77].

[Reference]

76 Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB. Altered pituitary-adrenal axis responses to provocative challenge tests in adul t survivors of childhood abuse. The American journal of psychiatry 2001; 158: 575-581 [PMID: 11282691, DOI: 10.1176/foc.1.3.282]

77 Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, Nemeroff CB, Price LH. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. Neuropsychopharmacology 2003; 29: 777-784 [PMID:14702025. DOI: 10.1038/sj.npp.1300375]

Comment 3

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.

REPLY 3: Sickness behavior has now been clearly explained in the section of the paper describing the cytokine hypothesis of depression.

REVISION 3

Page 8. The proinflammatory cytokine, NA, and DA promote CRF secretion, activate the sympathetic nerve system, and promote immune reactions. During this process, the temperature of the CNS increases and sickness behaviors may be induced[27]. Sickness behaviors refer to behavioral changes that are observed during an infection period. These include feelings of helplessness, depressive mood, anxiety, hypersomnia, loss of appetite, and inattention. Based on findings that patients with depression exhibit increased levels of proinflammatory cytokines in the plasma[23, 24], decreased levels of anti-inflammatory cytokines[28], and increased levels of PGE2 in the cerebrospinal fluid[29], depression is considered a sickness behavior.

Responses to Reviewer (#4)

Reviewer's code: 02445242

Reviewer's comments:

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.

REPLY 1: The comment has been addressed in the revision in the section dealing with limitations of the cytokine hypothesis of depression.

REVISION 1

Page 19. We may consider various 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 (diet, obesity, gut health, physical

condition, sleep deprivation, vitamin D deficiency), medical illness, differences of cytokine activities between animal models and human, inflammatory markers in suicide, and the influence of treatments like antidepressant drugs, psychotherapy, and electroconvulsive therapy.