6/16/2014

Number ID: 00211905
Dear Professor Lian-Sheng Ma,

Enclosed please find our manuscript entitled, “New insight in expression, transport, and secretion of BDNF: Implications in brain-related diseases” for your consideration as a publication in the World Journal of Biological Chemistry (WJBC).

Thank you very much for the email you sent on April 4, 2014 and for the critical comments and suggestions concerning our manuscript. They were very helpful, and we are now sending our revised version addressed almost all the issues pointed.

The revised manuscript consists of 56 pages of text, 3 figures, and a table. In this revision, we have included one figure (Figure 2) and one table (Table 1), and the number order of the figures has been shifted. The new number order reads as follows: Figure 3 (was Figure 2). Because we have additionally cited 135 references, the manuscript now contains 262 references. All the added and modified parts of the manuscript are indicated by red color. We are very happy to address all issues suggested by the reviewers. We really hope this revision is now suitable for the WJBC.

ANSWERS TO REVIEWERS

REVIEWER1
COMMENTS TO AUTHORS
ESPS Manuscript NO: 9688 Entitled - New insight in expression, transport, and secretion of BDNF: Implications in brain-related diseases
COMMENTS FOR AUTHORS The authors have reviewed both converting (from gene to mature protein) and spatial regulation (transport and secretion) processes of BDNF. They have highlighted recent findings suggesting implications of BDNF in the pathophysiology of the brain-related diseases.
GENERAL COMMENTS
(1) The importance of the research and the significance of the research contents. This is an area, which has generated considerable amount of research attention. Hence, a review on this subject is timely.
(2) The novelty and innovation of the research There are other recent reviews on the subject.

To add to them, the authors need to enlarge the sections related to BDNF alterations in individual disorders.
(3) Presentation and readability of the manuscript Currently, this is adequate, but can be improved.
(4) Ethics of the research No particular ethical issues involved.

SPECIFIC COMMENTS
Title and abstract Adequate
Review The initial sections on BDNF gene structure, transcriptional regulation in BDNF gene, and BDNF transport and secretion are well addressed. However, to link this basic physiology of BDNF with alterations in disease states, it would be helpful if the authors could add:
A section on neuronal functions of the BDNF in the developing and mature brain. This could include how BDNF acts as a signal for proper axonal growth during development, and how BDNF also serves essential functions in regulating synaptic plasticity in the mature brain, including its role in learning and memory processes.
ANSWER
We appreciate the specific and critical comments of the reviewer. According to the critical comments, we have modified our manuscript by adding several aspects of BDNF. Regulation in axonal growth and synaptic plasticity has been incorporated in ***Physiological roles of BDNF in the CNS*** section. Its role in learning and memory processes is also mentioned in the section.

2. A section on BDNF polymorphisms, including the most common BDNF single nucleotide polymorphisms (SNPs) resulting in the Val to Met (V66M) protein variant, which is associated with a decrease in the activity-dependent secretion of BDNF, and processing of pro-BDNF to mature BDNF.
ANSWER
We agree that Val66Met polymorphism in the BDNF gene is also important. Therefore, ***Polymorphism in BDNF gene*** section has been newly made.

3. Actions of the pro-BDNF
The sections on implication of BDNF alterations in brain diseases could also be enlarged. Firstly, the influence of BDNF on basic processes such as cognition and memory and stress regulation needs to be mentioned. The link with early trauma and altered HPA axis reactivity would also be helpful in understanding the role of BDNF in various psychiatric disorders. Secondly, the list of neuropsychiatric conditions potentially associated with alterations in BDNF needs to be enlarged. At the very least, its role in Parkinson’s disease, stroke, epilepsy, bipolar

disorders, substance use, neurodevelopmental disorders, eating disorders and anxiety disorders, and the effects of lithium and electroconvulsive therapy on BDNF need some mention. Thirdly, for each of the disorders covered, e.g. schizophrenia, major depression, or Alzheimer's disease, the findings with regard to the complex and often contradictory BDNF alterations need to be elucidated. - For example, in Alzheimer's disease, although reductions in BDNF or TrkB expression have been found in neurons of the hippocampus and the frontal and temporal cortices, reports have been variable due to brain cohort differences and the variable techniques used to measure their expression in Alzheimer's disease. In major depression variable expression of BDNF/TrkB has been reported in different brain regions. Animal models have suggested a role of altered stress regulation, as well as effects of antidepressants on BDNF. The contribution of the Val to Met (V66M) polymorphism to the pathological features of major depression, or to suicidality remains unclear. Similarly, in schizophrenia, most of the studies measuring serum BDNF have documented lower concentrations in patients, but increased or unchanged levels have also been reported. The association between the Val to Met (V66M) polymorphism and schizophrenia is not a consistent finding either.

ANSWER

To address the issues pointed by the reviewer, we have added a table to show changed BDNF expression levels in brain-related diseases in humans and animal models (see Table 1). Some evidence supporting an idea of possible involvement of BDNF in therapies are also included in the table. Furthermore, we mentioned that lower BDNF levels in schizophrenia and depression are still controversial. Results of association studies on Val66Met polymorphism in Alzheimer's disease, Huntington disease, depression, and schizophrenia have been incorporated in each disease section. Because the reviewer pointed out that alterations in BDNF have been suggested in several neuropsychiatric conditions, we mentioned about this issue at the start of the *Implication of BDNF in brain diseases* section. However, in this review, we discussed only four brain-related diseases in detail to avoid being obscure. We hope to show other brain-related conditions associated with BDNF dysfunction as another review paper in the near future.

REVIEWER2

COMMENTS TO AUTHORS

This is a very good manuscript, reviewing the biological role of BDNF in health and disease. Some minor points will help to improve the manuscript:

A figure describing graphically signaling pathways modulating the regulation of BDNF transcription and secretion.

A table describing main evidence for involvement of BNDF and brain diseases in humans.

A table describing main evidence for involvement of BNDF in cell and animal models for brain

diseases in humans.
A global description of existing genetic variants in human BDNF gene will be helpful.
ANSWER
Thank you very much for your comments that are very helpful to improve the quality of our manuscript. Yes, we have added a schematic illustration displaying the concept of activity-dependent BDNF secretion (Figure 2). A table describing suggested relationship between BDNF and brain diseases in humans and animal models has been added (Table 1). ***Polymorphism in BDNF gene*** section was also added in the paper.

Thank you in advance for your consideration.
We look forward to hearing from you in due course.
Sincerely yours,

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